CADTH REIMBURSEMENT REVIEW

Patient/Clinician/Industry Input

enzalutamide

non-sponsored

Indication: For the treatment of patients with non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk of metastasis (high-risk BCR)

June 20, 2024

This document compiles the input submitted by patient groups, clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions received.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: XTANDY® (Enzalutamide)
Indication: For the treatment of patients with nonmetastatic castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis.
Name of Patient Group: PROCURE – CANCER PROSTATE
Author of Submission: Marie-Christine Beauchemin

1. About Your Patient Group

PROCURE Website

Founded in 2003, PROCURE is a charitable organization in the fight against prostate cancer. It educates, supports, and informs people affected by this disease. It promotes and contributes to the financing of world-class research.

In canada, we are recognized by both the CUA and the AUQ as the leading authority on prostate cancer.

Our services include: Our full range of free support and information services aims to help people affected by prostate cancer and their loved ones. We offer quick access to healthcare professionals specialized in uro-oncology, available 7 days a week via a toll-free support line, as well as comprehensive information tools and a variety of resources to help individuals affected by prostate cancer—including caregivers, employers, the public, and healthcare professionals—better understand the disease and treatment options.

We raise awareness: We organize a variety of events throughout the year to raise awareness about prostate cancer. The funds we raise during these activities allow us to pursue our mission to help people affected by this disease and to fund world-class research projects.

We advance research: We are fully committed to prostate cancer research, and we play an essential role in its advancement by providing biospecimens and data of high scientific value from our PROCURE Biobank. We are doing everything we can to better understand this disease, diagnose it earlier and treat it in a targeted and precise manner.

2. Information Gathering

Analysis of patient calls to our specialized uro-oncology healthcare professionals through our toll-free line. Cohort of 3,500+ patients with localized, locally advanced, metastatic, recurrent, hormone-sensitive, or castration-resistant prostate cancer with or without metastasis. In addition to distress and treatment choices, the rising PSA level post-treatment, recurrence, hormone therapy and its side effects, and metastases are the main concerns of incoming patient calls. For such calls, more than 60 minutes are usually required, along with periodic follow-ups.

In 2023, 17% of our interventions were related to advanced prostate cancer, and another third of the patients initially treated for prostate cancer contacted us due to their cancer recurrence.

.

PROCURE's surveys

In May 2022, in collaboration with the Leger firm, PROCURE conducted an online Canadian survey on the quality of life of our patients treated for prostate cancer, in which 263 patients participated. According to this survey, the main challenges posed by treatment for 50% of respondents included managing side effects, living with uncertainty, and maintaining a positive attitude.

In March 2018, PROCURE conducted an online Quebec survey on the needs of our patients treated for a recurrence or advanced prostate cancer. In response to the question, "What do you hope for from future treatments for prostate cancer?"

- Slows down the progression of cancer: 95%
- Extends life expectancy: 94%
- Improves the quality of life: 98%
- Helps manage or diminish side effects: 93%
- Decreases PSA levels: 91%

3. Disease Experience

There are several types of prostate cancer: those that progress slowly (low risk), those with an intermediate risk of progression (low or high), those at high risk and very high risk of progression, and those that are aggressive. Prostate cancer is a highly complex disease. Like other types of cancers, this illness affects not only the patient but also their partner and family.

No patient receives an initial diagnosis of metastatic castration-resistant prostate cancer (mCRPC). Therefore, the side effects are often related to the initial treatment or a combination of treatments, which may include surgery, radiotherapy, and hormone therapy, among others.

In general

Physical impact: Side effects are a significant burden for patients: Incontinence and urinary disorders; erectile dysfunction and disorders (dry orgasms, loss of fertility); bowel issues and radiation-induced proctitis; side effects related to hormone therapy (hot flashes, loss of libido, irritability, weight gain and muscle loss, gynecomastia, risks of stroke, cardiovascular disease, osteoporosis, and diabetes).

