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Abstract Submission

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

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Introduction

177Lu-PSMA radioligand therapy (RLT) is an emerging option for metastatic castration-resistant prostate cancer (mCRPC). However, up to half of patients fail to show meaningful clinical benefit with this therapy. A dual-modality strategy seeks to increase 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.

Methodology

Adaptive EBRT and RLT for mCRPC (ARREST) is a registry-based phase 2, multi-center randomized controlled trial within the PERa prospective cohort (NCT03378856) planned to activate in 2025. Patients who are eligible to receive SOC 177Lu-PSMA, with no liver metastases and with targetable metastatic burden suitable for EBRT will be eligible. One hundred and thirty eligible patients will be randomized 1:1 to receive either SOC 177Lu-PSMA therapy alone (maximum 6 cycles) or to combined 177Lu-PSMA plus EBRT boost. Patients in the experimental arm will undergo FDG-PET at baseline and SPECT-CT after each cycle. Lesions selected for EBRT boost will be selected based on a set of criteria that include estimated suboptimal dose absorbed from 177LuPSMA, lesions demonstrating low PSMA but high FDG update, symptomatic lesions, and those at high risk for skeletal-related events. Selected lesions will receive single-fraction EBRT. Dose prescribed will range from 6-12Gy with the ideal goal of a combined total biological effective dose of ≥75 Gy ($\alpha/\beta = 1.4$) with priority to dose limits for organs at risk. A maximum treatment time of 60 minutes is permitted for each EBRT boost treatment. Patients in the experimental arm that achieve complete response measured by 177Lu-SPECT-CT and PSA will pause ARREST and resume at progression. The primary endpoint is overall survival at 2 years. Secondary objectives include skeletal-related events, 177Lu-SPECT-CT and PSA response, toxicity, and quality of life. The sample size is designed to detect a two-year overall survival benefit with a HR 1.6, two-sided alpha of 0.1 and 80% power.

Conclusion

ARREST is hypothesized to safely optimize tumor dose, offering a personalized hybrid approach that may lead to improved patient outcomes. In addition, this study will permit further understanding of these two distinct radiation delivery methods and their effect on tissues, thereby refining the relative biological effectiveness model for more precise treatment planning.