Name of Sponsor
Cancer Targeted Technologies, Inc.

Name of Investigational Products
CTT1403 – ^{177}Lu-PSMA targeting therapeutic agent
CTT1057 – ^{18}F-PSMA targeting diagnostic agent, or ^{68}Ga-PSMA-11

Title of Study
Phase 1 Dose Escalation/Expansion Study of CTT1403 in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC).

Study Phase
Phase 1

ClinicalTrials.gov Identifier
NCT03822871

Study Center(s):
University of California San Francisco

Principal Investigator
Confidential

Date
March 2, 2021

Study Objectives
Primary Objectives
Dose-Escalation Period
- Determine the safety and tolerability of CTT1403.
- Determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) following a single dose

Dose-Expansion Period
- Determine the preliminary antitumor activity of CTT1403 in patients with mCRPC as measured by objective tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in accordance with Prostate Cancer Working Group 3 (PCWG3) criteria.

Secondary Objectives
- Characterize the organ dosimetry and pharmacokinetics of CTT1403
- Determine the change from baseline in patient reported pain as assessed by Brief Pain Inventory (BPI)

Study Endpoints
Primary Endpoints
Dose-Escalation Period
- Frequency of DLTs at escalating dose levels of CTT1403 during Cycle 1 (6-week period)

Dose-Expansion Period
- Objective response rate by RECIST 1.1
- Adverse event profile by CTCAE v5 criteria

Secondary Endpoints
- Assessment of PK (distribution and elimination t1/2)
- Assessment of organ dosimetry of CTT1403 by SPECT/CT imaging at various timepoints
- Change from baseline in patient reported pain as measured by Brief Pain Inventory (BPI)

Study Design

This is a Phase 1, first-in-human (FIH), dose-escalation/dose expansion study evaluating multiple doses of CTT1403 (study drug) in patients with PSMA-avid mCRPC who have had progressive disease (PD) on at least one androgen signaling inhibitor (ASI), followed by a dose-expansion cohort to further evaluate the safety, tolerability, and efficacy of CTT1403. CTT1057 PET imaging will be used as a companion diagnostic to select patients with PSMA-avid disease for treatment.

After providing written informed consent, patients will be screened for study eligibility within 28 days before their first dose of study drug. After screening assessments, patients who are determined to be eligible for inclusion in the study will be enrolled and will receive their first dose of study drug on Cycle 1 Day 1 (C1D1). A treatment cycle is 6 weeks in length. Patients will receive up to two doses of CTT1403 in the absence of disease progression or unacceptable toxicity. Patients will then be followed long-term for disease progression and survival.

All patients will receive CTT1403 administered IV on Day 1 of every cycle; the dose of CTT1403 will depend on the specific cohort in which the patient is enrolled. Patients will be monitored for a minimum of 4 hours post-CTT1403 administration and will not be discharged from the treatment unit until radiation exposure levels are below the acceptable standard per SOP/institutional guidelines for radiopharmaceuticals.

The starting dose of CTT1403 is based upon the prior clinical safety of other lutetium agents such as ^{177}Lu-PSMA-617 and rat dosimetry data with CTT1403. Dose levels will include the following:

Dose Level	Number of Patients	CTT1403 Dose
1	1	0.75 GBq (20 mCi) (± 10%)
2	1	1.5 GBq (45 mCi) (± 10%)
3	1	2.0 GBq (54.1 mCi) (± 10%)
4	3+3	3.0 GBq (67.6 mCi) (± 10%)
5	3+3	4.5 GBq (121.6 mCi) (± 10%)
6	3+3	6.0 GBq (162.2 mCi) (± 10%)
7	3+3	7.5 GBq (202.7 mCi) (± 10%)
8	3+3	9.0 GBq (243.2mCi) (± 10%)
9	3+3	11.0 GBq (297.3 mCi) (± 10%)
10	3+3	13.5 GBq (364.9 mCi)(± 10%)

Intermediate dosing and/or alternative treatment schedules may be evaluated during the course of the Phase 1 study after the initial safety and dosimetry results are obtained.

During treatment, patients in both stages of the study will attend study center visits and have study evaluations performed as detailed in the schedule of events. All study visits will be conducted on an outpatient basis with monitoring as indicated above.

Patients may continue to receive study drug until any of the following events: the development of radiographic or clinical disease progression, unacceptable toxicity, another discontinuation criterion is met, withdrawal of consent, closure of the study by the Sponsor, or receipt of two doses of CTT1403. Patients with prostate-specific antigen (PSA)-only progression in the absence of radiographic or clinical progression should continue to receive protocol therapy per PCWG3 guidelines.

