Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

FAST FACTS

A032304: RADIOLIGAND EFFICACY COMPARISON BY INITIAL PSA-RESPONSE OUTCOME IN METASTATIC CRPC WITH LUTETIUM 177LU PSMA RLT (RECIPROCAL)

3.0 PATIENT SELECTION

3.1 On-study Guidelines

Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
For patients who have partners of childbearing potential, partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principal investigator, during the study and for 14 weeks after the last study drug administration

3.2 Pre-registration (Step 0) Eligibility Criteria

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1. Documentation of Disease:
   - Patients must have histological, pathological, and/or cytological confirmation of prostate adenocarcinoma.
   - Patients must have a positive PSMA PET/CT scan (either 68Ga-PSMA-11, 18F- DCFPyl, or 18F-rhPSMA-7.3), as defined as uptake greater than liver with no PSMA negative measurable soft tissue disease.
   - PSA greater than 2.0 ng/mL
   - Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
     - Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
     - Soft-tissue progression defined as an increase ≥20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
     - Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).

2. Prior Treatment
   - Patients must have prior orchiectomy and/or ongoing androgen-deprivation therapy and a castrate level of serum testosterone (<50 ng/dL or <1.7 nmol/L).
   - Patients must have received at least one ARPI (to include either apalutamide, darolutamide, enzalutamide, or abiraterone).
     - ARPI must be stopped at least 4 weeks prior to pre-registration

- Patients must not have previously received a taxane based chemotherapy regimen for mCRPC. Prior docetaxel for mHSPC or in the neoadjuvant or adjuvant setting is permitted if completed at least 12 months prior to pre-registration.
- Patients must have recovered to ≤ Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).
- Patients on a stable bisphosphonate or denosumab regimen for ≥30 days prior to pre-registration are eligible.
- Previous treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 or hemi-body irradiation within 6 months prior to pre-registration is not allowed. Previous PSMA-targeted radioligand therapy is not allowed.
- Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to pre-registration is not allowed.

3. Age ≥ 18 years

5. ECOG Performance Status ≤ 2

6. Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1,500/mm3
Platelet Count	≥ 100,000/mm3
Total bilirubin	< 1.5x ULN or <3 x ULN in patients with Gilbert's syndrome
Creatinine Clearance	eGFR ≥ 40 mL/min/1.73m2 using the Modification of Diet in Renal Disease (MDRD) equation
Hemoglobin	≥ 9.0 g/dl
ALT or AST	≤ 3.0 x ULN in patients without liver metastases
	≤ 5.0 x ULN in patients with liver metastases

7. No acute biliary or urinary obstruction

8. Patients with treated/stable brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression.
    - Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).

9. HIV/AIDS: Patients with known HIV infection on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial.

10. Hepatitis B: For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

11. Hepatitis C: Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

12. Cardiac function: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class II or better. No history of MI, CABG or angina pectoris within 6 months prior to pre-registration.

13. Concomitant Medications
    - No investigational agents within 28 days prior to pre-registration.
    - No other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
    - No known hypersensitivity to the components of the study therapy or its analogs.
    - No transfusion within 30 days of pre-registration.

