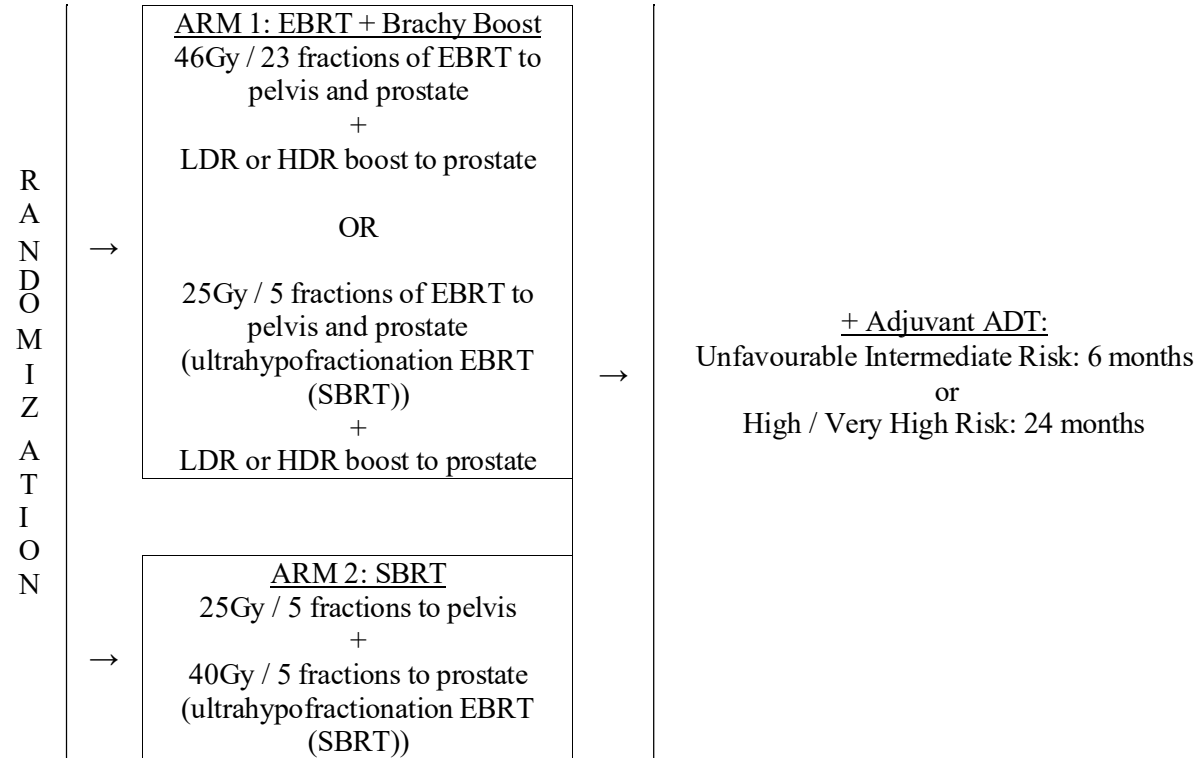
# CCTG-PR24 TREATMENT SCHEMA

This is a multi-centre, open-label, randomized phase III trial comparing a stereotactic body radiotherapy (SBRT) technique to conventional external beam radiotherapy (EBRT) with brachytherapy boost (LDR or HDR) for men with unfavourable risk, localized prostate cancer.

Stratification

- Risk (unfavorable-intermediate risk vs high/very-high risk)
- Systemic therapy intensification with 2nd generation anti-androgen (yes vs no)
- CT/PET scan (yes vs no)




N = 710 participants

# 4.0 STUDY POPULATION

The study population consists of men with histologically confirmed unfavourable risk, localized prostate cancer.

## 4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of enrollment. Questions about eligibility criteria should be addressed prior to enrollment.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that participants who enter this study are medically appropriate candidates for this therapy and to ensure that the results of this study can be useful for making treatment decisions regarding other participants with similar disease(s).

Participants must fulfil all of the following criteria to be eligible for admission to the study:

4.1.1 Histologically confirmed adenocarcinoma of the prostate diagnosed within the last 9 months. Participants on active surveillance may be enrolled if prostate biopsy was done within 9 months of enrollment and meets the histologic eligibility criteria.

