Cancer Research Consortium of West Michigan
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FAST FACTS

CCTG-PR26: A RANDOMIZED PHASE III CLINICAL TRIAL FOR THE ADDITION OF DOCETAXEL TO ANDROGEN RECEPTOR PATHWAY INHIBITORS IN PATIENTS WITH METASTATIC CASTRATION SENSITIVE PROSTATE CANCER AND SUBOPTIMAL PSA RESPONSE (TRIPLE-SWITCH)
NCT #06592924

STUDY POPULATION

The study population consists of men with metastatic castration sensitive prostate cancer who have suboptimal PSA response as defined by a PSA of ≥0.2 after at least 6 to 12 months of ADT and ≥4 months of ARPI.

Eligibility Criteria

1. Male ≥18 years of age.

2. Histologically/cytologically confirmed adenocarcinoma of prostate or participants with a PSA >100 ng/ml (100 ug/L) and radiographic evidence of metastatic disease at diagnosis.

3. Metastatic disease by conventional imaging (bone scan and/or computed tomography (CT) and/or MRI) or PSMA-PET scan at the time of ADT initiation.

4. PSA of ≥2.0 ng/ml (2.0 ug/L) prior to commencement of ADT (this refers to patients who have histologically/cytologically confirmed adenocarcinoma of prostate).

5. *Prior Therapy*
   Patients will have recovered from any treatment-related toxicities prior to enrollment (unless ≤ grade 1, irreversible, or considered by investigator as not clinically significant).

   Patients may enroll with persistent toxicities attributable to ADT, including hot flushes and fatigue, of any grade, provided these toxicities are clinically stable, not rapidly worsening, and not considered by the Investigator to pose a safety risk or impair the patient's ability to comply with study procedures. Such toxicities do not need to resolve to Grade ≤1 prior to study entry.

   Systemic Therapy
   - Receipt of ADT for mCSPC for at least 6 months and no greater than 12 months (+/- 3 weeks) at time of enrollment.
   - Receipt of ARPI (e.g. abiraterone acetate, enzalutamide, apalutamide, or darolutamide) for at least 4 months (+/- 2 weeks) at time of enrollment.

Radiotherapy

- Patients may have had radiotherapy to prostatic bed and/or metastatic sites prior to enrollment. Potential trial participants should have recovered from any radiotherapy-related toxicities prior enrollment (unless ≤ grade 1).

6. Serum testosterone < 1.7 nmol/L or 50 ng/dL.

7. PSA ≥ 0.2 ng/ml (0.2 ug/L) within 28 days of enrollment.

8. Candidate for docetaxel chemotherapy (per investigator).

9. ECOG Performance Status (PS) 0 to 2.

10. Adequate organ and marrow function measured within 28 days prior to enrollment including:

Hematology	Hemoglobin	≥ 80 g/L
	Absolute neutrophils	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
Biochemistry	Total Bilirubin	≤ 1.0 x ULN (upper limit of normal)*
	AST and/or ALT	≤ 1.5** x ULN
	Creatinine Clearance	≥ 30 mL/min; measured directly by 24-hour urine sampling OR as calculated by Cockcroft and Gault equation: Males: CrCl = [140-age (years)] x weight (kg) ÷ serum creatinine (mg/d/L) x 72
* If suspected Gilbert's, eligible providing a total bilirubin ≤ 2.0 x ULN ** With concurrent alkaline phosphatase ≤ 2.5 times the ULN		

11. Participant 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.

12. 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.

13. In accordance with CCTG policy, protocol treatment is to begin within 10 working days of participant enrollment.

14. If the participant and the participant's partner are of childbearing potential, they must agree to use medically accepted methods of contraception (e.g. barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 90 days after the last dose of study drug.

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

16. Participant access to all protocol therapies must be confirmed prior to enrollment.

Ineligibility Criteria

1. Confirmed PSA progression, defined by an increase in PSA of 25% above the nadir since achieving castration on ADT, an absolute increase in PSA value of 2.0 ng/ml (□g/L) above nadir, and a subsequent increase in PSA of 25% further separated by 3 or more weeks.

