INITIAL: 2024-OCT-07
UPDATE #4: 2025-MAR-05

CANADIAN CANCER TRIALS GROUP (CCTG)

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)

CCTG Protocol Number: **PR.26**
NCI/CTEP Number: **CCTG-PR26**
NCT Number: **NCT #06592924**

Study Exempt from IND Requirements per 21 CFR 312.2(b).

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Protocol Agents:

Other Agent(s): Docetaxel (NSC 628503), Abiraterone Acetate (NSC 748121), Enzalutamide (NSC 766085), Apalutamide (NSC 794776), and Darolutamide (NSC 815949)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by CCTG with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and NRG Oncology, and SWOG.

Participating Organizations

CCTG / Canadian Cancer Trials Group (lead)

ALLIANCE / Alliance for Trials in Clinical Oncology

ECOG-ACRIN / ECOG-ACRIN Cancer Research Group

NRG / NRG Oncology

SWOG / SWOG Cancer Research Network

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Document History

Modification	Version Date
Update #5	2025-Jun-20
Update #4	2025-Mar-05
Update #3	2024-Oct-07
Update #2	2024-Aug-22
Update #1	2024-Jul-29
Initial Submission	2024-Jun-03

(For contact information of study personnel see Final Pages.)

CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).

TABLE OF CONTENTS

STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol and any supplementary information that may be added to this document, contains information that is confidential and proprietary and must be kept in confidence.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, in accordance with any modifications that may occur over the duration of the study, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG of any such disclosure.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG with or without cause.

_____	_____	_____
Qualified Investigator Signature	Printed Name	Date

Protocol Number: CCTG PR.26

CENTRE: _____

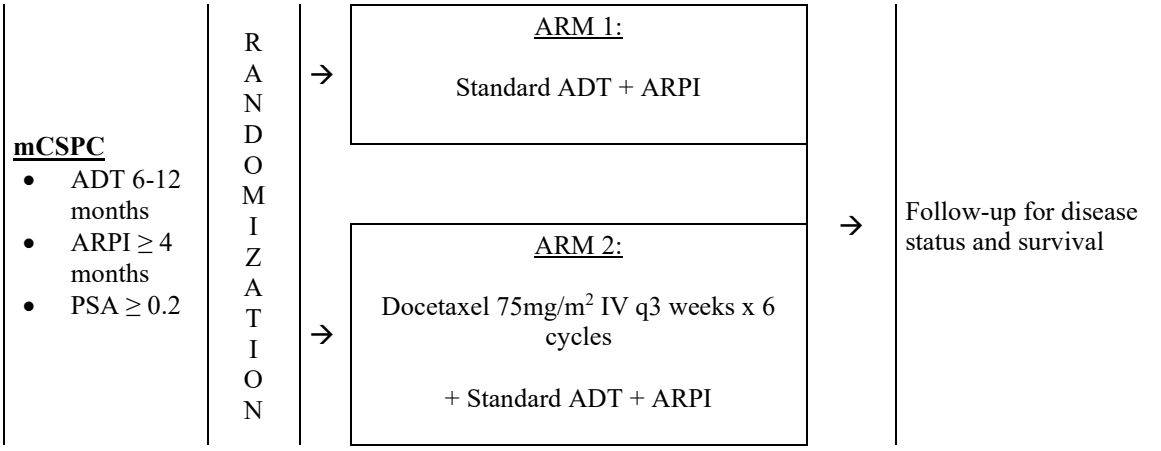
TREATMENT SCHEMA

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

1.0 OBJECTIVES

1.1 Primary Objective

To compare overall survival (OS) in participants with mCSPC who are receiving standard of care ADT (between 6-12 months exposure) + ARPI (≥ 4-months exposure) and have suboptimal PSA response (PSA ≥0.2 ng/ml at enrollment) with those who receive standard of care ADT + ARPI plus docetaxel chemotherapy.

1.2 Secondary Objectives

To compare both arms with respect to:

- PSA progression
- PSA response (PCWG3 criteria)
- PSA kinetics:
  - 90% PSA decline
  - PSA <0.2ng/ml
  - PSA <0.02ng/ml
- Clinical progression free survival

1.3 Tertiary Objectives

- To determine if detection and/or quantification of circulating tumour DNA (ctDNA) can be a potentially useful biomarker in addition to PSA for prognostication, prediction of docetaxel benefit, and whether somatic alterations detected in ctDNA can clarify mechanisms of resistance to (chemo)-hormonal therapy
- To explore OS by study arm using the following factors:
  - high-volume (defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis) versus low-volume mCSPC *[Sweeney 2015]*
  - from date of commencement of ADT
  - molecular characterization of copy loss or inactivating mutations or structural rearrangements of *TP53*, *PTEN*, or *RB1* and status of DNA-damage repair genes

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Prostate Cancer

Metastatic prostate cancer is one of the most common cancers affecting men and leads to death in approximately 40,000 men a year in Canada and the United States *[Cancer.Net 2023; Canadian Cancer Society 2023].* Although incurable, many men have good control of their prostate cancer for years by stopping the hormone testosterone (androgen) from stimulating the cancer. These men can survive longer and better using approved hormone therapy and chemotherapy. Hormone therapies lower or block testosterone very effectively and are lethal to most prostate cancer cells. Docetaxel chemotherapy causes prostate cancer cell death differently by disrupting cell microtubules, targeting both testosterone dependent and independent mechanisms. While clinicians universally recommend hormone therapy for metastatic prostate cancer, there is currently equipoise about who benefits from the early addition of chemotherapy, with prior data suggesting that aggressive tumours may benefit the most *[Vale 2023]*. It is recognized that patients have particularly poor prognosis if their prostate-specific antigen (PSA) levels on serial blood tests do not drop to near zero in the first 6 months of hormone treatment *[Hussain 2006; Hussain 2013; Sayegh 2022; Chowdhury 2023; Matsubara 2019; Shore 2023]*. These patients with suboptimal PSA response are the most likely to benefit from early chemotherapy by targeting prostate cancer cells that harbour detectable resistance to hormone therapy.

2.2 Current Standard of Care in Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

Docetaxel is a member of the taxane family of chemotherapeutics, which also includes paclitaxel and cabazitaxel. Taxanes are microtubule toxins that stabilize the microtubule by preventing depolymerization. This process prevents microtubule shortening, an essential process for cell division, ultimately resulting in mitotic arrest and apoptosis or mitotic slippage [*Herbst 2003*].

The ECOG-ACRIN E3805 CHAARTED trial *[Sweeney 2015]* was a landmark, "game-changing" trial that completely altered the landscape of metastatic castration-sensitive prostate cancer (mCSPC) treatment in 2014. This trial showed that the addition of docetaxel chemotherapy to ADT in mCSPC had a substantial survival advantage, improving median overall survival by 13.6 months compared with ADT alone (57.6 months vs. 44.0 months; hazard ratio (HR) for death in the combination group, 0.61; 95% confidence interval [CI], 0.47 to 0.80; P<0.001), improving median progression rate by 8.5 months (20.2 vs 11.7 months, HR 0.61; 95% CI, 0.51 to 0.72; P<0.001), and improving the rate of deep PSA response <0.2 ng/ml at 7 months (45.3% v 28.8%, p<0.001). Subgroup analyses show particular benefit in "high volume" disease (visceral metastases or ≥4 bony lesions), where median OS was improved by 17 months (49.2 vs. 32.2 months, p<0.001), and 8-year OS was doubled (28.5% vs 15.4%) *[Sweeney 2015; Kyriakopoulos 2018; Tripathi 2022]*. These data galvanized the field to focus on intensifying therapy in the mCSPC setting – rather than waiting until the development of resistant disease – and showed long-term survival benefits for a short-course (6-cycles) of chemotherapy intensification. Importantly these data show that early docetaxel exposure demonstrates a much greater magnitude of benefit than the same treatment given in the metastatic castration-resistant (mCRPC) setting (TAX327 trial *[Tannock 2004])*.

Subsequent to docetaxel being approved in mCSPC, multiple androgen-receptor pathway inhibitors (ARPI) were developed in phase III RCTs and have supplanted docetaxel use due to better tolerance and because they target a much broader cohort of mCSPC patients without need to consider subgroups that may benefit most from chemotherapy (e.g. "high-volume" mCSPC). Current clinical practice has therefore moved away from early docetaxel due to similar OS improvements of orally administered ARPI (abiraterone, enzalutamide, apalutamide and darolutamide) without consideration of volume status *[Chi 2019; Armstrong 2019; Fizazi 2017; James 2017; Sweeney 2023; Davis 2019]*.

Abiraterone acetate and prednisone (AAP), an inhibitor of the enzyme CYP17 in the adrenal androgen synthesis pathway, was the first ARPI to receive regulatory approval in mCSPC. Both LATITUDE and STAMPEDE arm G evaluated the efficacy of AAP plus ADT versus ADT alone and showed significant improvements in OS for patients with mCSPC (HR for OS 0.66 for LATITUDE and 0.63 for STAMPEDE) *[Kyriakopoulos 2018; Tripathi 2022].* These trials enrolled different populations with the LATITUDE study restricted to patients with "high risk synchronous mCSPC" (defined as two out of three of Gleason score >=8, >=3 bone lesions and visceral metastasis), while 48% of patients in the STAMPEDE study did not have metastatic disease evident on conventional imaging. Post hoc analyses of STAMPEDE confirmed efficacy of AAP across disease volume. Subsequent trials have confirmed the benefit of apalutamide (TITAN*) [Chi 2019]* and enzalutamide (ARCHES and ENZAMET) *[Armstrong 2019; Fizazi 2017; James 2017]* with very similar hazard ratios for survival as AAP, and have led to regulatory approvals for these drugs across the disease spectrum of mCSPC.

Indirect comparison of AAP and docetaxel based on analysis of the results from STAMPEDE and other studies showed better failure free survival (FFS) and progression free survival (PFS) with AAP, but not OS *[Sweeney 2023; David 2019; Fizazi 2022]*. Given these results, in the absence of direct comparative data, patient selection of chemotherapy versus ARPI is empirical and highly influenced by side effect profile, patient comorbidities, patient preferences, and access in a particular health care setting. For instance, AAP is best avoided in patients with diabetes, uncontrolled hypertension, or active cardiac comorbidities. Given its propensity to cause skin rash and thyroid issues, apalutamide is less preferred in patients who have pre-existing dermatological or thyroid disorders. Enzalutamide can cause neurological side effects including seizures and significant fatigue and is relatively contraindicated in patients with a previous history of seizure or who have significant baseline fatigue. Table 1 summarizes the phase III RCT data for docetaxel + ADT and various ARPI + ADT.