Significant psychological impact: Anxiety, depression, and loss of self-esteem related to the cancer diagnosis, post-treatment PSA levels, the announcement of a recurrence, hormone therapy-resistant cancer (nmCRPC), or metastatic cancer. The impact is also related to the side effects of treatments and changes in masculine characteristics. Physical and psychological fatigue often hinders activities. For men living alone, the impact of the disease and treatments is difficult to manage and often an obstacle to a new intimate relationship.

Partners unintentionally become caregivers. This role is demanding, accompanied by stress, anxiety, and resulting depression. They often have to mourn the loss of a satisfying sexual relationship. The same goes for intimate relationships: the loss of libido, fatigue, and changes in masculine characteristics often lead the man to avoid any intimate relationship with his partner. The consequences are significant.

Recurrence significantly impacts our patients, both physically and emotionally. The prospect of cancer returning often leads to increased anxiety and stress, as patients grapple with the uncertainty of their prognosis and the possibility of undergoing further treatments. This heightened anxiety can affect their overall well-being, leading to issues such as sleep disturbances, decreased appetite, and difficulty concentrating. As our nurses tell us: *These are our biggest concerns as nurses, as we strive to provide not only medical care but also emotional support and reassurance to help our patients navigate this challenging time.*

Advanced cancer creates anxiety within the couple, not knowing how much time they have ahead of them, in addition to having to manage the side effects of treatments. On the family level, children become at risk for the rest of their lives. If the cancer is aggressive and fatal, they will have to mourn their father at a young age.

If their father carries a BRCA genetic mutation and has prostate cancer, both boys and girls have an increased risk of developing certain types of cancers, such as prostate cancer, breast cancer, and ovarian cancer, if they inherit the altered gene.

.

Quality of life: For many patients, access to professionals such as sexologists, psychologists, physiotherapists, or kinesiologists is either non-existent, too expensive, or the waiting time is too long. Many of them have never met their care team except for their treating physician. Few have comprehensive information or answers to their questions to manage their expectations.

4. Experiences With Currently Available Treatments

Patients: They particularly struggle to comprehend when their specialist expresses a statement like "if I had to choose a cancer, prostate cancer would be at the top of my list." It's a complex cancer, especially when it has breached the capsule or is at an advanced stage.

Treating recurrent prostate cancer involves several strategies depending on the extent and timing of recurrence. Active surveillance may be suitable for slow-progressing cases. Radiation therapy, including external beam or brachytherapy, targets localized recurrences. Since surgery is rarely performed after radiation therapy, standard hormone therapy (ADT) is typically the initial approach to suppress testosterone levels when the recurrence is aggressive.

But when facing a recurrence of prostate cancer, patients often confront a range of concerns that can be both emotional and practical, namely treatment effectiveness, cancer progression and impact their long-term health and life expectancy.

5. Improved Outcomes

Given that patients do not all respond the same way to treatments, including new drugs or combination treatments, we believe it is important for patients and specialists to have access to all new agents and new indications that have demonstrated their effectiveness with minimal side effects, while maintaining stable PSA levels and a good quality of life.

Metastases are a very worrisome aspect for men.
Based o our surveys, the patients' expectations with regards to new treatments are as follow:

- Stabilize/control their cancer
- Delay the onset or eliminate metastases
- Decrease or keep their PSA levels stable over a long period (a source of anxiety)
- Prolong their life and quality of life
- Be heard and taken seriously

6. Experience With Drug Under Review

We have not had access to patients who participated in the EMBARK clinical trial for this evaluation. We have, however reviewed positions that are in the public domain:

2024 - XTANDI® (enzalutamide) Receives Health Canada Approval as the First and Only Treatment for High-Risk Patients with Non-Metastatic Castration-Sensitive Prostate Cancer (nmCSPC)

Key takeaway

- The EMBARK trial focused on men with high-risk BCR. Per the EMBARK protocol, patients with nmCSPC with high-risk BCR are those initially treated by radical prostatectomy or radiotherapy, or both, with a prostate-specific antigen (PSA) doubling time (PSA-DT) ≤ 9 months.
    - High-risk BCR patients with a PSA-DT of ≤ 9 months have a higher risk of metastases and death.
- The study showed that treatment with XTANDI plus ADT reduced the risk of metastasis or death by 58% versus placebo plus ADT

.

