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PRIMORDIUM - A Randomized, International, Trial-in-Progress of Adding Apalutamide to Radiotherapy and an LHRH Agonist in High-Risk Patients with PSMA-PET-Positive Hormone-Sensitive Prostate Cancer

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PRIMORDIUM

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Background

- After radical prostatectomy, 25% to 35% of patients develop elevation of serum prostate-specific antigen (PSA)[1,2]
- Positron emission tomography of radiolabeled prostate-specific membrane antigen (PSMA-PET) is more sensitive than conventional imaging for prostate cancer[3,4]
- Thus, PSMA-PET is a recommended imaging modality for patients with biochemical recurrence and PSA >0.2 ng/mL[5]
- Apalutamide, a next-generation nonsteroidal androgen receptor (AR) inhibitor, is approved in multiple countries for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) in adult men who are at high risk of developing metastatic disease,* or for the treatment of metastatic hormone-sensitive / castration-sensitive prostate cancer (mHSPC/mCSPC) in combination with androgen-deprivation therapy
- This trial-in-progress uses PSMA-PET-evaluated staging and efficacy outcomes to investigate adding apalutamide to radiotherapy (RT)† and a luteinizing hormone-releasing hormone agonist (LHRHa) in patients with high-risk, PSMA-PET-positive hormone-sensitive prostate cancer, nonmetastatic on conventional imaging
- This is one of the first randomized, controlled trials to use enhanced imaging methods for study enrolment and the primary study endpoint in prostate cancer with biochemical recurrence
- The study has two cohorts: interventional (PSMA-PET-positive patients) and observational (PSMA-PET-negative patients)

*In the SPARTAN study,[6] high risk was defined as PSADT ≤10 months

†For this study, RT is defined as whole pelvic salvage radiotherapy ± stereotactic body radiotherapy (SBRT)

Primary Objectives

Interventional Cohort

- To determine if the addition of apalutamide to RT+LHRHa delays metastatic progression as assessed by PSMA-PET (by blinded independent central review; BICR) or death compared with RT+LHRHa alone

Observational Cohort

- To describe the natural history, management, and outcomes for PSMA-PET-negative patients within routine clinical practice

Study Endpoints

Interventional Cohort

- **Primary**: PSMA-PET metastatic progression-free survival (ppMPFS), defined as the appearance of at least 1 new PSMA-PET-positive distant lesion compared with the previous scan as assessed by BICR, or death
- **Secondary**: time to PSA progression; PSA response rate; PSA levels at end of Week 26; time to locoregional progression by PSMA-PET; overall survival; prostate cancer-specific survival; and adverse events

References

1. Pound CR, et al. JAMA 1999; 281:1591-1597
2. Boorjian SA, et al. Eur Urol. 2011.59:893
3. Perera M et al. Eur Urol. 2020;77:403-417
4. Hofman MS et al. Lancet. 2020;395(10231):1208-1216
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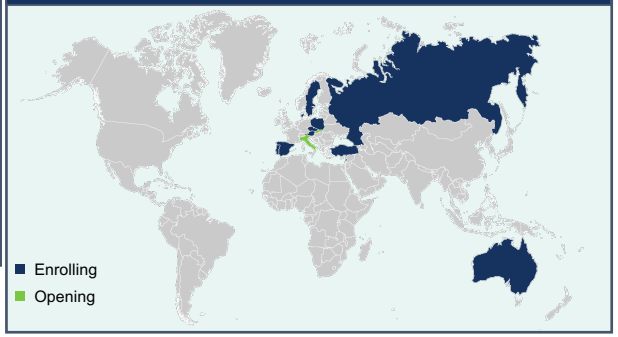
Principal Inclusion Criteria

- Male, ≥18 years of age
- Histologically confirmed adenocarcinoma of the prostate
- Previously treated with radical prostatectomy, with postoperative PSA <0.1 ng/mL
- Biochemically recurrent prostate cancer after radical prostatectomy with high risk of developing metastasis, defined as pathological Gleason score ≥8 or PSADT ≤12 months
- No evidence of metastases on screening CT/MRI of the chest/abdomen/pelvis, and ^{99m}Tc whole-body bone scan
- PSMA-PET at screening:
  - **Interventional Cohort**: Patients who are PSMA-PET-positive for ≥1 locoregional (pelvic) lesion with or without distant (extra pelvic) lesions at screening, as determined by BICR
  - **Observational Cohort**: Patients who are PSMA-PET-negative for any prostate cancer lesions (ie, no loco regional lesion and no distant lesions) at screening, as determined by BICR
- ECOG Performance Status Grade 0 or 1