In summary, the current standard of care in mCSPC treatment is generally the addition of ARPI to ADT, and there is no role for docetaxel + ADT in lieu of ARPI + ADT given the greater side effect profile of docetaxel and no evidence for survival advantage, and a greater breadth of indications for ARPI + ADT in mCSPC.

2.3 The Current Role of Docetaxel Chemotherapy in mCSPC

Currently, there is no RCT that demonstrates that docetaxel improves OS in ARPI-treated mCSPC. Use of docetaxel in mCSPC or mCRPC is also not currently enriched by any validated biomarker for treatment selection. However, increased use of docetaxel however has high potential to improve outcomes of mCSPC treatment, based on the results of prior RCTs including CHAARTED. The CHAARTED RCT pre-dated ARPI therapies, and more recent RCTs incorporating docetaxel do not randomize to its use *[Sweeney 2023; Fizazi 2022; Smith 2022]*. Therefore there is currently equipoise as to whether the addition of docetaxel to ADT + ARPI may further improve outcomes for a certain population of mCSPC who have poorer prognostic disease and higher likelihood of early PSA progression.

Some oncologists treat with docetaxel, ARPI and ADT ("Triplet therapy"), inferring potential OS benefit in those with poor prognostic features, while other oncologists do not treat with docetaxel, concerned that the immediate toxicities including alopecia, marrow suppression, and neurotoxicity affect QOL and may not be worthwhile in the absence of defined OS benefit in an RCT *[Wala 2023; Mittal 2023; Roy 2022]*. Current practice is to only consider docetaxel in ARPI-treated high-volume disease, but volume criteria have major weaknesses by failing to identify aggressive low-volume patients who may benefit from docetaxel and conversely overtreating high-volume patients with disease that is exquisitely sensitive to hormone therapy *[Clarke 2019; Hoeh 2023]*.

Optimal docetaxel use is important because: 1) earlier use of short-course docetaxel in mCSPC can have a very meaningful benefit for patients if they spend an extended time in the castration-sensitive state *[Wala 2023; James 2016]*; (2) multiple prostate cancer RCTs show docetaxel improves OS in other settings *[Sweeney 2015; Kyriakopoulos 2018; Tripathi 2022; Clarke 2019; James 2016; Tannock 2004; Petrylak 2004]*; (3) docetaxel is widely-available, off patent, inexpensive and has high familiarity worldwide *[Gillessen 2023]*; (4) economic analyses of docetaxel show favourable incremental cost-effectiveness ratio *[Wang 2022; Sathianathen 2019; Beca 2019]*; and, (5) docetaxel is already used later in ARPI-resistant metastatic castration-resistant prostate cancer (mCRPC), and could have a much larger impact given earlier *[Gillessen 2023]*. This trial innovatively selects patients with suboptimal 6-month PSA ≥0.2ng/ml for treatment – intensifying therapy for patients who need it most.

2.4 Correlative Studies

Circulating tumour DNA (ctDNA)

The detection and plasma fraction of ctDNA (as a proportion of total cell-free DNA) at baseline and on-treatment is an independent prognostic marker in many solid cancers, including prostate cancer *[Tolmeijer 2023]*. The characterization of selected genomic or epigenomic alterations in plasma ctDNA can also reveal tumour-specific mechanisms of resistance or response to systemic therapy. In this study, all sites must offer collection and banking of blood plasma and matched buffy coat layer for ***future exploratory analysis*** of ctDNA (which will be conducted after completion of study enrollment).

Hypotheses:

1. elevated baseline ctDNA fraction (despite ADT +/- ARPI initiation) is a poor prognostic factor (independent of clinical-pathologic factors) and may predict for improved outcomes with docetaxel addition.
2. Early on-treatment detection of ctDNA is associated with lack of docetaxel benefit
3. ctDNA (epi-) genotyping at end-of-treatment and disease progression will clarify acquired resistance mechanisms to docetaxel addition. Collection time points (2 x 10mL streck tubes): baseline (all patients), end of cycle 1 docetaxel (Arm 2), end of cycle 6 docetaxel/week 18 (all patients), progressive disease (all patients).

Future assay considerations: Since it is impractical (and would reduce trial feasibility) to mandate central tumour tissue banking (e.g. of archival diagnostic samples), we expect to apply emerging highly sensitive tumour-naïve ctDNA detection approaches including targeted methylation sequencing or whole-genome sequencing (leveraging mutational signatures or fragmentomic patterns) *[Nadauld 2021; Wan 2022; Cristiano 2019]*.

Molecular signatures in primary prostate cancer tissue

The primary site of prostate cancer is molecularly heterogeneous but cancers can be stratified into distinct subgroups based on shared genomic, transcriptomic or histological features *[Cancer Genome Atlas Research Network 2015; Warner 2024]*. At the genomic level, common somatic alterations include *SPOP* mutations, ETS gene rearrangements, *PTEN* alterations, *TP53* mutations, and DNA damage repair gene alterations. Selected genomic alterations have been linked with good (e.g. *SPOP*) or poor (e.g. *BRCA2*, *TP53*) outcomes across disease contexts *[Castro 2013; Swami 2020]*. At the transcriptomic level, most prostate cancers exhibit gene expression patterns consistent with luminal-like features and evidence of high Androgen Receptor (AR) pathway activity, but a significant minority exhibit more basal-like gene expression profiles *[Zhao 2017]*. Patients with basal tumours have a poorer prognosis while luminal tumours exhibit the greatest sensitivity to AR pathway inhibitors in both the adjuvant and metastatic settings. An example available test that measures tumour gene expression profiles is Decipher (Veracyte; San Diego, CA). Decipher provides a score between 0 and 1, and this score has been linked in correlative studies to differential absolute benefit in overall survival from the addition of abiraterone or docetaxel to ADT in mCSPC. At the histopathological level, recent advances in artificial intelligence have enabled the training of models that can predict specific outcomes in prostate cancers based on hematoxylin and eosin slide images *[Esteva 2022]*. Given that all of the above features can be captured by profiling formalin-fixed paraffin-embedded (FFPE) diagnostic prostate cancer needle biopsy cores, we plan to centrally collect archival tissue blocks, cores, or unstained slides when available from enrolled patients with the intent of relating genomic, transcriptomic, and histological features to clinical outcomes, in an exploratory analysis after accrual is complete. The submission of tumour tissue samples will be ***optional***.

2.5 Rationale for Current Study

The PR.26 TRIPLE-SWITCH phase III RCT aims to optimize use of docetaxel for patients with mCSPC who are treated with ADT and ARPIs. Selection criteria for docetaxel is currently debated even within the prototypical "high-volume, denovo" cohort of mCSPC that have been identified from the CHAARTED study and subsequent meta-analyses of phase III RCTs *[Vale 2023]*. Other cohorts of "high-volume, metachronous" and "low-volume, synchronous" mCSPC in these analyses have wider confidence intervals around survival benefit of docetaxel in mCSPC patients when added to ADT alone. There have not been phase III studies that have randomized patients to the addition of docetaxel to what is now standard-of-care ADT + ARPI for mCSPC patients. Therefore, PR.26 TRIPLE-SWITCH comes at a unique time when all ARPIs used in mCSPC will be approved and available based on positive phase III RCTs, and there is the availability of adding docetaxel to ARPI, but equipoise about the value of doing so due to a lack of data showing a survival benefit of docetaxel in this setting.

Nonetheless there remains significant interest to incorporate docetaxel optimally as the mechanistically it targets different prostate cancer clones than androgen-targeting therapies and a number of phase III mCSPC RCTs did enroll patients receiving ADT + docetaxel as standard of care and randomized patients to the addition of ARPIs *[Mittal 2023*; *Gillessen 2023]*. RCTs allowing docetaxel (investigator choice) + ADT ± ARPI suggest a potential benefit of triplet (PEACE-1 median PFS 4.5 vs 2 years, HR 0.50; median OS in the high-volume cohort 5.1 vs 3.5 years, HR 0.72 (95%CI 0.55-0.95); ARASENS median not reached vs. 42.4 months, HR 0.69, 95%CI 0.57-0.82 in the high-volume cohort), but these studies were not designed to evaluate efficacy of docetaxel administration *[Sweeney 2023; Fizazi 2022; Smith 2022]*. We and others have reported network meta-analyses documenting uncertain but potential survival benefit of docetaxel + ADT + ARPI as triplet therapy *[Roy 2022; Hoeh 2023; Gillessen 2023; Riaz 2023]*.

Notably, in general the benefit of docetaxel in randomized studies of ADT versus ADT + docetaxel has been greatest in patients with poor prognostic features, and particularly in the worst-prognosis cohort selected based on the clinical criteria of "high-volume, denovo" disease state which is well understood in the field as a selection criteria for docetaxel. However these criteria imperfectly characterize sensitivity of patients to androgen-targeted therapy, the prognosis of patients, and the potential impact of docetaxel treatment. For example, signals for potential benefit of docetaxel have been suggested for specific locally advanced (T4) prostatic involvement in mCSPC patients even in "low-volume" patients, and there appear to be potential signals of benefit from docetaxel in the "high-volume, metachronous" and "low-volume, synchronous" cohorts *[Vale 2023]*. These clinical criteria also do not take into account important molecular features that may influence prognosis and sensitivity to treatment, such as tumour suppressor genes (TP53, PTEN, RB1) and DNA-damage repair genes involved in homologous recombination repair (such as BRCA1, BRCA2, ATM, PALB2, CHEK2, CDK12, MLH1).

