TRIPLE-SWITCH(SWOG/CCTG-PR26): Randomized Phase III Clinical Trial of Docetaxel with Androgen Receptor Pathway Inhibitors for Metastatic Castration-Sensitive Prostate Cancer Patients with a Suboptimal PSA Response

Alexandra O. Sokolova*, Michael Ong*, Sebastien Hotte, Tanya Dorff, Kim Chi, Alexander Wyatt, Amir Goldkorn, Michael Kolinsky, Michael Brundage, Akunne Ndika, Seth P. Lerner, Wendy Parulekar, Keyue Ding, Mariam Jafri

The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; Oregon Health & Science University, Knight Cancer Institute, Portland, OR; Juravinski Cancer Institute, McMaster University, Hamilton, ON, Canada; City of Hope Comprehensive Cancer Center, Duarte, CA; University of British Columbia, BC Cancer, Vancouver Cancer Centre, Vancouver, BC, Canada; University of British Columbia, Vancouver, BC, Canada; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Cross Cancer Institute, Edmonton, AB, Canada; Cancer Centre Southeastern Ontario At KGH, Kingston, ON, Canada; Canadian Cancer Trials Group, Kingston, ON, Canada; Baylor College of Medicine, Houston, TX; Queen's University, Canadian Cancer Trials Group, Kingston, ON, Canada

Background

Patients with metastatic castration-sensitive prostate cancer (mCSPC) are generally recommended treatment with androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPI). Patients with poor prognostic features may also be offered the addition of docetaxel chemotherapy, but there is equipoise about the impact of docetaxel on survival outcomes due to a lack of randomized controlled trial data on an ADT + ARPI backbone. A very important prognostic factor for patients receiving ADT + ARPI is suboptimal prostate-specific antigen (PSA) response, defined as a PSA of ≥0.2 ng/ml after 6-12 months of treatment. These patients have a short time to castration-resistant disease and a median overall survival of only 30-36 months. Suboptimal PSA response may be a novel way to select patients for docetaxel treatment intensification.

CCTG-PR26 (TRIPLE-SWITCH) is a joint CCTG-SWOG trial run through the NCI National Clinical Trials Network. This study investigates whether the addition of docetaxel to ADT and ARPI, prior to the development of castration-resistant prostate cancer and regardless of disease volume, can improve overall survival in this high-risk patient subgroup with a suboptimal PSA response.

Methods

This international, open-label, randomized phase III trial is enrolling patients with mCSPC receiving ADT plus ARPI and having suboptimal PSA response, defined as a PSA ≥0.2 ng/mL after 6-12 months of ADT and at least 4 months of ARPI.

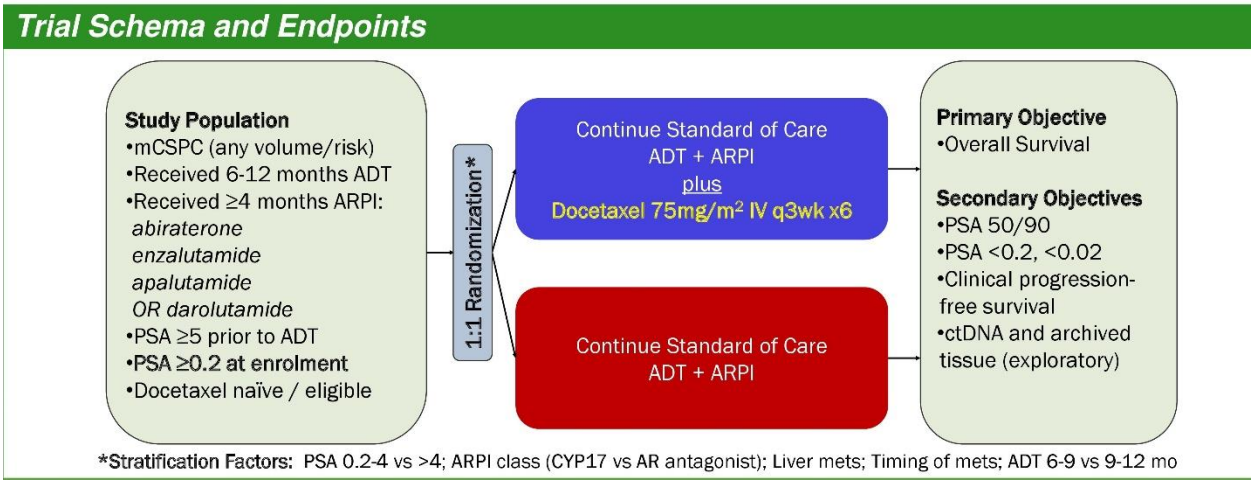
Participants are randomized to one of two arms:

- **Arm 1:** Patients will continue on standard ADT + ARPI (abiraterone acetate with prednisone, apalutamide, enzalutamide, or darolutamide).
- **Arm 2:** Patients will receive docetaxel at a dose of 75mg/m² intravenously every three weeks for up to six cycles, in addition to continuing their standard ADT + ARPI.

Randomization will be stratified by factors of PSA levels, the type of ARPI used, the presence of liver metastasis, disease recurrence status, and the duration of ADT.

Key eligibility criteria include: age ≥18 years; histologically confirmed prostate adenocarcinoma; metastatic disease confirmed by conventional imaging; a pre-ADT PSA ≥5.0 ng/mL; receipt of ADT for 6-12 months and ARPI for ≥4 months; a PSA ≥0.2 ng/mL within 14 days of enrollment; adequate organ and marrow function; ECOG performance status 0-2; and eligibility for docetaxel. Patients must not have had evidence of disease progression on ADT prior to enrollment. The primary endpoint is overall survival. Secondary endpoints include PSA response, PSA kinetics, and clinical progression free-survival. Correlative studies will explore the prognostic and predictive value of circulating tumor DNA and the association between molecular signatures in primary prostate cancer tissue and clinical outcomes. The trial aims to enroll 830 patients to detect a targeted 33% improvement in overall survival. The trial was activated January 2025 with enrollment commencement June 2025. Clinical trial information: NCT06592924.

Table, Graph, or Illustration



Funding Acknowledgements: Canadian Institutes of Health Research NCI National Clinical Trials Network (NCTN), Canadian Cancer Society; Hope Foundation, Prostate Cancer Foundation

Conflicts of Interest Disclosure Statement

AOS: Consulting or honorarium: Astra Zeneca, Astellas, CELC-G, Research Funding: Janssen, Astra Zeneca, Novartis

AWW has served on advisory boards and/or received honoraria from AstraZeneca, Astellas, Bayer, EMD Serono, Janssen, Merck, Pfizer; contract research agreements (institutional) with ESSA Pharma, Tyra Biosciences, and Promontory Therapeutics.

SPL: Aura Bioscience, FKD, JBL (SWOG), Genentech (SWOG), Merck (Alliance), QED Therapeutics, Surge Therapeutics, Vaxiion, Viventia. Consultant/Advisory Board:Aura Bioscience, BMS, C2iGenomics, Ferring, Immunity Bio, Incyte, Gilead, Pfizer/EMD Serono, Protara, Surge Therapeutics, Tyra Biosciences, UroGen, Vaxiion, Verity; Patent – TCGA classifier; Honoraria – Grand Rounds Urology, UroToday