4.1.2 Participants with unfavourable risk prostate cancer are eligible according to the following NCCN classification guidelines (Version 4.2022 – May 10, 2022):

- Unfavourable-intermediate risk – has one or more of the following:
  - 2 or 3 Intermediate Risk Factors (IRFs): cT2b-cT2c, Gleason 7 (grade group 2 or 3), and/or PSA 10-20 ng/ml;
  - Gleason 4+3 (grade group 3)
  - $\geq$ 50% biopsy cores positive
- High risk – has one of the following:
  - cT3a
  - Gleason 8-10 (grade group 4 or 5)
  - PSA > 20 ng/ml
- Very-high risk – has at least one of the following:
  - cT3b-cT4
  - Primary Gleason pattern 5
  - 2 or 3 high risk features: cT3a, Gleason 8-10 (grade group 4 or 5), and/or PSA > 20 ng/ml
  - > 4 cores with Gleason 8-10 (grade group 4 or 5)

4.1.3 ECOG performance status of 0, 1 or 2.

4.1.4 Participants must be $\geq$ 18 years of age.

4.1.5 Judged to be medically fit for brachytherapy.

4.1.6 Participant is able (i.e. sufficiently fluent) and willing to complete the quality of life and/or health utility questionnaires in either English, French or Spanish. The baseline assessment must be completed within required timelines, prior to enrollment. Inability (lack of comprehension in English, French or Spanish, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the participant ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the participant ineligible.

4.1.7 Participants consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each participant must sign a consent form prior to enrollment in the trial to document their willingness to participate.

4.1.8 Participants must be accessible for treatment and follow-up. Investigators must assure themselves the participants enrolled on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

4.1.9 In accordance with CCTG policy, protocol treatment* is to begin within 12 weeks of participant enrollment. (*Protocol treatment includes both radiation therapy and ADT)

4.1.10 Participants must be willing to take precautions to prevent pregnancy while on study. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention). However, if at any point a previously celibate participant chooses to become heterosexually active during the time period for use of contraceptive measures, they are responsible for beginning contraceptive measures.

4.1.11 *Prior Therapy*

*Systemic Therapy*

- ADT (LHRH agonists or antagonists) and anti-androgen therapy for prostate cancer are permitted for up to 185 days before study enrollment*.
- 5-alpha reductase inhibitors (5-ARI) are allowed, but baseline PSA will be corrected if 5-ARI use occurs within 6 months of enrollment.

*Other Systemic Therapy*

Participants may NOT have received other therapies including chemotherapy, PARPi, radioligand or other investigational drugs for prostate cancer.

*PSA and prostate volume must have been collected prior to start of ADT. PSA must also meet the protocol requirements for the timeline (see Section 5.0). Prostate volume must meet the protocol requirements for the value prior to start of ADT (see Section 4.2).

4.1.12 Participants 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.

4.1.13 Urinary function defined as International Prostate Symptom Score (IPSS) < 20. Alpha blockers are allowed to treat baseline urinary function.

4.1.14 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

4.2 Ineligibility Criteria

Participants who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Prior pelvic radiotherapy.

4.2.2 Contraindication to radical prostate radiotherapy (e.g. connective tissue disease or inflammatory bowel disease).

4.2.3 Anticoagulation medication (if unsafe to discontinue for gold seed insertion or brachytherapy implant) and/or prior or current bleeding diathesis.

4.2.4 Prior steam vaporization (Rezum), transurethral resection of the prostate (TURP), prostatectomy (simple or radical), or any ablative therapy to the prostate (cryotherapy, HIFU, TULSA, focal laser ablation, photodynamic therapy).

4.2.5 Prostate volume > 60cc before start of androgen deprivation therapy.

4.2.6 Anatomy that would preclude precise brachytherapy implant (such as arch interference or large median lobe).

4.2.7 Evidence of castrate resistance (defined as a rising PSA > 3.0 ng/ml while testosterone is < 3.0 nmol/l).

4.2.8 Definitive nodal or distant metastatic disease on staging investigations.

4.2.9 Hip prosthesis (unilateral hip replacement is allowed if dose constrains can be reasonably achieved).