Summary of changes in the 2025 Canadian Urological Association–Canadian Urologic Oncology Group Guideline on metastatic castration-naive and castration-sensitive prostate cancer

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See full guideline at ***cua.org*** and ***cuaj.ca***

INTRODUCTION

This brief review highlights changes in the new Canadian Urological Association–Canadian Urologic Oncology Group guideline on metastatic castration-naive and castration-sensitive prostate cancer (mCNPC/mCSPC). Since the previously published guidelines in 2022, new data have emerged to prompt alterations in recommendations for the management of this patient group.

UPDATE 1: GENETIC TESTING

■ **All patients with mCNPC/mCSPC should undergo both germline testing and genomic profiling of tumors** *(Level of evidence 2, Strong recommendation)*.

As outlined in the CUA guideline for genetic testing in prostate cancer, men with metastatic disease should undergo both germline testing and genomic profiling of tumors.[1] Germline testing is crucial, as multiple studies have found a significantly higher prevalence of pathogenic or likely pathogenic variants (P/LP) in patients with metastatic disease compared to patients with localized disease.[2-4] In some metastatic prostate cancer (PCa) series, the frequency of germline P/LP variants was as high as 18%.[2]

As stressed in the 2023 CUA guideline, genetic testing in PCa identifies P/LP variants to inform future cancer risk and to initiate cascade testing in family members. Genomic profiling of the tumor should also be performed in patients with metastatic disease. The purposes of tumor testing include prognostication and identification of those that may benefit from targeted therapy.[1] If somatic testing is done first and shows no P/LP variants, germline testing may not be necessary.

UPDATE 2: SYSTEMIC THERAPY: DAROLUTAMIDE

■ **Darolutamide (600 mg twice a day) is a treatment option for men with mCNPC/mCSPC regardless of volume of disease** *(Level of evidence 1, Moderate recommendation)*.

Darolutamide is an androgen receptor (AR) pathway inhibitor that competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. The use of darolutamide and androgen deprivation therapy (ADT) in metastatic PCa was studied in the ARANOTE study.[5] This double-blind, placebo-controlled, phase 3 trial randomized, in a 2:1 ratio, 669 metastatic PCa patients to receive darolutamide (600 mg twice a day) and ADT or placebo and ADT. The primary endpoint was radiographic progression-free survival (rPFS), with secondary efficacy endpoints being overall survival (OS), time to prostate-specific antigen (PSA) progression, time to castration-resistant prostate cancer (CRPC), and time to initiation of subsequent systemic anticancer therapy.

Darolutamide plus ADT significantly improved rPFS, reducing the risk of radiologic progression or death by 46% vs. placebo plus ADT (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.41–0.71, $p<0.0001$), with consistent benefits across subgroups, including high- and low-volume disease. At a median followup of 24 months, OS results trended to benefit with darolutamide vs. placebo (HR 0.81, 95% CI 0.59–1.12); clinical benefits were seen across all other secondary endpoints, including delayed time to metastatic CRPC (HR 0.40, 95% CI 0.32–0.51).

Although the duration and size of the study did not allow for a proper OS assessment compared to other, more mature studies assessing androgen receptor pathway inhibitors (ARPis) in CSPC, a recent network meta-analysis suggested oncologic equipoise to the already known doublet therapies for PFS.[6]

UPDATES 3 & 4: TRIPLET THERAPY

■ **Enzalutamide in combination with ADT and docetaxel is a treatment option for men with mCNPC/mCSPC in those with synchronous (de novo) metastases** *(Level of evidence 2, Weak recommendation).*

ENZAMET was an open-label study that randomized 1125 men with mCNPC/mCSPC to receive ADT and enzalutamide daily (160 mg) or a non-steroidal antiandrogen (NSAA: bicalutamide, nilutamide, or flutamide) with a primary endpoint of OS. High-volume disease was present in 602 (54%) of 1125 participants and 683 (61%) had synchronous metastatic disease.[7] Concurrent use of docetaxel was allowed and the decision to treat with chemotherapy was at the discretion of the investigator. At initial analysis, use of chemotherapy was well-balanced between the two arms (45% of those receiving enzalutamide and 44% of those receiving a NSAA planned for early docetaxel use).[8]

In the updated analysis at 470 deaths and a median followup of 68 months, the use of chemotherapy continued to be balanced between the control arm and enzalutamide arm (n=240 vs. n=243).[7] Although docetaxel use was not randomized, subgroup analysis showed that the benefit of the addition of enzalutamide to docetaxel was seen only in those with synchronous metastases (HR 0.73, 95% CI 0.55–0.99) and not those with metachronous metastases (HR 1.1, 95% CI 0.55–0.99); however, the authors stress that the numbers in each group may be too small to make a conclusion on this, with only 141 patients in the docetaxel group with metachronous metastases. Interestingly, the benefit of the addition of enzalutamide to docetaxel in the synchronous subgroup was seen in both high- and low-volume patients (low-volume disease: HR 0.57, 95% CI 0.29–1.12; and high-volume disease: HR 0.79, 95% CI 0.57–1.10), but numbers in these groups were small.

■ **In patients who can safely tolerate docetaxel and in whom docetaxel is felt to be appropriate, triplet regimen (docetaxel plus ARPi and ADT) should be the treatment option, and not docetaxel and ADT alone** *(Level of evidence 1, Strong recommendation).*

The ARASENS, PEACE-1, and ENZAMET trials all show the benefits of adding an ARPi to docetaxel in CSPC.[7,9,10] These studies show the benefits of triplet therapy (ADT, ARPi, and docetaxel) compared to ADT and docetaxel; as such, in those patients in which docetaxel is considered, an ARPi should be added.

COMPETING INTERESTS: Dr. Saad has been an advisory board member for and received honoraria from Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Janssen, Merck, Novartis, Tolmar, TerSera, and Pfizer; and has participated in clinical trials supported by Abbvie, Amgen, Astellas, AstraZeneca, Bayer, BMS, ESSA, Janssen, Merck, Novartis, Pfizer, Point Biopharma, Tolmar, and TerSera.

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