After discontinuation of CTT1403 treatment, patients will complete an EOT visit within 42 days after their last dose of study drug. The EOT visit will include a safety assessment; additional follow-up may be required if study drug-related AEs have not resolved at that time. Patients who discontinue study drug for reasons other than for PD will also be assessed for clinical evidence of disease progression. Patients without evidence of PD at the EOT visit and who do not start another therapy will be followed every 4 weeks up to 12 weeks, and again 6

months after final dose.

During the dose-escalation and expansion period, biopsy of tumor metastasis is optional at screening and disease progression.

Serial blood samples for PK will be collected from all patients in the dose-escalation period during Cycle 1 and on Day 1 of Cycle 2.

Organ dosimetry will be assessed by SPECT/CT imaging at the specified timepoints in the Study Calendar.

Dose-Escalation Period

It is estimated that up to 10 dose levels will be evaluated during the dose-escalation period of the study using an accelerated scheme for the first 3 doses (n=1/dose level), followed by a 3+3 dose escalation scheme for the final 7 doses. One patient will be enrolled at each of the first 3 dose levels. If a Grade ≥ 2 treatment-related AE is experienced during the DLT window of 6 weeks, then dose escalation schema will convert to a 3+3 design. Starting with enrollment of dose level 4, the study will convert to a 3+3 dose design, if not initiated sooner. All safety data from all patients enrolled in each cohort will be reviewed by the Data Safety Monitoring Committee (DSMB), with members minimally including the Principal Investigator and Sponsor, and sponsor Medical Monitor, to confirm any DLTs that were experienced, and to make a determination regarding enrollment in the next cohort. Based on the evaluation of the data, it may be decided that enrollment at an intermediate dose level or alternative dosing schedule not specified in the protocol will take place. If < 33% of patients (i.e., 0 of 1 (dose level 1-3) or 0 of 3 (dose level 4-10), 1 of 6 patients (all dose levels requiring additional enrollment) within a cohort have a DLT within the DLT window, then enrollment of the next cohort may commence with approval from the Medical Monitor. If ≥ 33% of the patients (≥ 2 of up to 6 patients) within a cohort experience a DLT in the DLT window, then the MTD will have been exceeded and the previous dose level will be considered the MTD.

Definition of Dose-Limiting Toxicity

A DLT is defined as any of the following AEs occurring during Cycle 1 (6-week length), regardless of Investigator attribution to CTT1403, unless the AE can be clearly attributed to an extraneous cause (e.g., disease progression):

- Grade 4 neutropenia lasting > 5 consecutive days.
- Grade 3 or 4 febrile neutropenia.
- Grade 4 thrombocytopenia lasting ≥ 7 days, or Grade 3 or 4 thrombocytopenia with clinically significant bleeding or requirement for platelet transfusion.
- Any nonhematologic AE ≥ Grade 3, with the exceptions of Grade 3 nausea, vomiting, diarrhea, electrolyte abnormality, constipation, fever, fatigue, or skin rash that resolves to Grade ≤ 2 within 72 hours with optimal medical management.
- Any other treatment-related toxicity that results in delay of Cycle 2 administration of CTT1403 by > 21 days and/or toxicity considered by the Investigator and Sponsor's medical representatives to be dose-limiting.

Dose-Expansion Period

A total of up to 10 patients will be treated at the MTD, or maximum tested dose (if no MTD is identified), or at a dose below the MTD (if there is evidence suggesting a favorable risk/benefit

profile) to provide further characterization of the safety, tolerability, PK, and pharmacodynamics of CTT1403.

Duration of Treatment and Study Participation

Patients will be administered CTT1403 once every 6 weeks for up to two doses in the absence of disease progression by PWCG3 criteria, unacceptable toxicity, another discontinuation criterion is met, withdrawal of consent, or closure of the study by the Sponsor.

Following completion of treatment, patients will undergo EOT assessments 30 (+ 7) days after their last dose of study drug, and will continue to be followed via telephone for survival status and clinical evidence of disease progression.

Number of Patients (planned)

A total of up to 43 patients will be enrolled, consisting of up to 33 patients during the dose-escalation period of the study, and approximately 10 patients during the dose-expansion period of the study, if this period is warranted.