2024 - NIH - Enzalutamide Gets Added Approval for Prostate Cancer That Hasn't Spread
2024 - What benefits of Xtandi Have been showned in studies in non-metastatic prostate cancer

Key takeaway
Another study involved 1,068 previously treated patients with rapidly rising levels of PSA whose prostate cancer had not spread and was hormone sensitive. In this study patients given Xtandi with leuprolide (a medicine that blocks the production or action of male hormones) or Xtandi on its own lived longer without their disease becoming metastatic compared to those treated with placebo given with leuprolide. Within the study patients' blood levels of PSA were monitored; if their PSA levels were undetectable after 36 weeks, treatment was paused and restarted if their PSA levels began to increase again.

OncLive
June 2024 - Enzalutamide Treatment Suspension Has No Significant Impact on QOL in nmHSPC

Key takeaway
- Ceasing enzalutamide-containing regimens did not significantly impact global QOL in patients with biochemically recurrent nmHSPC.
- Enzalutamide, with or without leuprolide, significantly reduced the risk of metastasis or death in high-risk nmHSPC patients.

May 2024 - Enzalutamide Improves Undetectable PSA Rates Alone and With Leuprolide in Nonmetastatic CSPC

Additional sources- PubMed
Fear of cancer recurrence and PSA anxiety in patients with prostate cancer: a systematic review
Support Care Cancer. 2022; 30(7): 5577–5589.
Published online 2022 Feb 1. doi: 10.1007/s00520-022-06876-z

Results
One thousand one hundred forty-eight individual records underwent screening with 32 studies included. Median prevalence of significant FCR and PSA anxiety was 16% and 22% respectively across all studies. Longitudinal studies demonstrated severity of both symptoms peaks at diagnosis, with little variability, even several years following this. Evaluating associating factors revealed younger age, generalised quality of life and mental health symptoms to be important factors for both outcomes. Few studies evaluated associations and differences between other patient, disease and treatment characteristics.

Conclusion
FCR and PSA anxiety are prominent symptoms for prostate cancer patients and importantly when present, are associated with poorer quality of life and mental health symptoms. Screening for these constructs and referral to appropriate services should form part of routine follow-up care.

7. Companion Diagnostic Test

<Enter Response Here>

8. Anything Else?

In our view, Enzalutamide is a well-established treatment for advanced prostate cancer with or without metastasis (M+). Recently, its indication has been expanded to include non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis. Given its proven efficacy and potential to improve patient outcomes, it is crucial for patients and specialists to have access to this treatment's new indication.

.

Clinical benefits

1. **Delaying metastasis**: Clinical trials have demonstrated that Enzalutamide significantly delays the time to metastasis in patients with nmCSPC. Delaying the progression to metastatic disease can extend the patient's life and improve their quality of life.
2. **Reducing PSA levels**: Enzalutamide has been shown to effectively reduce prostate-specific antigen (PSA) levels, which is a key marker of disease activity. Lower PSA levels are associated with slower disease progression and less aggressive disease. In addition, if a patient's PSA levels are undetectable after 36 weeks, treatment can be paused and restarted if their PSA levels begin to increase again. This treatment pause is beneficial as it can reduce the side effects and overall burden of continuous therapy while still managing the disease effectively.
3. **Improving survival rates**: Although long-term survival data for the new indication is still emerging, the delay in disease progression is expected to translate into improved overall survival, as seen in other prostate cancer populations treated with Enzalutamide.

