Protocol Title:

A Multinational, Multicenter, Prospective, Randomized, Controlled, Open-Label, Phase 2/3 Study of Lutetium Rosopatamab Tetraxetan plus Standard of Care vs. Standard of Care alone for Patients with PSMA Positive Metastatic Castration-Resistant Prostate Cancer Previously Treated Androgen Receptor Pathway Inhibition

Protocol Number: ^{177}Lu-TLX591-203

Version Number & Date: 1.0; 14-Nov-2023

Compound: Lutetium rosopatamab tetraxetan (^{177}Lu-TLX591)

Brief Title: A Phase 2/3 study of ^{177}Lu-TLX591 plus SOC vs. SOC alone in Patients with mCRPC (ProstACT GLOBAL)

Study Phase: 2/3

Sponsor Name: Telix Pharmaceuticals (Innovations) Pty Ltd

Sponsor Address: Level 4, 55 Flemington Road, North Melbourne, VIC 3051, Australia

Confidentiality Statement

Duration:

- The treatment duration of ^{177}Lu-TLX591 will be up to 15 days. Standard of care medications will be taken until confirmed radiographic progression or death, whichever occurs first.
- The study duration will be up to 7 years.
- A participant's participation may be up to 5 years.

Number of Participants:

Approximately 400 participants will be enrolled, where 267 participants will be enrolled into Group A and 133 participants will be enrolled into Group B in order to observe 321 events (Group A: 207, Group B: 114).

Inclusion Criteria:

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Be a male, at least 18 years old, with documented adenocarcinoma of the prostate defined by histological / pathological confirmation.
2. Be of ECOG Performance Status 0, 1, or 2 and have an estimated life expectancy of ≥6 months.
3. Have metastatic disease (defined as ≥1 metastatic lesions present on baseline CT, MRI) or bone scintigraphy).
4. Have castration-resistant PC (defined as disease progressing despite castration by orchiectomy or ongoing use of luteinizing hormone-releasing hormone [LHRH] analogues) and must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L) at time of study entry.
5. Must have received a minimum of 12 weeks of prior therapy with an ARPI in any disease setting.
6. Have a disease that is progressing at study entry, despite a castrate testosterone level (<50 ng/dL or <1.7 nmol/L), by the demonstration of at least one of the following:
    a. 2 rising Prostate Specific Antigen (PSA) values done in sequence at least 1 week apart and with a minimal starting value of 2.0 ng/mL.
    b. Progressive disease or new lesion(s) in the viscera or lymph nodes as per RECIST1.1 or in bone as per PCWG3. Any ambiguous results are to be confirmed by other imaging modalities (e.g., CT or MRI scan).
7. Have disease that is PSMA-positive, as demonstrated by a ^{68}Ga-PSMA-11 PET/CT scan and confirmed as eligible by the Sponsor's central reader.

PSMA positivity is defined as at least one site of metastatic disease with SUVmax ≥1.5 times the SUV of normal liver. However, if there is 1 or more soft tissue lesion of 2 cm that is not PSMA positive, then the patient is to be excluded on the grounds that there is substantial disease that might not respond to the therapy.

8. Must have recovered to ≤ Grade 1 from all clinically significant toxicities related to prior therapies (i.e., surgery, local radiotherapy, ARPI, chemotherapy, etc.) with the exception of alopecia. Specific conditions may be discussed with the medical monitor as needed.
9. Have adequate organ function at Screening:
    a) Bone marrow:
        i. Platelets ≥150×10^9/L.
        ii. Absolute neutrophil count ≥2×10^9/L.
        iii. Hemoglobin >10g/dL (with no red blood cell transfusion in the previous 4 weeks).
        iv. Lymphocyte count >1.0x 10^9/L
    b) Liver function:
        i. Total bilirubin ≤ 1.5×the upper limit of normal (ULN). For participants with known Gilbert's Syndrome ≥3×ULN is permitted.
        ii. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤3×ULN OR ≤5×ULN for participants with known liver metastases.
    c) Renal function:
        i. Serum/plasma creatinine ≤1.5×ULN or creatinine clearance ≥45 mL/min determined using the Crockcoft-Gault formula.
10. Have the capacity to understand the study and be able and willing to comply with all protocol requirements.
11. Participants must comply with the radiation protection rules (including hospital admissions and isolation) that are used by the treating institution in order to protect their contacts and the general public, especially if a female partner of the participant is or could be pregnant.
12. Must agree to practice adequate precautions to prevent pregnancy in a partner and to avoid potential problems associated with radiation exposure to the unborn child (Refer to Clinical Trials Facilitation Group, 2020: Recommendations related to contraception and pregnancy testing in clinical trials Version 1.1, [CTFG (Clinical Trial Facilitation Group), 2020)].

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

1. Is unable to understand or is unwilling to sign a written informed consent document or to follow investigational procedures in the opinion of the Investigator.
2. Has PC associated with pathological findings consistent with small cell or any histology other than adenocarcinoma of the prostate. If there are minor (<20%) elements of neuroendocrine histology, this is acceptable.
3. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, participants with a prior history of malignancy that has been adequately treated and who have been disease-free for more than 3 years are eligible, as are participants with adequately treated non-melanoma skin cancer, and superficial bladder cancer.

4. Is at increased risk of hemorrhage or bleeding, or with a recent history (within the last 6 months) of a thrombolytic event (e.g., deep vein thrombosis [DVT]/ pulmonary embolism [PE]) and have been administered long-term anti-coagulant or anti-platelet agents, with the exception of low dose aspirin (75 to 100mg daily).
5. Has received prior treatment with monoclonal antibody (mAb) J591 or HuJ591 or any other PSMA targeted therapy.
6. Have received chemotherapy in the mCRPC setting (note: prior taxane use in the hormone sensitive setting is permitted if >12 months prior to study entry, i.e., signing the informed consent).
7. Has known allergies, hypersensitivity, or intolerance to the investigational drug or its excipients.
8. Has received prior systemic anti-cancer therapy (e.g., chemotherapy, immunotherapy, or biological therapy) and/or radiation therapy within 4 weeks of randomization (excluding ARPI and/or LHRH analogues).

OR

if any significant AEs have not resolved to National Cancer Institute (NCI) AE Criteria ≤ 2;

OR

are receiving other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.

9. Has received prior treatment with radioisotopes, including but not limited to: ^{89}Strontium, ^{153}Samarium, ^{186}Rhenium, ^{188}Rhenium, ^{223}Radium, or hemi-body irradiation within 6 months prior to randomization.
10. Has received other investigational therapy within 4 weeks of randomization.
11. Has known brain metastases > 1cm or hepatic metastases >1cm.
12. Has a history of seizure and/or stroke within the past 6 months.
13. Has clinical or radiologic findings indicative of impending spinal cord compression or experience symptomatic spinal cord compression.
14. Has evidence of a serious active or sub-clinical infection or angina pectoris (New York Heart Association [NYHA] Class III or IV), significantly prolonged QT interval or other serious illness(es) involving the cardiac, respiratory, central nervous system, renal, hepatic or hematological organ systems, that might impair the ability to complete this study or could interfere with determination of causality of any adverse effects experienced in this study, or which require treatment that could interact with study treatment, particularly with enzalutamide.
15. Has received treatment with any PARP inhibitors (i.e., Olaparib) or with any platinum based anti-neoplastic drugs.

Independent Data Monitoring Committee:

An IDMC will be appointed for this study. The IDMC is a group of independent scientists and clinicians who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, for harms, or for futility.