Inclusion Criteria (Dose-Escalation and Dose-Expansion Periods)

To be enrolled in the study, patients will be required to meet all of the following criteria:

1. Patients must have histologically confirmed prostate adenocarcinoma that is metastatic and castration resistant (mCRPC). Patients with de novo small cell carcinoma of the prostate are excluded from participation.
2. At least 3 metastatic foci avid for PSMA-specific PET agent (CTT1057) uptake on Screening PSMA PET. PSMA avidity is defined as SUV_{max} > mediastinal blood pool.
3. Has received docetaxel, ineligible for docetaxel, or refused docetaxel for the treatment of prostate cancer.
4. Has progression by the PCWG3 criteria during or after treatment with abiraterone, enzalutamide, and/or apalutamide.
5. Has serum testosterone < 50 ng/dL during screening. Patients without a history of bilateral orchiectomy are required to remain on luteinizing hormone-releasing hormone (LHRH) analog during the course of protocol therapy.
6. Male Age ≥ 18 years.
7. Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 2).
8. Demonstrate adequate organ function as defined below:

<u>Adequate bone marrow function:</u>	
Leukocytes	≥3,000/mcL
Absolute neutrophil count (ANC)	≥1,500/mcL
Hemoglobin	> 9 g/dL and no red blood cell transfusions during the 14 days before administration of first dose of study drug
Platelets	≥100,000/mcL and no platelet transfusions during the 14 days before administration of the first dose of study drug
<u>Adequate hepatic function:</u>	
Total bilirubin	< 1.5 X ULN or direct bilirubin < ULN in patients with known/suspected Gilbert's syndrome
Aspartate aminotransferase	≤2.5 X institutional upper limit of normal (patients with hepatic metastases must have AST/ALT < 5 X ULN
Alanine aminotransferase	≤2.5 X institutional upper limit of normal

Adequate renal function:	
Creatinine clearance	≥60 mL/min/1.73 m^2 as estimated by CKD-EPI equation

9. Ability to understand a written informed consent document, and the willingness to sign it.
10. Must agree to, and be capable of, adhering to the study visit schedule and other protocol requirements, including follow-up for overall survival.

Exclusion Criteria (Dose-Escalation and Dose-Expansion Periods)

Patients who meet any of the following criteria at screening will not be enrolled in the study:

1. Has received previous treatment with radium-223 or another radiopharmaceutical within 3 months prior to first dose of CTT1403.
2. Has received prior systemic anti-cancer therapy (excluding radiopharmaceutical) within 14 days, or 5 half-lives, whichever is shorter, prior to first dose of CTT1403.
3. Has received external-beam radiation within 14 days prior to first dose of CTT1403.
4. Has received cabazitaxel for the treatment of mCRPC.
5. Has received previous treatment with a therapeutic targeting PSMA.
6. Has had a major surgical procedure 28 days before first dose of CTT1403.
7. Has persistent clinically significant toxicities (Grade ≥ 2; per National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) version 4.03) from previous anticancer therapy (excluding alopecia which is permitted and excluding Grades 2 and 3 laboratory abnormalities if they are not associated with symptoms, are not considered clinically significant by the Investigator, and can be managed with available medical therapies).
8. Has evidence of diffuse bone marrow involvement by prostate cancer in the judgment of study investigator.
9. Clinically significant urinary obstruction or moderate/severe hydronephrosis on baseline imaging.
10. Has an additional active malignancy requiring therapy that may confound the assessment of the study endpoints.
11. Has clinically significant cardiovascular disease including, but not limited to:
    a. Uncontrolled or any New York Heart Association Class 3 or 4 congestive heart failure
    b. Uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months before study entry
    c. Uncontrolled hypertension or clinically significant arrhythmias not controlled by medication.
12. Has a history of untreated brain metastases (central nervous system [CNS] imaging is not required before study entry unless there is a clinical suspicion of CNS involvement).
    a. Patients with previously treated brain metastases are eligible if lesions are stable on follow up imaging performed ≥ 4 weeks following completion of treatment
    b. Patients with history of leptomeningeal disease are excluded from study participation
13. Has a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days before CTT1403 administration. Inhaled or topical steroids and adrenal replacement doses ≤ 10 mg daily prednisone equivalents are permitted.
14. Has uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation, or psychiatric illness/social situations that would limit compliance with study requirements.
15. Has known positive status for chronic hepatitis B or hepatitis C (screening is not required). Chronic hepatitis B or C defined as having positive viral load at the time of study entry. Patients that are HIV+ an undetectable viral load and on stable anti-retroviral regimen for >12 weeks prior to study entry will not be excluded.
16. Known or suspected myelodysplastic syndrome.
17. Has any medical condition which in the opinion of the Investigator places the patient at an unacceptably high risk for toxicities.