The PR.26 TRIPLE-SWITCH trial takes an innovative biomarker-based approach to selecting mCSPC patients for study, specifically selecting patients with "suboptimal response" in PSA >0.2 ng/ml after 6-12 months of androgen-targeting therapy because this cohort is recognized to have poor prognosis compared to those who achieve PSA≤0.2ng/ml. Multiple post-hoc analyses of phase III RCTs (TITAN, LATITUDE, ARCHES) reveal 6-month PSA>0.2 to be a strong negative prognostic marker in patients receiving ADT + ARPI *[Sayegh 2022; Chowdhury 2023; Matsubara 2020; Shore 2023; Harshman 2018]*. The 6-month PSA>0.2 population have median OS of 36-38 months, represent 50% of the ARPI-treated population, and have quicker deterioration in QOL and physical well-being than 6-month PSA≤0.2 *[Small 2023]*. Notably, a third of PSA>0.2 patients have low-volume cancer burden at diagnosis and are not typically offered docetaxel. Conversely, half of high-volume patients have 6-month PSA≤0.2 on ADT-ARPI and could potentially be spared up-front docetaxel *[Gebrael 2023]*. Landmark analyses have explored the optimal timing to evaluate PSA response at 3-, 6-, 9-, and 12-month time points, showing the majority of PSA≤0.2 is achieved by 6-months with little change at subsequent landmarks *[Chowdhury 2023]*.

Prior exploratory post-hoc analyses of TITAN using a multivariable Cox regression model adjusting for major covariates has been conducted and it suggest the 6-month PSA>0.2 cohort may have an ARPI-resistant tumour phenotype. While the 6-month PSA ≤0.2 group had improved 3- and 4-year OS if they received apalutamide rather than placebo, the 6-month PSA>0.2 group showed no benefit of apalutamide *[Roy n.d.]*. This suggests that apalutamide and other ARPI may be less active than presumed in those with 6-month PSA>0.2, and rationalizes non-ARPI-based intensification such as docetaxel.

We have also stratified patients based on entry-level PSA, recognizing clear demarcations in prognosis based on prior data in the SWOG9346 RCT (a randomized study of continuous versus intermittent ADT in mCSPC). SWOG 9346 showed a significant separation in survival time of mCSPC by PSA at 6-7 months after ADT initiation: PSA<0.2 = 6.25 years; PSA 0.2-4 = 3.67 years; and PSA >4 = 1.08 years *[Hussain 2013].* Similar analyses of CHAARTED show distinct separation in survival time by PSA at 7 months (ADT + docetaxel): PSA </=0.2 = 5.03 years; PSA >0.2-4.0 = 3.79 years; and PSA >4 = 2.10 years *[Harshman 2018].* Therefore these data rationalize the use of the PSA >0.2-4 versus >4 ng/ml stratification used.

While other investigational agents are being evaluated in mCSPC, including phase III RCTs of PARP inhibitors, PSMA-radiopharmaceuticals, AKT inhibitors, and CDK4/6 inhibitors, the PR.26 TRIPLE-SWITCH RCT will remain highly relevant as a majority of patients are likely to be treated with a backbone of ADT+ARPI given the excellent tolerance and initial effectiveness, and because these new agents require uncommon biomarkers (e.g. *BRCA1/2, ATM, AKT*) or very high levels of infrastructure (PSMA-PET) *[James 2017]*. Even now, genomic tests are inconsistently performed in time to allow PARP inhibitor eligibility for mCRPC *[Hussain 2020]* and universal access to PSMA-based therapies and PSMA-imaging is poor due to high cost and infrastructure bottlenecks. Therefore, the question of whether docetaxel adds value to ADT+ARPI is one that has longevity and can have widespread impact even in under resourced healthcare settings.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Androgen Receptor Pathway Inhibitor

3.1.1 *Abiraterone Acetate (NSC 748121)*

Abiraterone acetate is used for the treatment of prostate cancer. It is licensed for the treatment of castration-resistant prostate cancer (mCRPC) and castration-sensitive prostate cancer (mCSPC) in combination with prednisone. Abiraterone acetate is given orally. It is converted *in vivo* to abiraterone which acts by inhibiting 17α hydroxylase/C1, 20-lyase involved in androgen biosynthesis and mineralocorticoid production. It also inhibits the formation of the testosterone precursors dehydroepiandrosterone (DHEA) and androstenedione *[Cancer Care Ontario 2024]*.

Serious warnings/ precautions associated with Abiraterone acetate include hypertension, hypokalemia and fluid retention due to mineralocorticoid excess, and hepatotoxicity. It should be used with caution in patients with cardiovascular disease and hepatic impairment.

Please refer to the most recent Product Monograph / Prescribing Information / Package Insert for additional information.

Please refer to Section 7.1 for the schedule of administration on study.

3.1.2 *Enzalutamide (NSC 766085)*

Enzalutamide is an androgen receptor inhibitor used in the management of prostate cancer. Enzalutamide is licensed for the treatment of patients with non-metastatic castration-sensitive prostate cancer (nmCSPC), the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC), the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC), and for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC). It is given orally. Enzalutamide binds to the androgen receptor and competitively inhibits the binding of androgen to the receptor, preventing nuclear translocation of androgen receptors as well as their interaction with DNA *[Astellas Pharma Canada, Inc 2024]*.

Serious warnings/ precautions associated with Enzalutamide include seizures and posterior reversible encephalopathy syndrome.

Please refer to the most recent Product Monograph/ Prescribing Information / Package Insert for additional information.

Please refer to Section 7.1 for the schedule of administration on study.

3.1.3 *Apalutamide (NSC 794776)*

Apalutamide is a nonsteroidal androgen receptor inhibitor that is used in the treatment of prostate cancer. It is indicated for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) and mCSPC. Apalutamide is given orally. It binds directly to the androgen receptor ligand-binding domain and inhibits nuclear translocation, DNA binding, and AR-mediated transcription *[Cancer Care Ontario 2024]*.

Apalutamide should be used with caution in patients with cardiac disorders and QTc prolongation.

Please refer to the most recent Product Monograph/ Prescribing Information / Package Insert for additional information.

Please refer to Section 7.1 for the schedule of administration on study.

3.1.4 *Darolutamide (NSC 815949)*

Darolutamide is a non-steroidal androgen receptor inhibitor. It is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC) and for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) in combination with docetaxel. It is given orally. It competitively inhibits androgen binding, androgen receptor nuclear translocation, and androgen receptor mediated transcription *[Cancer Care Ontario 2024]*.

Please refer to the most recent Product Monograph/ Prescribing Information / Package Insert for additional information.

Please refer to Section 7.1 for the schedule of administration on study.

For this trial any routinely funded ARPI can be utilized. Darolutamide is not currently approved in Canada as initial treatment for mCSPC without docetaxel and therefore cannot be used in Canada. If approved for use at U.S. sites, this can be used as an ARPI in the US.

3.2 Androgen Deprivation Therapy

Agents not listed (standard of care). This protocol allows physicians choice of ADT provided it is licensed in this this indication.

3.3 Docetaxel (NSC 628503)

Docetaxel is an established chemotherapeutic agent in solid tumour oncology. It is licenced for metastatic prostate cancer and is recommended in guidelines in the treatment of castration sensitive prostate cancer as well as castration resistant prostate cancer in combination with prednisone *[National Comprehensive Cancer Network 2024; Canadian Urological Association 2022]*. Docetaxel is delivered by intravenous infusion and acts by disrupting the microtubular network in cells that is essential for vital mitotic and interphase cellular functions.

Docetaxel acts by disrupting the microtubular network in cells that is essential for vital mitotic and interphase cellular functions. Docetaxel promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. Docetaxel binds to free tubulin thereby decreasing the critical intracellular concentration of tubulin. The promoted polymerization of microtubules leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, resulting in the inhibition of mitosis in cells. The binding of docetaxel to microtubules does not alter the number of protofilaments in the bound microtubules.

This trial incorporates docetaxel at standard dosing per multiple prior RCTs. Pre-medication with dexamethasone, prednisone, granulocye-colony stimulating factor (GCSF) (provided it is routinely funded at the site), and antiemetics will be per investigational site-standard. ADT and ARPI administered will be physician's choice of ARPI (for Canadian patients, this must be Health Canada-approved and reimbursed SOC drug at standard dosing). Patients may have been dose reduced or switched in the presence of toxicities prior to trial enrollment.

Serious warnings/precautions associated with Docetaxel include immunosuppression with infection, allergic reactions, enterocolitis and second malignancies.

All drugs for this trial are commercially available. These are to be obtained from the Canadian or U.S. market, or available through compassionate release, and will not be supplied for this study.

Please refer to the most recent Product Monograph / Prescribing Information / Package Insert for additional information.

Please refer to Section 7.1 for the schedule of administration on study.

4.0 STUDY POPULATION

The study population consists of men with metastatic castration sensitive prostate cancer (mCSPC) 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.

4.1 Eligibility Criteria

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).

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

Patients must fulfil all the following criteria to be eligible for admission to the study.

4.1.1 Male ≥18 years of age.

4.1.2 Histologically/cytologically confirmed adenocarcinoma of prostate.

4.1.3 Metastatic disease by conventional imaging (bone scan and/or computed tomography (CT)). PET-PSMA scan is allowed only if CT component is of diagnostic quality. Importantly, disease must be present based on conventional imaging (CT and/or bone scan) for enrollment on the study.

4.1.4 PSA of ≥5.0 ng/ml (5.0 ug/L) prior to commencement of ADT.

4.1.5 *Prior Therapy*

Systemic Therapy

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

Radiotherapy

- Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

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

4.1.7 PSA ≥ 0.2 ng/ml (0.2 ug/L) within 14 days of enrollment. If there is any rise in PSA since starting ADT and achieving castrate-level testosterone, PSA must be repeated and must not fulfill ineligibility criteria 4.2.1.

4.1.8 Candidate for docetaxel chemotherapy (per investigator).

4.1.9 ECOG Performance Status (PS) 0 to 2.

4.1.10 Adequate organ and marrow function measured within 14 days prior to enrollment including:

Hematology	Hemoglobin	≥ 90 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 if no liver involvement < 5.0 x ULN if liver metastases are present
	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		

4.1.11 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.

4.1.12 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.

4.1.13 In accordance with CCTG policy, protocol treatment is to begin within 5 working days of participant enrollment.

4.1.14 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.

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

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

4.2 Ineligibility Criteria

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

4.2.1 Two consecutive rises in PSA since achieving castration on ADT at least 2 weeks apart with at least one PSA ≥5% above the PSA nadir and with at least one PSA having an absolute increase of ≥0.5 ng/ml above the PSA nadir.

4.2.2 Evidence of radiographic progression or clinical progression since start of ADT.

4.2.3 Docetaxel criteria:

- Prior treatment with taxane chemotherapy
- Grade 2 or worse peripheral neuropathy
- Severe hypersensitivity to drugs formulated with polysorbate 80

4.2.4 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class II or better.