Safety profile

1. **Manageable side effects**: Enzalutamide has a well-characterized safety profile. Common side effects are generally manageable and less severe compared to those of chemotherapy. This makes it a suitable option for use in patients with nmCSPC.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astellas (Xtandy)				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Marie-Christine Beauchemin
Position: Information and Support Coordinator
Patient Group: PROCURE – CANCER PROSTATE
Date: June 17, 2024

.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PX0366
Generic Drug Name (Brand Name): enzalutamide
Indication: For the treatment of patients with non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk of metastasis (high-risk BCR)
Name of Clinician Group: Genitourinary Cancer Drug Advisory Committee
Author of Submission: Dr. Girish Kulkarni

1. About Your Clinician Group

OH(CCO)'s Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered by videocall.

3. Current Treatments and Treatment Goals

Currently there is no defined treatment in this setting. Patients with a rising PSA can receive ADT alone but there are no criteria for when to initiate the ADT.

The project scope lists abiraterone-prednisone as a comparator however, it is not a comparator in this setting.

The goal is to decrease the risk of metastatic disease, improve overall survival, and maintain quality of life.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

If ADT is used in this setting alone, there are no criteria for when to initiate therapy plus the combination of ADT + enzalutamide improves metastasis-free survival.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Patients with a rising PSA and a doubling time ≤ 9 months with PSA > 2 after radiation or > 1 after prostatectomy, without metastatic disease on conventional imaging.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients that meet the indication are best suited for treatment with enzalutamide plus ADT.

Patients who do not meet the criteria (see above, i.e. a slow doubling time or very low PSA values).

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

A decrease in the PSA level, and imaging (CT and/or bone scan) as per physician discretion.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Side effect profile of combination therapy and symptomatic progression of disease.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

This can be managed in an outpatient setting by a specialist with expertise in prostate cancer management.

6. Additional Information

The GU DAC advocates for the use of enzalutamide-ADT as well as enzalutamide alone, as per the EMBARK trial. Enzalutamide-ADT has a slightly better absolute metastases-free survival compared to enzalutamide alone.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH (CCO) provided a secretariat function to the group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Girish Kulkarni
Position: Lead, OH (CCO) GU DAC
Date: 19-06-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Aly-Khan Lalani
Position: Member, OH (CCO) GU DAC
Date: 19-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astellas		X		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Sebastien Hotte
Position: Member, OH (CCO) GU DAC
Date: 19-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Astellas		X		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Urban Emmenegger
Position: Member, OH (CCO) GU DAC
Date: 19-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Astellas			X	
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Christina Canil
Position: Member, OH (CCO) GU DAC
Date: 19-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Astellas	X			
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Chris Morash
Position: Member, OH (CCO) GU DAC
Date: 19-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Astellas		X		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Non-Sponsored Reimbursement Review

Industry Input

CADTH Project Number: PX0366-000
Generic Drug Name: Enzalutamide
Indication: Xtandi® (enzalutamide capsules) is indicated for the treatment of patients with non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk of metastasis (high-risk BCR).
Name of Organization: Astellas Pharma Canada, Inc.
Author of Submission: [redacted]

1. Does the proposed project scope accurately reflect the treatment landscape?

Population

Canada's Drug Agency (CDA-AMC) has broadly defined the population in alignment with the phase 3 EMBARK clinical trial which evaluated enzalutamide in patients with non-metastatic prostate cancer who are at a high risk of biochemical recurrence (BCR).[1] This is also aligned with Xtandi's most recent indication for the treatment of patients with non-metastatic castration-sensitive prostate cancer (nmCSPC) with BCR at a high risk of metastasis (high-risk BCR)[2]

Intervention

CDA-AMC has identified enzalutamide as the intervention. The EMBARK study evaluated the efficacy and safety of enzalutamide plus androgen-deprivation therapy (ADT) and enzalutamide monotherapy, as compared with ADT alone.[1]

Comparator(s)

ADT monotherapy is a comparator in this space. Prior to the Health Canada approval of Xtandi for nmCSPC patients with high-risk BCR, the systemic standard of care for these patients was ADT alone.[3] Astellas requests that CDA-AMC re-evaluate abiraterone-prednisone (AAP) as comparator and exclude it. AAP does not have a Health Canada indication for prostate cancer patients who are non-metastatic.[4]