Investigational Product, Dosage, and Mode of Administration

CTT1403, a ^{177}Lu-targeting PSMA radiotherapy, will be administered intravenously for up to two doses spaced 6 weeks apart.

The starting dose is displayed above.

Duration of Treatment and Study Participation

In the absence of treatment delays due to AEs, treatment be administered every 6 weeks, for up to 2 doses or until one of the following occurs:

1. Disease progression
2. Inter-current illness that prevents further administration of treatment
3. Unacceptable AE(s)
4. Patients decides to withdraw from the study
5. Significant patient non-compliance with protocol
6. General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.
7. The patient has received 2 doses of CTT1403
8. A second dose of CTT1403 will not be given if the estimated cumulative kidney exposure exceeds 23Gy as determined by SPECT dosimetry following the first dose of CTT1403.

Following completion of treatment, patients will undergo EOT assessments 42 (+ 7) days after their last dose of study drug and will continue to be followed every 4 weeks up to 12 weeks and at 6 months post-treatment. Patients not exhibiting PD at the EOT assessment will be contacted every 90 days following final CTT1403 administration to report on disease progression for up to 6 months after last dose of study drug. Patients will undergo physical examination and lab donation of blood for assessment of CBC and creatinine every 4 weeks thereafter for 12 weeks after the last dose, until patient withdrawal from study, or death, whichever occurs first. Upon observation of delayed CBC recovery or other demonstration of drug related toxicity, the long-term observation period will be extended until recovery is observed and/or toxicities are resolved. Patients removed from study for unacceptable treatment related AEs will be followed until resolution or stabilization of all treatment related AEs Grade 2 or above.

Reference Therapy, Dosage, and Mode of Administration

Not applicable.

Concomitant and Prohibited Medications

Usage of Concurrent/Concomitant Medications

Comprehensive supportive care is permitted during the study, including but not limited to anti-emetic and antidiarrheal agents, appetite stimulants, stimulants (i.e., modafinil), anticachexia therapy (ie, fish-oil supplements), antidepressants, opiate and non-opiate analgesics, antibiotics, selective use of corticosteroids, and platelet/neutrophil growth factors as indicated above.

Patients who enter the study receiving ongoing RANK ligand targeting agents, bisphosphonate or denosumab therapy may continue to receive these agents during study participation. mCRPC patients who are receiving LHRH agonists as medical castration should continue receiving these agents during the study.

In the setting of thrombocytopenia or neutropenia, administration of thrombopoietic agents (i.e., romiplostim, eltrombopag) or granulocyte-stimulatory agents (i.e., filgrastim, pegfilgrastim) is permitted in accordance with institutional or American Society of Hematology (ASH) / American Society of Clinical Oncology (ASCO) guidelines. Erythropoietin analogs are also permitted. These

agents should not be employed during Cycle 1 unless severe cytopenias consistent with a DLT are identified.

Dietary Restrictions

There are no dietary restrictions associated with this protocol.

Prohibited Medications/Therapies

Enrolled patients may not receive investigational or approved anticancer agents including cytotoxic chemotherapy agents, anticancer tyrosine kinase inhibitors, or therapeutic monoclonal antibodies not included as a study drug on this protocol for the duration of participation. Palliative radiation is not permitted during study enrollment.

Study Assessments

Assessments for safety, efficacy, and PK will be performed according to the schedule of events.

Safety Assessments

Safety assessments will include AEs, serious AEs (SAEs), DLTs, physical examinations, vital sign measurements, clinical laboratory tests, ECGs, and treatment discontinuation due to toxicity. The AE-reporting period begins with the initiation of study drug and continues through 3 months after the last dose of study drug. All AEs that occur in treated patients during the AE-reporting period specified in the protocol must be reported to the Sponsor, whether or not the event is considered related to study drug. Any known untoward event that occurs beyond the AE-reporting period that the Investigator assesses as related to study drug should also be reported as an AE.

Adverse events will be assessed by the Investigator using the NCI CTCAE, version 4.03.

Efficacy Assessments

Efficacy assessments include disease response and progression per PCWG3 and RECIST v1.1, duration of response, and survival.