2. Evidence of confirmed radiographic progression or clinical progression since start of ADT. Participants may be enrolled on the study if in the opinion of the investigator any new bone lesions on bone scan and CT represent flare or treatment effect.

3. Docetaxel criteria:
    - Prior treatment with taxane chemotherapy
    - Grade 2 or worse peripheral neuropathy
    - Severe hypersensitivity to drugs formulated with polysorbate 80

4. Clinically significant cardiac disease including:
    - History of unstable angina pectoris, symptomatic pericarditis, or myocardial infarction within 6 months prior to study entry.
    - History of documented congestive heart failure (New York Heart Association functions classification III-IV).

5. Patients with uncontrolled intercurrent illness or any other significant condition(s) that would make this protocol unreasonably hazardous. Patients with a prior or concurrent malignancy whose natural history of treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

6. Concurrent treatment with other anti-cancer systemic therapy other than ADT and ARPI.

7. Live attenuated vaccination administered within 30 days prior to enrollment/randomization. **Note:** Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and not allowed.

8. For participants with history of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

9. Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

10. High-grade neuroendocrine prostate cancer or small cell features (except if a participant has no histological diagnosis but a PSA >100 ng/ml (>100 ug/L) at diagnosis and radiographic evidence of metastatic disease).

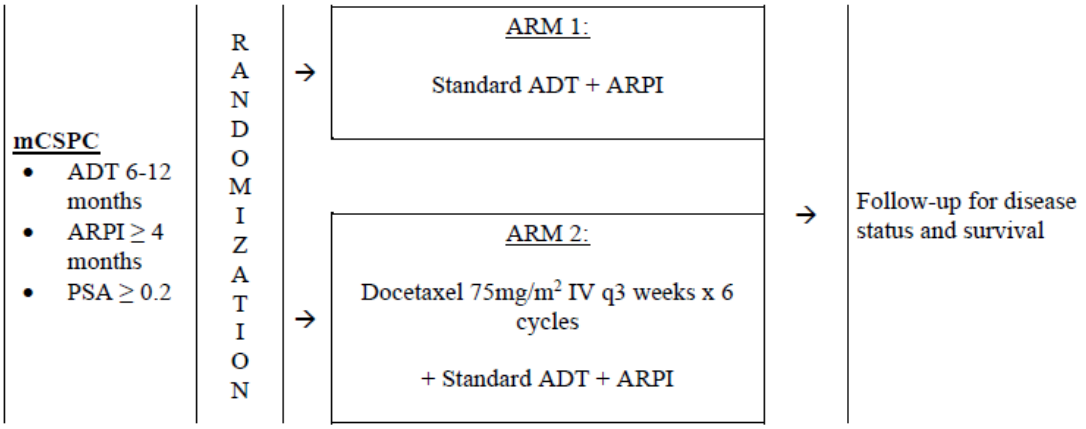
TREATMENT SCHEMA

This is an international multi-centre, open-label, randomized phase III trial comparing Docetaxel chemotherapy added to standard of care Androgen Deprivation Therapy (ADT) + Androgen-Receptor Pathway Inhibitor (ARPI) versus standard of care Androgen Deprivation Therapy (ADT) + Androgen-Receptor Pathway Inhibitor (ARPI) in participants with metastatic castration sensitive prostate cancer (mCSPC) who have a suboptimal PSA response after 6-12 months of androgen-targeting therapy.

Stratification:

- PSA 0.2 – 4 vs >4
- ARPI-type: CYP17 inhibitor (Abiraterone acetate) vs AR antagonist (Apalutamide, Enzalutamide, Darolutamide)
- Liver metastasis vs no liver metastasis (liver metastasis identified on screening conventional CT scan)
- De novo vs Recurrent (at time of diagnosis of mCSPC)
- Time from ADT start: ≥6 to <9 months vs ≥9 to 12 months

Patients will be randomized 1:1 to one of two arms.



N = 830 participants