Principal Exclusion Criteria

- History of pelvic radiation for malignancy
- History of androgen deprivation therapy or chemotherapy for prostate cancer
- Prior treatment for biochemical recurrence
- CYP17 inhibitor, AR antagonist, medication that lowers androgen levels, or bilateral orchiectomy
- Small cell or neuroendocrine carcinoma of the prostate
- Clinically significant cardiovascular disease
- Use of 5-alpha-reductase inhibitor or an investigational agent ≤4 weeks prior to randomization
- History of seizure or at increased risk of seizure

Study Regions



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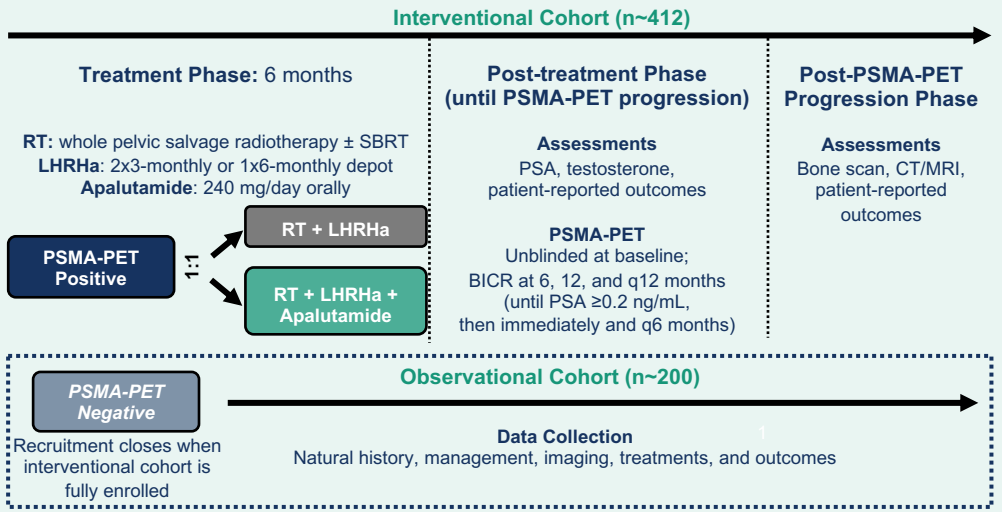
Study Design



EudraCT

NCT

Treatment

Interventional Cohort

- Patients are randomized 1:1
  - RT + LHRHa or apalutamide + RT + LHRHa
  - Stratified by location of PSMA-PET-positive lesions, PSADT, and planned use of SBRT
- RT (both groups): whole pelvic salvage radiotherapy ± SBRT
  - At sites where it is a standard approach, SBRT may be used for ≤3 PSMA-avid distant metastases; the decision to use SBRT must be made before randomization
- LHRHa (both groups): selected by site: either 2x3-monthly depot or 1x6-monthly depot
- Apalutamide (one group): 240 mg/day orally, for 26 weeks

Observational Cohort

- Patients receive standard-of-care per local practice

Assessments

Interventional Cohort

- PSA is measured every 3 months until the primary endpoint
- If PSA remains <0.2 ng/mL, PSMA-PET is assessed by BICR at 6 and 12 months, then annually until PSMA-PET progression
- If PSA rises to ≥0.2 ng/mL, PSMA-PET is done immediately then every 6 months until PSMA-PET progression
- Investigators are blinded to PSMA-PET lesion locations after randomization until PSMA-PET progression
- Patient-reported outcomes, biomarkers, PSA progression, safety, metastasis by conventional imaging and survival are assessed
- An exploratory substudy evaluates response with whole-body MRI

Observational Cohort

- Data collected during routine clinical practice are recorded, including therapies administered and clinical evaluations

Study Status

May 2020	February 2021	16 August 2021	Interim Analysis
Registered with EudraCT	First patient randomized	45 sites in 11 countries	Data monitoring committee will review interim safety and efficacy data