Patients with uncontrolled intercurrent illness or any other significant condition(s) that would make this protocol unreasonably hazardous.

4.2.5 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.

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

4.2.7 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.

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

4.2.9 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.

4.2.10 High-grade neuroendocrine prostate cancer or small cell features.

5.0 PARTICIPANT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All participants entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix III.

This study adheres to the NCI standard practices for streamlined data submission as determined by the Clinical Trials and Translation Research Advisory Committee (CTAC). In accordance with these practices, the patient evaluation flowsheet below indicates investigations that are required for submission to the clinical trial database. These however, do not override or otherwise affect participating sites' standard of care and/or practice guidelines for collecting clinical information and recording it in the local medical record.

Required Investigations	Pre-study prior to enrollment	During Protocol Treatment		At Progression[#] and end of treatment for reasons other than progression	After Protocol Treatment
		Every 3 weeks for 18 weeks	Every 12 weeks after week 18		Every 12 weeks until Death
History and Physical Exam[A, D]					
History and Physical exam (includes height at baseline only, weight)	Within 14 days				
ECOG PS	Within 14 days	As per institutional standards			
Survival Status		X	X	X	X[D]
Hematology*[B]					
Absolute neutrophils, hemoglobin, platelets	Within 14 days				
Biochemistry*[B]					
Bilirubin, AST or ALT, Alkaline Phosphatase, creatinine clearance	Within 14 days				
Radiology[C,F]					
CT chest/abdomen/pelvis	Within 28 days			X	
99m technetium bone scan	Within 28 days			X	
CT/MRI brain (only required if known brain metastases or otherwise clinically indicated)	Within 28 days			X	
Other Investigations [B]					
PSA	Within 14 days	X	X	X	X
Serum testosterone	Within 14 days	As per institutional standards		X	As per institutional standards
Correlative Studies [C]					
Whole blood (for ctDNA) – mandatory request[E]	Within 5 days of randomization** (Arm 1 and 2)	End of cycle 1 docetaxel (Arm 2)	End of cycle 6 docetaxel/week 18 (Arm 1 and 2)	X	
Archival tissue blocks (optional)[E]	For consenting participants				
Adverse Events [A]					
Adverse events assessment (CTCAE Grade ≥3).	Within 14 days	Continuously			
Canadian Specific Activity: Please see separate Canadian Appendix for details*** [A,E]					

footnotes on next page…

*	Pre-treatment blood draws may be done up to one/two working days prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
**	For Arm 2, this should be before the first dose of docetaxel
***	This is a mandatory request by sites for Canadian patients but optional for patients, and not required for randomization.
#	Refer to Section 8.4 for the definition of PSA Progression and Clinical Progression in this study. Patients with PSA of progression must also demonstrate clinical progression before coming off treatment. Patients with clinical progression may come off treatment even in the absence of PSA progression.
A	These study visits may be conducted by phone or videoconferencing technology (i.e. "virtual visits"), including adverse event assessments, in accordance with local laws and regulations.
B	These laboratory tests may be performed locally for all visits. Results must be sent to the Qualified Investigator for review and for study data entry.
C	Visits requiring protocol-mandated imaging and correlative blood sample collection must be performed at the enrolling centre.
D	Follow-up visits after confirmed progression are for survival tracking only, and may be performed virtually in accordance with local laws and regulations.
E	Mandatory for U.S. and Canadian centre participation but optional for participants
F	Positron emission tomography - Prostate-specific membrane antigen (PET-PSMA) scans may be used for determining metastatic disease status only if corroborated by findings on conventional imaging

5.1 Telehealth Visits

As noted in the table above (see footnotes A-D), certain visits may be performed virtually via telehealth. The Qualified Investigator is required to ensure that all labs and assessments that fall on a telehealth visit are completed. If labs are performed locally, results must be made available to the Qualified Investigator. The manner of the visit should be documented (site visit, video visit, etc.). Visits that require imaging and correlative blood collection must be performed at the enrolling centre. For guidance on decentralized clinical trial activities also refer to Section 7.1 and Appendix VI.

5.2 Follow-up for Ineligible Participants

The follow-up requirements for ineligible participants who have received no protocol therapy, include submission of the Baseline Report and End of Treatment Report.

Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

6.0 ENTRY/ENROLLMENT PROCEDURES

6.1 Investigator and Research Associate Registration with CTEP:

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) — advanced practice providers (e.g. NP or PA) or graduate level researchers (e.g. PhD);
- Associate Plus (AP) — clinical site staff (e.g. RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges; and
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	
GCP training	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional)	✓	✓	✓	

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster,
- Selection as the treating, credit or consenting person in OPEN,
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page or the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

6.2 Local Activation Process

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

6.2.1 *Site Registration Procedures*

IRB Approval

U.S. Sites:
As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB prior to March 1, 2019. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRB Manager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal locinated in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

Canadian Sites:
Each investigator or group of investigators at a clinical site must obtain REB approval for this protocol, and submit approval and supporting documentation to CCTG before they can be approved to enroll participants. Once site credentialing is approved, CCTG will notify CTSU directly.

See trial website for additional details.

All Sites:
In addition, the Site-Protocol PI (i.e. the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status,
- Have an active status at the site(s) on the IRB/REB approval (*applies to U.S. and Canadian sites only*) on at least one participating organization's roster,
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements:

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
- An active roster affiliation with the NCI CIRB roster under as least one CIRB Signatory Institution (U.S. sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

6.2.2 *Downloading Regulatory Documents*

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *CCTG* and protocol number *CCTG-PR.26*.
- Click on *Documents, Protocol Related Documents* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

6.2.3 *Protocol Specific Requirements For Site Registration*

Protocol Specific requirements for the trial include:

- Protocol Specific Training

Canadian Sites: Additional details for local activation will be available on the trial website.

6.2.4 *Submitting Regulatory Documents*

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

Institutions with participants waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org to receive further instruction and support.

6.2.5 *Checking Your Site's Registration Status*

Site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

6.3 Enrollment Procedures

Participant enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). Confirmation of enrollment will be provided electronically.

All eligible participants enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG. The serial number will be assigned after registration for screening and will remain the same following enrollment.

The following information will be required at time of screening and enrollment:

- trial code (CCTG-PR.26);
- centre;
- participant's initials (may be coded);

- informed consent version date(s), date(s) signed by participant, name of person conducting consent discussion and date(s) signed;
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values;
- height and weight;
- stratification factors (PSA: 0.2-4 vs >4; ARPI type: CYP17 inhibitor vs AR antagonist; Liver metastases vs. no liver metastases; De novo vs Recurrent (at time of diagnosis of mCSPC); and Time from ADT start: ≥6 to <9 months vs ≥9 to 12 months).

6.3.1 *OPEN / IWRS*

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of participant registration/randomization assignment. OPEN will populate the participant enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to participant enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a participant transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Participant has met all eligibility criteria within the protocol stated timeframes, and
- All participants have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6.3.2 *OPEN/IWRS Questions?*

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6.3.3 *General Guidelines*

At the time of enrollment, all data reported within the Patient Enrollment folder must be accurate, complete and verifiable against source documentation. CCTG should be contacted for assistance if there are questions about participant eligibility or data entry in the OPEN system. Under no circumstances should inaccurate data be entered in order to permit enrollment.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all participants entered into the trial. Under no circumstances, therefore, may an allocated participant's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible participants admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the participant is indeed eligible before requesting enrollment.

All enrolled participants are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible participants are outlined in Section 5.2

All subsequent data entry tasks will be done through a web-based, password-operated Electronic Data Capture (EDC) system. Data must be submitted electronically using Medidata Rave® at the following URL: https://login.imedidata.com/selectlogin.

- If prompted, select the "CTEP-IAM IdP" link.
- Enter your valid and active CTEP-IAM User ID and password. This is the same account used for the CTSU members' website and OPEN.

You may also access Rave® via the trial website. If sites experience difficulties accessing the system and/or enrolling participants, please contact the help desk or the PR.26 Study Coordinator.

6.4 Inclusion of Minorities

The appropriate mix of racial and/or ethnic patients will be recruited to reflect the prostate cancer population. The study was designed to include minorities but was not designed to measure differences of intervention effects.

Planned Enrollment Report:

Based on prior studies involving similar participant populations, estimated sizes of racial and sex subsets for participants randomized to this study are shown in the following tables:

US DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	16	0		16
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	86	0	0	86
White	0	340	0	28	368
More Than One Race	0	0	0	0	0
Total	0	442	0	28	470

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	28	0	0	28
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	28	0	0	28
White	0	286	0	18	304
More Than One Race	0	0	0	0	0
Total	0	342	0	18	360

7.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of participants rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 5 working days of participant enrollment.

7.1 Chemotherapy Treatment Plan

7.1.1 *Drug Administration*

Arm	Agent(s)	Dose	Route	Duration	Schedule
1	ARPI**	Standard dosing	Oral	Until progression*	As per Product Monograph/ Prescribing Information / Package Insert
	ADT	Standard dosing	Physician choice	As per SOC	As per SOC
2	Docetaxel	75mg/m^2	IV	6 cycles or until progression*	every 21 days
	ARPI**	Standard dosing	Oral	Until progression*	As per Product Monograph/ Prescribing Information / Package Insert
	ADT	Standard dosing	Physician choice	As per SOC	As per SOC

* Refer to Section 8 for definition of PSA progression and clinical progression.
Patients with PSA progression must also demonstrate clinical progression before coming off treatment. Patients with clinical progression may come off treatment even in the absence of PSA progression.
** ARPI choice is dependent on local licensing and funding

Standard of care protocol-specified therapy (ARPI, ADT, Docetaxel) may be administered by a local healthcare provider (HCP) with appropriate reporting of therapy administration data and adverse event information to the Qualified Investigator. All decisions on care within the clinical trial are made by the Qualified Investigator. The Qualified Investigator is still required to report any protocol deviations and unanticipated problems that occur per standard procedures. Refer to Appendix VI for guidance on decentralized clinical trial activities.

In the United States, Docetaxel may be administered at satellite sites if allowed per institutional policy or local/state laws. If treatment of docetaxel is allowed at satellite sites (or local facilities), the appropriate reporting of therapy administration data and adverse event information must be provided to the responsible investigator. For guidance on decentralized clinical trial activities refer to Appendix VI. Generic docetaxel is acceptable for use in this trial.

