### Treatment Plan
See Section 5.0 for Complete Treatment Details

All patients will receive a SOC PET/CT (mid thigh level to skull base or skull vertex) on a qualified PET/CT scanner at baseline, prior to any treatment planning/delivery (during Step 0 registration or up to 16 weeks prior). Patients will then be placed into one of two cohorts:

**PET-Negative for Extra-Pelvic Metastases:**
- **Arm A**—Planned SOC RT + STAD
- **Arm B**—Planned SOC RT + STAD + Apalutamide

**PET-Positive for Extra-Pelvic Metastases**
- **Arm C**—Planned SOC RT + STAD + Apalutamide + Metastasis-Directed RT to PET-positive lesions
- **Arm D**—Planned SOC RT + STAD + Apalutamide + Metastasis-Directed RT to PET-positive lesions

A repeat 18F-fluciclovine PET/CT will only be performed in patients who received 18F-fluciclovine for PET1 and were enrolled on Arms C/D. The repeat PET will be performed at time of PSA progression or 12 months after completion of enhanced systemic therapy, whichever occurs first.

**NOTES:**
- **SOC RT** is external beam RT to the prostate bed and pelvic lymph nodes; **SOC RT** can start anywhere from 7 days prior to **STAD** initiation up to 3 months after the start of **STAD**
- For **STAD**, see protocols for acceptable GnRH agonist/antagonist (goserelin, leuprolide, triptorelin, relugolix, degarelix); patients should start **STAD** within 14 days after Step 1 randomization
- **Apalutamide** is 240 mg PO (taken whole) once daily for 6 months; must be started within 14 days of starting **STAD**
- RT dose and fractionation to the prostate bed and pelvic nodes will follow standards as detailed in NRG-GU002 or NRG-GU008, i.e., 30 Gy in 3 fractions for SBRT or 50 Gy in 10 fractions for Non-SBRT

### Patient Population
See Section 3.0 for Complete Eligibility Details

**Step 0—Registration Eligibility Criteria:**
- Male ≥ 18 years old; ECOG PS 0-2; adequate lab values
- Must have had a radical prostatectomy (RP) as definitive therapy for histopathologically-proven prostatic adenocarcinoma; must have biochemical recurrence (BCR) after RP, with rising PSA defined per protocol
- Must be negative or equivocal for extra-pelvic metastatic disease (defined per protocol) by CIMP (anatomic imaging with CT and/or MRI and bone scintigraphy, or equivalent) within 26 weeks prior to Step 0 registration
- Must be a candidate for standard of care (SOC) post-prostatectomy radiation therapy (RT) to the prostate bed and pelvic nodes with androgen deprivation therapy (adjuvant); must not have started androgen deprivation therapy for BCR prior to baseline study PET/CT
- No history of seizures/know condition that may cause predisposal to seizures within 1 year prior to registration
- No history of inflammatory bowel disease
- HIV/HBV/HCV patients permitted per protocol
- Patients with known history/current symptoms of cardiac disease/history of treatment with cardiotoxic agents, should be NYHA class I or II (by patient symptoms) or A or B (by objective assessment)
- Must not have had prior pelvic radiation therapy for any reason

**Step 1—Randomization Eligibility Criteria:**
- Must have completed a baseline SOC PET scan, per protocol, with results of extra-pelvic metastases involvement known (positive or negative)
  - **Patients with negative extra-pelvic metastases:** PET-imaging status of intra-pelvic nodes must be known (positive or negative)
  - **Patients with positive extra-pelvic metastases:** the number of extra-pelvic lesions must be known (1-5 or > 5 extra-pelvic lesions)

### Patient Enrollment
All Sites: Oncology Patient Enrollment Network (OPEN) [https://open.ctsu.org](https://open.ctsu.org)

### Protocol Information
ECOG-ACRIN Operations-Boston: 857-504-2900, [http://ecog-acrin.org](http://ecog-acrin.org) (Member Login)

Please Enroll Your Eligible Patients!