Adaptive External Beam and Radioligand Radiotherapy for MEtaSTatic castration resistant prostate cancer (ARREST) : a phase II registry-based RCT proposal

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INTRODUCTION

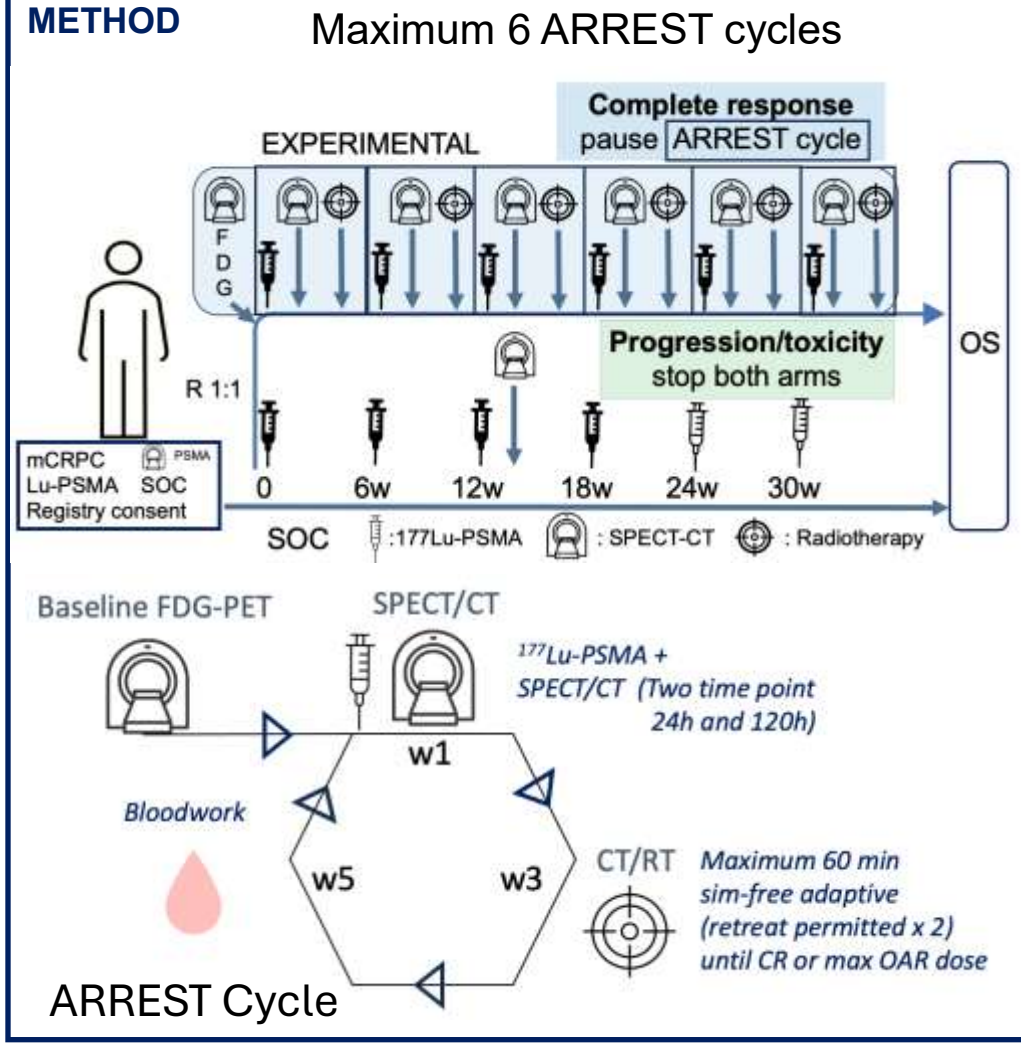
177Lu-PSMA radioligand therapy (RLT) is an emerging option for metastatic castration-resistant prostate cancer (mCRPC). However, **some patients fail to show meaningful clinical benefit** with this therapy, possibly due to **underdosed tumor regions.**

AIM

ARREST seeks to intensify tumor dose via **complementary external beam radiotherapy (EBRT)** in underdosed tumor regions.

We hypothesize that by combining both modalities (EBRT and RLT) in an hybrid, adaptive approach, we can **safely improve survival outcomes** when compared to standard-of-care (SOC) 177Lu-PSMA alone.

METHOD



Multicenter RCT 1:1 planned to activate 2025

Rando	177Lu-PSMA + EBRT boost vs. SOC 177Lu-PSMA
Eligibility	Eligible to SOC 177Lu-PSMA. No liver metastasis. Burden suitable for EBRT.
Critieria for EBRT boost	1. Low 177Lu-PSMA vs FDG uptake (only first cycle) 2. Symptomatic lesions if RLT BED < 30 Gy; 3. Bone lesions at risk of SRE (≥ 2 cm, junctional or post spine, hip or sacroiliac joint, long bone 1/3-2/3 cortical thickness) if BED < 30 Gy; 4. Lesions with BED < 30 Gy.
EBRT dose	6-12Gy / fraction to achieve cumulative **BED ≥30 Gy** (α/β = 5 Gy)
1st endpoint	Overall Survival at 2 years
2nd endpoint	Rate SRE, 177Lu-SPECT-CT and PSA response, toxicity, and quality of life.
Sample	N=130. HR 1.6. Two-sided α 0.1. β 0.8%.

CONCLUSIONS

1) ARREST aims to safely optimize tumor dose through a personalized, hybrid approach combining EBRT and RLT.
2) Hypothesized to improve survival outcomes
3) Generate insights into the biological effects of EBRT and RLT, helping to refine models of relative biological effectiveness for more accurate treatment planning.

PSMA: Prostate-Specific Membrane Antigen, FDG: Fluorodeoxyglucose, SPECT/CT: Single Photon Emission Computed Tomography / Computed Tomography, BED: Biologically Effective Dose, SRE: Skeletal-Related Events, HR: Hazard Ratio, PSA: Prostate-Specific Antigen, RCT: Randomized Controlled Trial, CR: Complete Response, OAR: Organs At Risk.