7.1.2 *Premedication and Supportive Therapy*

Patient premedication and supportive therapy should be performed as per standard of care. Please refer to the Product Monograph / Prescribing Information / Package Insert for further details.

For patients on Arm 2 receiving docetaxel chemotherapy:

a) Dexamethasone pre-medication is to be given per local practices according to standard of care

b) Gram-colony stimulating factor (G-CSF) for primary prophylaxis of chemotherapy-induced febrile neutropenia or neutropenic sepsis is not mandatory, but encouraged if available per local practices.

c) G-CSF for secondary prophylaxis of chemotherapy-induced febrile neutropenia or neutropenic sepsis is mandatory if patient experiences these events after receiving docetaxel chemotherapy, in addition to considering a dose modification per Sections 7.1.3 and 7.1.4.

d) Antiemetics are to be given per standard of care local practices

7.1.3 *Participant Monitoring*

All patients should be closely monitored according to guidelines in Section 9.0 and be advised to contact the treating centre in the case of significant toxicities.

7.1.4 *Dose Modifications (Arm 2)*

Dose modifications (slowing/interruption of infusion rate, omission of a dose, or permanent discontinuation) based on treatment related toxicity will be allowed for docetaxel. Investigators may choose to reduce dosage of investigational drug at their discretion. If the infusion cannot be administered, it should be omitted until the next planned infusion. The next cycle should not be given until the laboratory criteria are met and resolution of all drug-related toxicity to ≤ grade 2. Discuss with CCTG if asymptomatic/not felt to be clinically significant.

If the start of the next treatment cycle is delayed by > 21 days due to an adverse event(s) that is deemed related to docetaxel, the treating investigator should contact CCTG for approval before restarting dosing.

7.1.5 *Dose Adjustments (Arm 2)*

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix IV).

Docetaxel
The major toxic effects of docetaxel which are anticipated to limit dosing are: myelosuppression including febrile neutropenia and neutropenic sepsis (may be fatal in 1%), severe hypersensitivity infusional reactions, enterocolitis, dose-dependent sensory neuropathy, and docetaxel-induced fluid retention.

If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that requires the greatest dose adjustment or delay. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix IV).

Once a dose reduction has occurred, dose re-escalation with subsequent treatment cycles is not permitted. Only 2 dose reductions are permitted.

Table 1: Dose reductions for Docetaxel

Dose schedule	Docetaxel dose level
Starting dose	75 mg/m^2
First dose reduction	60 mg/m^2
Second dose reduction	45 mg/m^2
Third dose reduction	Discontinue

Centres may use their written institutional/provincial dose modification guidelines, or the guidelines provided below.

Table 2: Guidelines for Hematologic / Non-Hematologic Toxicities – Docetaxel

Toxicity/CBC (x10^9/l)	Dose modification
ANC <1.5 but greater than 0.5 for ≥7 days OR platelets <100 but ≥ 25	Hold* and consider dose reduction by 1 dose level (DL) or add G-CSF
Febrile neutropenia or ANC <0.5 for ≥7 days OR platelets <25	Hold* and restart at below 1DL
Grade 3 related organ/non-hematologic	Hold* and restart at below 1DL
Grade 4 related organ/non-hematologic	Discontinue

*Participants should only re-start treatment with docetaxel once AE has recovered to grade 2 and below and platelets ≥100 x10^9/l and neutrophils ≥1.5 x10^9/l.

Table 3: Guidelines for Hepatic Toxicities – Docetaxel

Bilirubin	AST and/or ALT		Alkaline Phosphatase	Dose Modification
	≤1.5 x ULN	and	≤ 2.5 x ULN	Standard dose
	1.6 to 5 x ULN	and	2.5 to 5 x ULN	Reduce by 1DL
	> 5 x ULN	and/or	> 5 x ULN	Discontinue
> ULN				Discontinue

In this trial, to ensure safe and effective use of docetaxel, product monograph/package insert/prescribing information recommendations on cautions, dose adjustments and monitoring should be followed.

7.1.6 *Duration of Therapy*

Duration of Therapy (Arm 1)
Patients will remain on ADT+ARPI until protocol defined progression (see Section 8) or intolerable toxicity.

Duration of Therapy (Arm 2)
Patients randomized to docetaxel will receive 75mg/m^2 IV every 21 days for up to 6 cycles dependent on treatment tolerance and absence of protocol defined progression. Patients will continue on ARPI + ADT until protocol defined progression (see Section 8) or intolerable toxicity.

7.1.7 *Toxicity Events Monitoring*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix IV). Only grade 3, 4 and 5 toxic events will be reported.

7.2 Concomitant Therapy

7.2.1 *Permitted*

Standard of care supportive medications including those antiemetics, steroids, antihistamines, GCSF and analgesics are permitted provided they are locally funded and not contraindicated in the docetaxel Product Monograph/ Prescribing Information / Package Insert.

7.2.2 *Not Permitted*

- Administration of any other anti-cancer therapy is not permitted while the participant is receiving protocol therapy. Thereafter, participants may be treated at the investigator's discretion.
- Live attenuated vaccines, during treatment and for 30 days post discontinuation of docetaxel. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Overall Survival*

Overall survival is defined as the time from randomization to the time of death from any cause or the date the participant was last known to be alive.

8.1.2 *Evaluable for Adverse Events*

All participants will be evaluable for adverse events from the time of their first dose of protocol therapy.

8.1.3 *Evaluable for Radiographic Progression*

All participants who have received a dose of protocol treatment and have had imaging are evaluable for radiographic progression.

8.1.4 *Evaluable for PSA Response*

All participants who have at least two additional PSA values after baseline, which are measured at least 4 weeks apart, will be evaluable for PSA response *[Bubley 1999]*.

8.2 PSA Kinetics

8.2.1 *PSA 90*

90% PSA decline from baseline (PSA within 14 days prior to enrollment) at any timepoint from baseline until clinical progression.

8.2.2 *PSA <0.2*

PSA decline to <0.2ng/ml at any timepoint from baseline (PSA within 14 days prior to enrollment) until clinical progression.

8.2.3 *PSA <0.02*

PSA decline to <0.02ng/ml at any timepoint from baseline (PSA within 14 days prior to enrollment) until clinical progression.

8.3 Evaluation of Endpoints

Progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee *[Eisenhauer 2009]* and the recommendations of the Prostate Cancer Clinical Trials Working Group *[Scher 2008; Scher 2016]*.

8.3.1 *Measurable Disease*

Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.3.2 *Non-measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.3.3 *Target Lesions*

When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

8.3.4 *Non-target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

8.3.5 *Radiographic Progression*

Participants with PSA progression only will need to have imaging assessment to confirm radiographic progression as defined below before coming off treatment:

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden appears to have increased by at least 73% in volume or, in select instances where tumour burden has increased sufficiently to require urgent intervention (e.g. radiation for spinal cord compression or drainage of a fluid collection). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 1: Integration of Target, Non-Target and New Lesions into Radiographic Progression Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
Target lesions ± Non target lesions			
Not all evaluated	Non-PD	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
Non target lesions ONLY			
No Target	Not all evaluated	No	NE
No Target	Unequivocal PD	Any	PD
No Target	Any	Yes	PD

8.4 PCWG3 Criteria for PSA Response and Progression

(as defined by Scher 2016)

All participants will be evaluable for PSA response provided follow-up PSA values are obtained to allow application of the definitions below *[Bubley 1999]*.

Response: 50% fall in PSA from baseline maintained for ≥ 4 weeks, and without evidence of disease progression documented at time of confirmatory values.

Non Response: Failure to achieve PSA response criteria.

PSA response duration will be measured from the time the measurement criteria for response are first met until the PSA increases by at least 25% above the nadir OR ≥ baseline value AND an absolute increase of ≥ 2 μg/L.

8.4.1 *PSA Progression*
(as defined by Scher 2016)

In PSA non-responders: PSA progression is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL (µg/L) or more from the nadir (or baseline if no decrease from baseline is documented), which is confirmed by a second value obtained 3 or more weeks later.

In PSA responders: rise in PSA of 25% (minimum 2 ng/ml (µg/L)) above nadir value and confirmed by a second increasing value obtained 3 or more weeks later.

Time to PSA progression will be calculated from date of enrollment to date of PSA progression. If interval PSA values are collected or reported during cycle, only the end of cycle PSA (PSA collected for Day 1) will be used in response evaluation.

NOTE: Because with systemic treatment an initial rise in PSA may be followed by a drop, it is recommended participants receive at least 12 weeks of therapy even if PSA is rising, provided no other evidence of symptomatic or objective progression is seen, palliative radiation is not required and protocol therapy is tolerable (see Section 10.0).

Participants in whom PSA progression is confirmed after 12 weeks on study should have confirmatory scans for radiographic progression and then discontinue treatment, unless discussed with CCTG; exceptions may be made for participants who are believed to have symptomatic improvement or stability providing there is no objective disease progression.

8.4.2 *Clinical Progression*

Clinical progression is defined by progression on imaging (PCWG3 criteria for bone lesions and RECIST 1.1 for soft tissue lesions), development of symptoms attributable to cancer progression, a change in anti-cancer regimen recommended by the investigator, or cancer related decrease in ECOG performance status to ≥ 3.

8.4.3 *Bone Disease Progression*

For the purpose of evaluation of bone disease in this study, a bone scan will be done at baseline and will be repeated at progression to confirm PD.

Only bone lesions on a bone scan will be considered for PD status.

Suspected PD at the first post-baseline bone scan:

- PD is suspected if ≥ 2 new bone lesions are seen on the first post-baseline scan and confirmed if 2 additional new bone lesions are seen at a repeat scan ≥ 6 weeks later.
- After the first post-baseline scan, PD is suspected if ≥ 2 new bone lesions are seen and confirmed if the same lesions are seen on a subsequent scan.
- The date of progression is the date of the first post-baseline scan, when the first two new lesions were documented.

Additionally, if a new bone lesion(s) are seen on the participant's CT it will also need to be confirmed with a bone scan and will ONLY be considered PD if the criteria above are met.