14. No symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.

15. Ability to read and comprehend English or Spanish.

3.3 Registration (Step 1) Eligibility Criteria

1. Completion of 2 doses of 177Lu PSMA RLT.

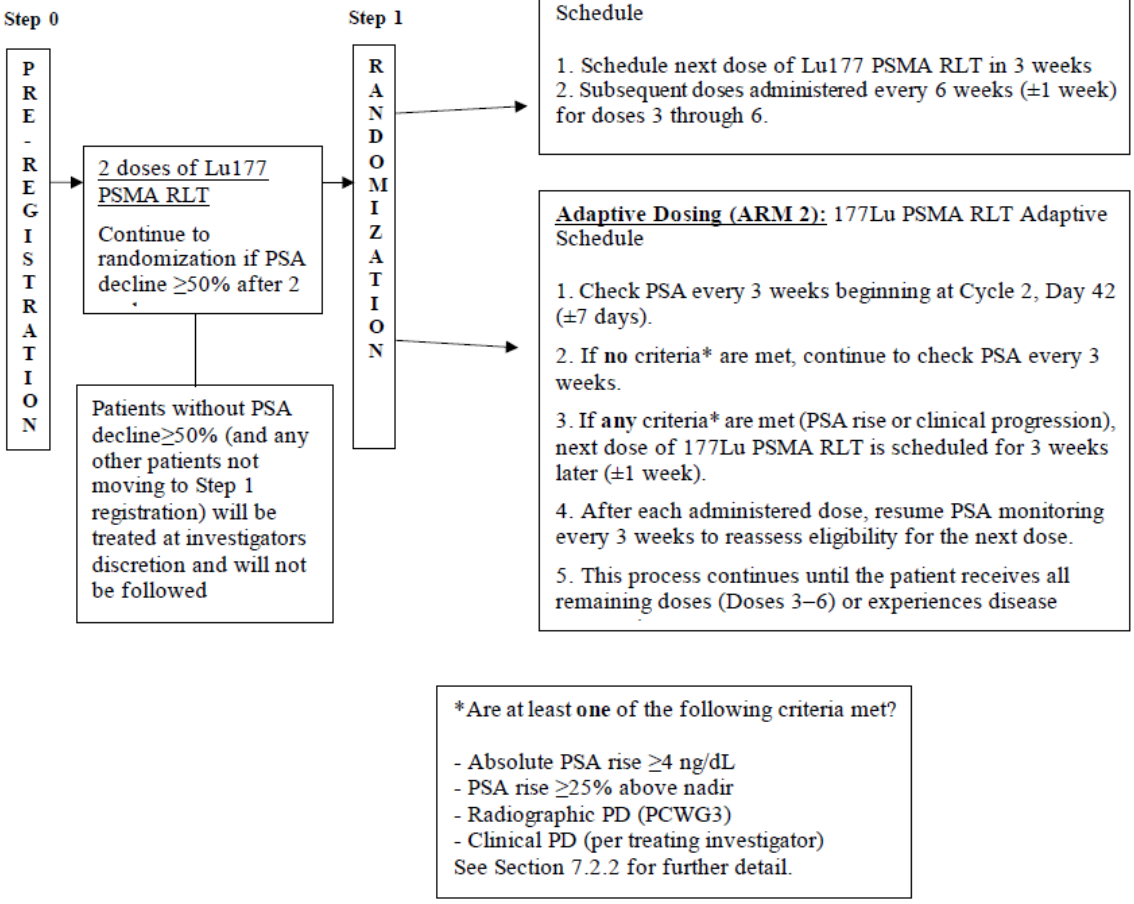
2. PSA decline≥50% between C1 D1 (screening) and C2 D22 +/-3 days.

3. ECOG Performance Status ≤ 2

4. Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine Clearance	eGFR ≥ 40 mL/min/1.73m2 using the Modification of Diet in Renal Disease (MDRD) equation
Hemoglobin	≥ 9g/dL (transfusions allowed)
ALT or AST	≤ 3.0 x ULN in patients without liver metastases
	≤ 5.0 x ULN in patients with liver metastases

Schema


Step 0
PRE-REGISTRATION
2 doses of Lu177 PSMA RLT
Continue to randomization if PSA decline ≥50% after 2
Patients without PSA decline≥50% (and any other patients not moving to Step 1 registration) will be treated at investigators discretion and will not be followed
Step 1
RANDOMIZATION
Standard Dosing (ARM 1): 177Lu PSMA RLT Standard Schedule
1. Schedule next dose of Lu177 PSMA RLT in 3 weeks
2. Subsequent doses administered every 6 weeks (±1 week) for doses 3 through 6.
Adaptive Dosing (ARM 2): 177Lu PSMA RLT Adaptive Schedule
1. Check PSA every 3 weeks beginning at Cycle 2, Day 42 (±7 days).
2. If no criteria* are met, continue to check PSA every 3 weeks.
3. If any criteria* are met (PSA rise or clinical progression), next dose of 177Lu PSMA RLT is scheduled for 3 weeks later (±1 week).
4. After each administered dose, resume PSA monitoring every 3 weeks to reassess eligibility for the next dose.
5. This process continues until the patient receives all remaining doses (Doses 3–6) or experiences disease
*Are at least one of the following criteria met?
- Absolute PSA rise ≥4 ng/dL
- PSA rise ≥25% above nadir
- Radiographic PD (PCWG3)
- Clinical PD (per treating investigator)
See Section 7.2.2 for further detail.