All patients must have imaging within 28 days before their first dose of study drug as follows: bone scintigraphy and computed tomography (CT) scan of chest/abdomen/pelvis or magnetic resonance imaging (MRI), if indicated. Additional body sites should be imaged as clinically indicated (e.g., neck). Patients with skin, subcutaneous, or lymph node metastases may also have tumor evaluations (including measurements, with a ruler) by means of physical examination.

Patients will undergo CTT1057 PET or 68GaPSMA-11 PET during Screening and at the time of first tumor assessment (week 6-7, 1 week prior to C2D1 dose of CTT1403).

Tumor measurements and disease/composite response assessments, as described above, are to be performed at screening (within 28 days before the first dose of study drug); after every third cycle (ie, within 7 days before Day 1 of Cycle 2, and of every 9 weeks thereafter until development of PD; and at the EOT visit (for subjects who discontinue the study for reasons other than PD).

To accommodate early flare phenomena, the appearance of 2 new lesions on the first bone scan performed after treatment is insufficient to warrant treatment discontinuation. Instead, to document disease progression, 2 additional lesions would need to be observed on a subsequent follow-up scan performed 6 weeks or longer after the first scan.

Patients who discontinue from the study will be assessed for clinical evidence of disease progression (for patients who discontinued for reasons other than PD) every 90 days until up to 6 months after their last dose of study drug.

Measurements of PSA in blood will be performed on Day 1 and 29 of each 8-week treatment cycle, then every 4 weeks thereafter until radiographic or clinical disease progression.

Pharmacokinetic and Dosimetry Assessments

Blood samples for assessment of PK parameters for CTT1403 and SPECT/CT imaging for organ dosimetry determination will be collected from all patients treated in the dose-escalation period of the study according to the detailed schedule.

Phaarmacokinetics and Dosimetry Schedule for Cycle 1

Cycle	*Day*	*PK Blood/Urine Sample Collection Timepoint*	*SPECT/CT for Organ Dosimetry*
Cycle 1 (6 weeks)	Day 1	• Timepoints after END of infusion: ○ 30 minutes (min) ± 5 min ○ 2 hours ± 30 min	• Timepoints after infusion: ○ 2 hours (± 30 minutes)
	Day 2	24 hours (± 12 hours) after infusion	24 hours (± 12 hours) after infu observed in prior SPECT
	Day 3	72 hours (± 12 hours) after infusion	72 hours (± 12 hours) after infu observed in prior SPECT
	Day 8	168 hours (± 24 hours) after infusion	168 hours (± 24 hours) after infu observed in prior SPECT
	Day 15	336 hours (± 24 hours) after infusion	

Statistical Methods

Randomization: No randomization will be utilized in this study.

Safety

Demographics (e.g., gender, age, race) and baseline characteristics (e.g., ECOG performance status, height, weight, and previous prostate cancer therapy) will be summarized with descriptive statistics. Treatment-emergent AEs (TEAEs) through 30 days after last dose of study drug will be summarized by MedDRA version 20.0 system organ class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. Adverse events will also be summarized by NCI-CTCAE version 4.03 grade and by causality (attribution to study treatment). Dose-limiting toxicities, Grades 3 and 4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will be summarized by preferred terms.

Incidences of laboratory abnormalities will be summarized with descriptive statistics. Vital signs and physical examination results will be summarized with descriptive statistics.

Efficacy

Efficacy parameters will be defined for all patients and for the Dose Expansion cohort.

The primary efficacy endpoint for Dose Expansion is the composite response rate. Composite response rate is defined as the proportion of patients achieving an objective radiographic response by RECIST 1.1 criteria and/or PSA decline > 50% from baseline.

Duration of radiographic response (DoR) is defined as the time from the date measurement criteria are first met for partial response (PR) or complete response (CR) to the date measurement criteria are first met for PD. Radiographic PFS is defined as the time from the date of initiation of treatment to the date measurement criteria are first met for radiographic PD or death from any cause, whichever occurs first (per PCWG3 criteria). PFS6 is defined as the percentage of patients alive and progression-free at 6 months (26 weeks) after the first dose of CTT1403. Distributions for PFS, DoR, duration of complete response (DoCR), and OS will be estimated by Kaplan-Meier methodology.

The mean percent change from baseline on BPI will be descriptively reported for the study cohort.

Pharmacokinetics

PK parameters values that will be calculated to assess distribution and elimination half-life and reported as a mean +/- standard deviation.

Dosimetry

Organ dosimetry (primarily kidney and tumor is warranted) will be measured from SPECT/CT imaging at the timepoints listed above, following the first CTT1403 injection.