8.5 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. While on study, all lesions recorded at baseline should have their actual measurements recorded at progression, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

8.5.1 *Clinical Lesions*

Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.5.2 *Chest X-ray*

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.5.3 *CT, MRI*

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case [RECIST 1.1]. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

8.5.4 *Bone Scan*

99mTc-methylene diphosphonate radionuclide bone scintigraphy is the standard for bone imaging.

8.5.5 *Ultrasound*

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

9.0 SAFETY ISSUES

9.1 Documentation of REB Submission of Product Monographs (PMs) / Prescribing Information (PN) Required For Local Activation

Canadian sites only
Written documentation must be obtained confirming that the Product Monograph (PM) for Docetaxel was forwarded to the REB. The PM must be retained and filed with the trial protocol at your centre.

The PMs/PNs for standard of care agents are accessible on the manufacturer's website and not required for REB submission.

9.2 Serious Adverse Event Reporting

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix IV). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines and other adverse events must be reported as outlined in Section 9.2 and 9.3. All "reportable" serious adverse events are subject to expedited reporting using the CTEP-AERS reporting system (see Section 9.2, 9.3 and 9.4), as defined below.

9.2.1 *Adverse Event Lists for Commercial Agents*

Please refer to Sections 3.1, 3.2 and 3.3 and the Package Insert/PM for comprehensive list for AEs for Androgen-Receptor Pathway Inhibitor (ARPIs), Androgen Deprivation Therapies (ADTs), and Docetaxel used.

9.2.2 *Adverse Event Characteristics*

This study adheres to the NCI standard practices for streamlined data submission as determined by the Clinical Trials and Translation Research Advisory Committee (CTAC). In accordance with these practices only AEs or grade 3 or higher will be collected and AE attribution will not be requested on the Case Report Forms.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **Attribution** of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

9.2.3 *Expedited Adverse Event Reporting*

9.2.3.1 *CTEP-AERS*

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (https://ctepcore.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in Section 9.3.2 below.

9.2.3.2 *Expedited Reporting Guidelines*

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumour growth or progression: clinical deterioration associated with a disease process) should be submitted.

9.2.3.3 *Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Administration of Study Agent*[1,2,3]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 3 Calendar Days

table continues on next page…

NOTE: Protocol specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR **Expedited AE reporting timelines are defined as:** • "24-Hour notification, 3 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report. • "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.
1 SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-Hour notifications are required for all SAEs followed by complete report:** Within 3 calendar days for: • All Grade 4-5 SAEs Within 10 calendar days for: • Grade 1-3 SAEs 2 For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

9.3 Routine Adverse Event Reporting

Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions if criteria in Section 9.2.2 is met.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

9.4 Expedited Reporting Instructions – Participating Centres Responsibilities

It is the investigator's responsibility to investigate and report the date/cause of death of any participant entered on a trial.

Serious adverse events must be reported via the NCI U.S. CTEP-AERS web application.

Expedited Reporting Guidelines:
Use the NCI protocol number and the protocol specific patient ID provided during trial enrollment on all reports.

Copies of reports for this trial submitted via the CTEP-AERS web application will be automatically forwarded by the CTEP-AERS system to the CCTG Central Office for review. You may be contacted by the CCTG Study Coordinator or Senior Investigator for additional information.

CTEP-AERS web application interruption:
In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497 and to the PR.26 CCTG Study Coordinator by telephone at 613-533-6430. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately electronically into CTEP-AERS by the original submitter at the site.

Local internet interruption:
Please follow the instructions above for CTEP-AERS web application interruption. In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

9.5 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.5.1 *Pregnancy Prevention*

Participants of childbearing potential who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criteria 4.1.15. Investigators may wish to additionally advise the partners of participants about pregnancy prevention guidelines when appropriate and compliant with local policy. Newborn infants should be followed until 30 days old, provided the appropriate level of consent is obtained.

9.5.2 *Pregnancy Reporting for Canadian Sites*

The investigator is required to report to CCTG **and** CTEP any pregnancy occurring in partners of participants. Pregnancies occurring up to 90 days after the completion of study treatment must also be reported.

The investigator should report the pregnancy within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage, under the "Toolbox" link. The pregnancy must also be reported within 24 hours of learning of the pregnancy via CTEP-AERS. In addition to the submission of a CTEP-AERS report, the investigator is also required to complete the Pregnancy Information Form and fax to CTEP at 301-897-7404 and CCTG at 613-533-2812 or by Email at safety-desk@ctg.queensu.ca.

The pregnancy reporting forms should be updated to provide the outcome of the pregnancy. All follow-up reports must be submitted to CCTG and CTEP in a timely manner.

Information from the trial participant's pregnant partner can only be collected following informed consent. A copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG. Centres that require additional informed consent for the pregnancy notification and/or outcome from the pregnant partner must submit a copy of the signed signature page of the Pregnancy Follow-up consent to CCTG.

Additional information regarding the CTEP requirements (including guidance on grades, Standard of Care (SOC), the Pregnancy Information Form and other reporting instructions) can be found in the "NCI Guidelines for Investigators: Adverse event reporting requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" document. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

If the pregnancy results in death (i.e. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an "inpatient hospitalization" for the purposes of pregnancy reporting.

Pregnancy loss is defined in CTCAE as "Death in utero". Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

9.5.3 *Pregnancy Reporting for United States Sites*

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. In addition, the Pregnancy Information Form included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a participant's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

Pregnancy loss is defined in CTCAE as "Death in utero". Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

9.5.4 *Exposure Reporting (Non-study Participants) for Canadian Sites*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non- study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure, ideally within 24 hours of learning of the exposure using the CCTG Exposure Reporting Form available from the trial webpage, under the "Toolbox" link.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual for 30 days. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

9.5.5 *Secondary Malignancy*

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g. treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g. acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Secondary malignancies should be captured on the medical history form in the relevant follow-up folder, within 30 days of being issued and the pathology report uploaded.

9.5.6 *Second Malignancy*

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

9.6 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Investigator Brochure / Product Monograph), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

9.7 NCI Responsibility for Reporting Serious Adverse Events to FDA

Reports submitted via CTEP-AERS will be submitted to the FDA through the mechanism of voluntary MedWatch reporting.

9.8 Reporting Safety Reports to Investigators

Canada
CCTG will notify Investigators of all Safety Reports, including all serious adverse events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment (SUSARs) from this trial as well as Safety Updates (SUs) (single reports or line listings) from other clinical trials) as reported to the CCTG.

The reports will be posted to the CCTG trial PR.26 web-based safety monitoring utility, available on the CCTG trial webpage, under the "Toolbox" link. Relevant safety reports requiring REB submission that are not submitted at the time of initial REB approval should be submitted to the REB as soon as possible (suggest within 30 days of the date of local activation). REB submissions greater than 90 days from the date of local activation will be regarded as delinquent and a major deficiency will be assigned. Centres being activated later in the life of the study only need to submit the latest version of the PM and safety reports as described above.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the Safety Report such as protocol and/or informed consent changes. Safety reports that are not mandated by CCTG to be submitted to the REB are marked as "NR" (not required) in the safety report monitoring utility. However, local policy may still require REB submission of this information.

The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial PR.26 web-based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

United States
Investigators will be notified of Safety Reports, including all serious adverse events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment (SUSARs) from this trial as reported via the CTSU Broadcast.

Investigators must notify any local IRBs of events required per local policy.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Participants may stop docetaxel (Arm 2) in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.
- Clinical progression as defined in Section 8
- PSA progression with confirmed radiographic progression as defined in Section 8.
- Request by the participant.
- Completion of therapy as outlined in Section 7.
- Efforts should be made to maintain the investigations schedule and continue follow-up, even if participants discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment is Stopped

Subsequent therapy after protocol treatment is stopped is at the discretion of the investigator. Participants on Arm 1 may not receive docetaxel until they have experienced progression as defined in Section 8. Concurrent administration of docetaxel and ARPI is not allowed on Arm 1.

10.3 Follow-up Off Protocol Treatment

Patients will be followed every 12 weeks until death.

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Data Review

CCTG receives core support from the Canadian Cancer Society. To ensure efficient use of limited funding, the CCTG has, over the past 40 years, optimized their risk based trial oversight and monitoring program. A critical component is central data review of submitted deidentified source documents, allowing source data verification and confirmation of key aspects including eligibility, endpoints and safety outcomes. Depending on the trial's design, these source documents may include such source documents as surgical and histopathology reports to confirm disease stage and type, imaging reports to confirm extent of disease and assess efficacy or include submission of tumour samples (to confirm diagnosis and eligibility or DICOM images (to verify response or radiation therapy planning). These source documents are reviewed by experienced data managers and physicians and are critical to ensuring the accuracy of the data and consistency of conclusions drawn.

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from participants' charts (i.e. source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP) application at https://sdp.ctsu.org/login. This application is also available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with any Rave roles on a relevant site roster can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU SDP application Browser > Document Repository in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

See Appendix III (Documentation for Study) for details of supporting document requirements for this trial and for requirements for the redaction of personal identifiers. Although it remains the centres responsibility to ensure adequate redaction of any information provided to CCTG, submitted source documents are reviewed prior to acceptance at CCTG; in the case of incomplete redaction, documents are removed and the site assigned a deviation and required to resubmit.

All participants will provide written informed consent for submission of source documents, and the rationale and documents to be collected will be detailed in the informed consent document.

11.2 Central Radiology Review

There will be no central radiology review for this study.

11.3 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the PR.26 trial specific website, which will include details regarding sample preparation, handling and shipping.

Specimens collected may be used by researchers now or in the future to better understand the nature of prostate cancer and how participants respond to treatment. Samples will be used for research purposes only and will not be sold. Participants will not be identified by name. The only identification on any sample will be by a patient study number assigned at the time of enrollment to the trial the surgical/ histology number and/or participant initials. Material issued to researchers will be anonymized and only identified by a coded number.

Genetic Testing

Canadian Sites Only

In the course of genetic testing for this study, there is a chance that "material incidental findings" may occur; these refer to unanticipated discoveries made in the course of research but that are outside of the scope of the research being conducted and that are reasonably determined to have significant welfare implications for the potential participant/participant [TCPS2]. These findings could be inherited changes that might predispose a person to particular cancers or other diseases, and may be passed on in families.

As the genetic testing done for this study will be conducted in a research lab, the results may not be validated. In order to validate the results, the testing must be repeated in a certified laboratory.

During the informed consent process, participants will be told about the remote possibility of material incidental findings being discovered, and given the opportunity to make informed choices about whether they wish to receive this information.

If a material incidental finding is discovered during the testing for this study and a participant consented to learning about the results, one of the following options will be followed:

- Results of the testing will be provided to the study QI/SI at the enrolling institution by the CCTG study team when a potential material finding is identified in one of their study participants by the research laboratory. The QI/SI at the enrolling institution will be responsible for following local SOPs with regard to confirming the result, ensuring if genetic counseling is available, obtaining REB approval (if required) and contacting the study participant.

12.1 Protocol-Mandated Correlative Studies

Whole Blood Collection for ctDNA

The submission of whole blood is mandatory for U.S. and Canadian centre participation and optional for participants in this trial.

Specimens will be collected at the following time points:

1. Baseline (all participants)
2. End of Cycle 1 Docetaxel (Arm 2)
3. End of Cycle 6 Docetaxel / week 18 (all participants)
4. Progression (all participants)

Time Point	Specimen	Send Specimens To:
Baseline		
	• 2 x 10 mL blood in Streck ctDNA tube	CCTG Tissue Data Repository
End of Cycle 1		
	• 2 x 10 mL blood in Streck ctDNA tube	CCTG Tissue Data Repository
End of Cycle 6 / week 18		
	• 2 x 10 mL blood in Streck ctDNA tube	CCTG Tissue Data Repository
At Progression		
	• 2 x 10 mL blood in Streck ctDNA tube	CCTG Tissue Data Repository

When received at the CCTG Tissue bank (in 2 x 10mL Streck ctDNA tubes), whole blood will be centrifuged to obtain plasma and buffy coat, and frozen until time of correlative analyses. At that point, the plasma and buffy coat fractions will be used for ctDNA and white blood cell DNA (germline DNA surrogate; WBC DNA) extractions and QC according to standard protocols. It is expected that deep ctDNA and WBC DNA targeted sequencing will be performed using custom hybrid-capture technology and Illumina machinery. A minimum of 25ng of DNA from each sample is typically required for library preparation. Library preparation will incorporate unique molecular identifiers to aid in downstream digital error suppression and PCR de-duplication. Bioinformatic estimation of ctDNA fraction (ctDNA%), and detection of germline and somatic mutations, copy number changes, and structural rearrangements will be carried out in accordance with published protocols and computational pipelines (current examples include Tolmeijer et al., Clin Cancer Res 2023; Herberts et al., Nature 2022).

We expect to evaluate the following correlative objectives:

- The extent to which baseline ctDNA% and cycle 6 / week 18 ctDNA% (i.e. ctDNA dynamics/kinetics) can inform on patient response to treatment.
- Potential mechanisms of acquired resistance to docetaxel and ARPI +ADT by searching for changes in genomic profiles at progression (relative to baseline).
- Residual plasma from DNA extraction will banked for future biomarker analyses.
- To determine if ctDNA can be used as a biomarker to introduce docetaxel in patients treated with ADT and ARPI

Tumour Tissue Collection

The submission of a representative block (or alternatively, cores or unstained slides) of the diagnostic tumour tissue at the request of the CCTG Central Tumour Bank is mandatory for U.S. and Canadian centre participation AND optional for participants in this trial. One tumour block is requested from any of the biopsies or resections of the primary tumour. Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to enrollment of the first participant to allow cores (two 2 mm cores of tumour from the block) and/or 10 - 20 unstained slides of representative tumour tissue to be substituted in response to the Central Tumour Bank request. Blocks are the preferred material to collect, as it is well known that tissue materials (including protein and nucleic acid integrity) on unstained sections begin to deteriorate within 3-6 months after preparation. Submission of blocks will optimize the amount of tissue available to investigators and permit the preservation of the block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request. It is expected that the archival tissue will be used for tumour DNA, RNA and/or protein profiling, to correlate prostate cancer molecular subtypes and features with participant clinical outcomes. Recurrent somatic genomic alterations including those affecting DNA damage repair pathways (e.g. within BRCA2, ATM, CDK12, MSH2), gene, ETS family members (ERG, ETV1), tumour suppressors (TP53, PTEN, RB1), androgen receptor signalling (SPOP, FOXA1, HSD3B1), are associated with different prognoses in certain clinical settings. Transcriptomic subtypes of prostate cancer (e.g. luminal versus basal), or continuous risk scores derived from expression signatures, can stratify participants based on risk of metastatic progression and have been linked with outcomes in the context of systemic therapy.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

This is an international multi-centre, open-label, randomized phase III trial in participants with mCSPC who have a suboptimal PSA response. Patients will be randomized with a 1:1 ratio to one of two arms: ARPI + ADT (Arm 1) or Docetaxel + ARPI + ADT (Arm 2), stratified by the following factors: PSA: 0.2 – 4 vs >4; ARPI-type: CYP17 inhibitor vs AR antagonist, Liver metastasis: Yes vs No; De novo vs Recurrent (at time of diagnosis of mCSPC); Time from start of ADT: ≥6 to <9 months vs ≥9 to 12 months.

The primary objective is to determine if the addition of docetaxel chemotherapy to SOC ADT + ARPI will improve OS of patients with mCSPC who have suboptimal PSA response (6-12 month PSA >0.2ng/ml) after treatment with ADT (between 6-12 months exposure) and ARPI (≥ 4-months exposure).

Secondary objectives will evaluate study treatment effect on: time to PSA progression; 90%, ≤0.2ng/ml and ≤0.02ng/ml PSA decline.

Exploratory objectives are: To assess whether ctDNA can be a potentially useful biomarker in addition to PSA for prognostication, prediction of docetaxel benefit, and clarifying mechanisms of resistance to (chemo)-hormonal therapy; to explore OS in participants in each study arm using the following factors: high-volume (defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis) versus low-volume mCSPC, from date of commencement of ADT and molecular characterization of loss or inactivating mutations or structural arrangements of TP53, PTEN, or RB1 and status of DNA-damage repair genes.

13.2 Primary Endpoints and Analysis

All efficacy analyses will be based on the intention to treat population. The primary endpoint is OS, defined as the time from randomization to date of death from any cause or censored at last known alive before or on the data cut-off point for each analysis. OS distribution by treatment arm will be estimated using the Kaplan-Meier product-limit method and compared using the log-rank tests stratified by stratification factors at randomization. The Cox regression model will be used to estimate the treatment effect and its appropriate confidence interval (C.I.) adjusted for stratification factors at randomization. Two interim analyses will be performed when 50% and 75% of required OS events for final analysis are observed.

13.3 Secondary Endpoints

The time to PSA progression and time to clinical progression will be analyzed with methods similar to those for OS analysis; PSA 90% response rate and proportion achieving <0.2ng/ml and <0.02 ng/ml; the Cochran–Mantel–Haenszel test stratified by stratification factors at randomization will be used to test the difference between treatment arms.

13.4 Subgroup Analyses

Subgroup analyses will be performed according to stratification variables and other specified important variables. Any findings will be included in presentations and publications reporting trial results and will be reported as hypothesis-generating.

For the following variables, analysis on OS, PSA and clinical progression endpoints will be explored with estimates of treatment effect and the corresponding 95% confidence intervals (CIs):

1. ctDNA analysis plan is outlined the correlative science section 12.0
2. high-volume vs low-volume status
3. ethnicity
4. race
5. OS from date of commencement of ADT
6. molecular characterization of loss or inactivating mutations of TP53, PTEN, or RB1
7. status of DNA-damage repair genes affecting DNA repair genes

13.5 Sample Size and Duration of Study

The sample size for this study is determined to detect a targeted 33% improvement in overall survival time (hazard ratio (HR) of 0.75). Assuming a median survival time of 36 months for the control group, accrual of 21 eligible patients per month for 39 months, follow-up of 36 months, using a 1-sided 0.025 level test with 85% power, the total sample size is 830 after adjusted for 2 interim analyses and 5% ineligibility/lost to follow up. The required number of events for final analysis is 443.

Patients will be enrolled at Canadian sites and participating SWOG and other member sites within the U.S. NCTN network. We expect an accrual rate of 21 patients/month which will allow us to reach our target accrual of 830 patients in 39 months.

13.6 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings.

The CCTG Data Safety Monitoring Committee (DSMC) will review progress and safety data (including SAEs and fatal SAEs) bi-annually.

13.7 Interim Analysis

Two interim analyses at 50% and 75% of information for OS with O'Brian-Fleming type of efficacy boundaries and futility boundaries specified as follows: At 50% of information, the Wieand rule will be used for stopping for futility; at 75% information, we suggest stopping the trial for futility if a HR > 0.9 is observed. If the study treatment had the targeted effect, we will have around 95% chance to proceed to final analysis. We will claim efficacy of study treatment if a 1-sided p-value of 0.0015, 0.009 and 0.022 or smaller is observed at 1st, 2nd interim analysis or final analysis respectively.

14.0 PUBLICATION POLICY

The PR.26 trial represents a partnership between the Canadian Cancer Trials Group and SWOG Cancer Research Network. The trial has co-Chairs of Dr. Michael Ong (CCTG) and Dr. Alexandra Sokolova (SWOG), who have equal responsibility for trial design, concept and protocol development, trial conduct, analysis and dissemination of results. All trial communications and reports will note the joint leadership of the trial. CCTG will operationalize the trial within the NCTN. Authorship will be based on alignment with CCTG and SWOG publication policies, and will follow the principles as per below:

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 The results of this study will be published as joint CCTG and SWOG research. The following rules will apply regarding the primary publication/presentation of the study:

- The first authors will be Dr. Ong and Dr. Sokolova.
- A limited number of the members of the Canadian Cancer Trials Group, SWOG, and other participating NCTN collaborative groups and the U.S. NCI(s) may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chairs.

14.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A joint study of the Canadian Cancer Trials Group and SWOG Cancer Research Network. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

14.2 Responsibility for Publication

It will be the joint responsibility of the Study Chairs to write up the results of the study within a reasonable time of its completion. If after a period of one year following maturation of the data and completion of the final statistical analysis the primary study manuscript has not been submitted for publication, the CCTG central office reserves the right to make other arrangements to ensure timely publication.

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

This study is affiliated with the U.S. National Cancer Institute (NCI US). Therefore, the conduct of this study must comply with the U.S. regulations regarding the Protection of Human Subjects (Title 45, Part 46, US Code of Federal Regulations).

15.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the participant or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the participant is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this participant subsequently regains capacity, the participant should be re-consented as a condition of continuing participation.

15.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the study. In conjunction with GCP 4.8.2, the communication of this information must be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a participant is unable to read then informed consent may be obtained by having the consent form read and explained to the participant.

15.3.1 *Obtaining Consent for Pregnancy Reporting*

Information from the pregnant person should not be collected from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information from them. If the main consent form adequately addresses the pregnancy notification and collection of information regarding the outcome of a pregnancy of a trial participant, a Pregnancy Follow-up consent form will not be required by CCTG. CCTG also considers the main consent form signed by the trial participant adequate consent for notification and collection of the outcome of a pregnancy of a trial participant's pregnant partner. Any information collected from the trial participant's pregnant partner can only be collected following their informed consent. Local REB policy should be followed to ensure appropriate consent is obtained.

A trial-specific consent form for Pregnancy Follow-up can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant such as the pregnant partner.

Participants will not be withdrawn from the main trial for refusing or withdrawing permission to provide information related to the pregnancy. Similarly, trial participants will not be withdrawn from the main study should their partner refuse or withdraw permission.

15.3.2 *Obtaining Consent for Exposure Reporting – Canadian Sites Only*

Information from and/or about the subject (i.e. the exposed individual) should not be collected from and/or about them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about and/or from them.

A trial-specific consent form for Exposure Follow-up can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant (such as the exposed individual).

Participants will not be withdrawn from the main trial for a refusal or withdrawal of permission from a non-trial participant to provide information related to the exposure.

15.3.3 *Obtaining Consent for Research on Children – Canadian Sites Only*

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an Exposure Follow-up consent form (even if they are a participant in the main study) prior to collecting information about the child.

15.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of participants participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

15.5 Retention of Participant Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 15 years following the completion of the trial at the centre (15 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

For international participating regions, local regulatory guidance should be followed with respect to duration of records retention, unless otherwise contractually dictated.

15.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

15.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres during the study as part of the overall quality assurance program. The monitors/auditors will require access to participant medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

The above-mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

As the trial is NCI U.S. affiliated, the findings will be reported to the NCI U.S. Clinical Trials Monitoring Branch as required.

15.8 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, participant-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s).

All Study Investigators at participating sites who register/enroll participants on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution’s data safety monitoring plan.

15.8.1 *Method*

Required submission of participant demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

See Appendix III for additional details of data reporting and source document upload.

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APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

All drugs for this trial are commercially available. These are to be obtained from the Canadian or U.S. market, or available through compassionate release, and will not be supplied for this study.

Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler unless they have another agreement for supply in place. The use of generic chemotherapy agents are acceptable.

For Canadian sites please refer to the relevant Product Monographs.

For U.S. sites please refer to individual FDA-approved Package Insert / Prescribing Information.

APPENDIX III - DOCUMENTATION FOR STUDY

Data Submission/Data Reporting:

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
- Rave Investigator role, must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR), and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the centre of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave Resources > Medidata Account Activation and Study Invitation (to activate your iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management Rave Resources section or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

The ELECTRONIC CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required at	To be completed electronically	Supporting Documentation *	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Patient Enrollment	Prior to enrollment	At the time of patient enrollment/assignment to treatment	Consent form** Diagnostic pathology report(s), baseline PSA report, baseline radiology reports	Additional clinical, PSA, laboratory or imaging reports that may impact on decision regarding eligibility
Baseline Report	At the time of enrollment	Within 2 weeks after enrollment		
Correlative Studies Report	Continuous running-log folder	Update after collection / shipment of samples.		
Treatment Report – First 18 Weeks	Every 3 weeks for first 18 weeks of study treatment	Within 2 weeks after each visit	Radiology reports relevant to disease assessment and study endpoints	PSA reports and additional clinical, or imaging reports that may inform evaluation of endpoints or safety
Treatment Report – Week 18 Onwards	Every 12 weeks, after week 18, during study treatment	Within 2 weeks after each visit	Radiology reports relevant to disease assessment and study endpoints	PSA reports and additional clinical, or imaging reports that may inform evaluation of endpoints or safety
End of Treatment Report	At the time of **permanent** discontinuation of ARPI / Docetaxel Treatment	Within 2 weeks after permanent discontinuation of ARPI / Docetaxel Treatment		
Follow-up Report	At each follow-up visit after patient off study treatment, prior to progression	Within 2 weeks after each visit	Radiology reports relevant to disease assessment and study endpoints	PSA reports and additional clinical, or imaging reports that may inform evaluation of endpoints or safety
Relapse/Progression Report	Upon progression	Within 4 weeks of progression criteria met	Relevant PSA, radiology and pathology reports	Other relevant documentation (e.g. abnormal clinical findings)
Short Follow-up Report	At each follow-up visit after patient off study treatment, after progression	Within 2 weeks after each visit		
Death Report	At time of participant death	Within 4 weeks of participant death	Autopsy report if performed	Additional clinical, laboratory or imaging reports that may inform evaluation of cause of death
SAE Report***	At the time of SAE	Within 1 working day		Additional clinical, laboratory or imaging reports that may inform evaluation of safety including, admission and discharge summaries/notes

footnotes on next page…

* Scan and upload in the Supporting Document Portal (SDP). Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) for Canadian sites as not submitted. All participant identifiers, other than the CCTG patient ID assigned at enrollment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements. Acceptable methods include:

- **fully opaque** sticker/tab placed over the identifiers prior to scanning
- **fully opaque** black marker; prior to upload please ensure that the information is no longer visible on the scanned document
- electronic black box placed over identifiers in PDF document that is subsequently printed and then scanned. (*NOTE:* do not send the unprotected PDF file with black boxes included as those can be moved / removed easily after opening)
- electronic stripping of identifiers prior to upload (typically only possible for DICOM images)

Note that supporting documents must include the participant's trial code, CCTG patient serial number, and participant initials (or a two/three masking letter code assigned by your centre).

** Required for Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated. Centres are expected to redact the participant's name/signature on the submitted copy, either partially (leaving only a portion to confirm that a person has signed but that cannot identify the individual) or fully, depending on local policy.

*** See Section 9.0 Serious Adverse Event Reporting for details.

Data Quality Portal:

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topic button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display N/A for the Total Delinquencies summary count.

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX V – GUIDELINES FOR DECENTRALIZED TRIAL ACTIVITIES

Remote Consent:

- *US Sites:* Section 2.3.8 of NCI CIRB's Standard Operating Procedures (www.ncicirb.org/about-cirb/sops) includes information on remote consent, eSignature, and eConsent.
- *Canadian Sites:* Must follow the policies and procedures of their institution and their REB of record for the trial, as well as consult with CCTG.

Telehealth:

The Qualified Investigator (QI) must record telehealth visits in medical records, and where required, timely data submission of data in the study data management system. The QI is responsible for making any decisions related to protocol specifications.

Local Performance of Laboratory Tests:
Results must be made available to the QI for review per protocol timing and for study data submission, when required.

Local Performance of Imaging Tests:

The imaging tests indicated in protocol section 5 may be performed at site closer to where the participant lives if approved by the QI. The QI must ensure that the results, and images if required by protocol, will be provided to the QI.

Administration of Commercial Agents by Local Health Care Professional (HCP):

ADT and ARPI therapy may be administered by a local HCP with appropriate reporting of therapy administration and adverse event reporting to the QI. The QI is required to report any protocol deviations and unanticipated problems that occur (e.g. non-compliance with protocol therapy) per standard procedures. In such cases, when the study is under the NCI CIRB as the IRB of record, the trial site must include the policy/standard operating procedures on the use of Local HCPs as part of their local context review via the Annual Signatory Institution Worksheet for the NCI CIRB. This policy should include how the QI documents the local HCP's and their institution's approach to providing non-investigational agents and study records. For trial sites not using the NCI CIRB (e.g. Canadian sites), the trial site of the QI must have institutional policies that allow the use of local HCPs, including REB awareness.

APPENDIX VI - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial as well as any associated sub-studies should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of participants are permissible.

In these rare circumstances, minor deviations that do not impact participant safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB and review the trial website for additional guidance specific to the trial.

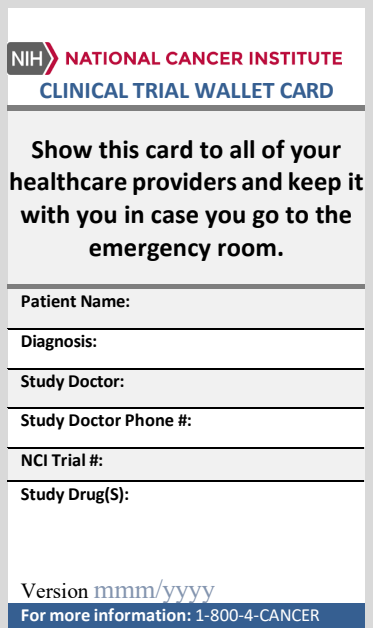
Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. *Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.*
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Participant care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*.
  **Must be approved by CCTG or acceptable per further instruction from CCTG.*
- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if participants are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact participant safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

APPENDIX VII – PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

Version mmm/yyyy

For more information: 1-800-4-CANCER

LIST OF CONTACTS

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to allocation.	Amanda Bontje Clinical Trials Assistant, CCTG Email: abontje@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Akunne Ndika Study Coordinator, CCTG Email: andika@ctg.queensu.ca	613-533-6430	613-533-2941
	or: Dr. Mariam Jafri Senior Investigator, CCTG Email: mjafri@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CO-CHAIRS	Dr. Michael Ong Study Chair Email: mong@toh.ca or Dr. Alexandra Sokolova Study Co-Chair Email: sokolova@ohsu.edu		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Mariam Jafri Senior Investigator, CCTG Email: mjafri@ctg.queensu.ca or Akunne Ndika Study Coordinator, CCTG Email: andika@ctg.queensu.ca	613-533-6430	613-533-2941

Additional U.S. contact information:

CONTACT INFORMATION		
For regulatory requirements:	**For participant enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at https://www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with participants waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org for regulatory assistance.	Please refer to the participant enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. participant eligibility or treatment-related): See Contacts page above this table		
For non-clinical questions (i.e. unrelated to participant eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		