The evidence investigating AAP in high-risk BCR prostate cancer is limited. The STAMPEDE platform trial had an open-label arm that investigated AAP in combination with ADT vs. ADT alone in men with high-risk nmCSPC.[5] However, only 3% of the patient population investigated had high-risk BCR. The lack of evidence for AAP in this patient population has led to international guidelines not including AAP as a recommended treatment for nmCSPC with high-risk BCR..[6,7]

An acknowledgement that AAP is not an appropriate comparator in this space has also been made by local experts. CDA-AMC conducted a review of AAP in high-risk non-metastatic prostate cancer in 2023. The Formulary Management Expert Committee (FMEC) specifically evaluated the evidence of treating with AAP in the BCR subpopulation of nmCSPC. The FMEC noted there is limited evidence to support AAP in the BCR population and thus did not recommend AAP for use in patients with high-risk BCR.[8] Excluding AAP as a comparator in this instance would be consistent with the CDA-AMC review.

Outcomes

The outcomes noted by CDA-AMC to be evaluated are all clinically important. Metastasis free survival (MFS) was the primary endpoint of the EMBARK study.[1]

Given the intervention within this population is at an earlier stage of the disease, endpoints that evaluate disease progression and quality of life are important. In the EMBARK study, these would include: time to prostate specific antigen (PSA) progression, first use of new antineoplastic therapy, the percentage of patients who achieved undetectable PSA, the median duration of treatment suspension, the proportion of patients who remain treatment-free 2 years after suspension of study drug treatment, time to resumption of any hormonal therapy following treatment suspension, time to castration resistance, and Health Related Quality of Life. In addition to outcomes noted by CDA-AMC, these endpoints are also important outcomes to consider.

2. Are you aware of relevant published studies that you would like considered in the clinical review?

The only relevant published study that Astellas is aware of for this patient population is the EMBARK study. EMBARK is a phase 3 randomized study of enzalutamide plus ADT and enzalutamide monotherapy in high-risk nmCSPC with rising PSA after local therapy.[1]

3. Do you have additional comments that you feel are pertinent to this review?

The policy question that CDA-AMC is evaluating is aligned with the most recent Health Canada approval of Xtandi.

The first and second research questions proposed are answered within the EMBARK study. The third research question appears to be a cost comparison between enzalutamide and other regimens reimbursed in this space. Astellas has conducted an economic analysis that suggests that enzalutamide is a cost-effective treatment option in this space. A manuscript is in preparation for publication. Astellas would request that in its cost comparison CDA-AMC consider some parameters beyond direct drug acquisition costs.

One important consideration included in the economic analysis is the evaluation of treatment suspension when assessing the cost and cost-effectiveness of therapies. An economic benefit of a treatment suspension is reduced drug costs. In the EMBARK study, after 9 months of treatment, treatment was suspended for patients who achieved a PSA blood concentration of less than 0.2 ng/mL, and treatment was restarted when patients passed a PSA concentration threshold ($\geq$ 5 ng/mL for patients without a prior radical prostatectomy (RP), and $\geq$ 2.0 ng/mL for patients with a prior RP). As the clinical review will unveil, a higher proportion of the patients randomized to the enzalutamide arms underwent a treatment suspension, and patients on enzalutamide + ADT had a longer duration of treatment suspension. It would be important that a cost comparison of enzalutamide vs. ADT also consider the reduced costs associated with a treatment suspension.

References

1. Freedland, S.J. et al. (2023). Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. *The New England Journal of Medicine*. 389(16):1453-1465. DOI: 10.1056/NEJMoa2303974.
2. PrXtandi® Product Monograph. Updated Jan 2024. https://www.astellas.com/ca/system/files/pdf/xtandi_pm_05jan2024_en.pdf Accessed June 7, 2024.
3. Danielson, B., Saad, F., So, A., Morgan, S., Hamilton, R.J., Malone, S., Park-Wyllie, L., Zardan, A., Shayegan, B. (2019). Management algorithms for prostate-specific antigen progression in prostate cancer: Biochemical recurrence after definitive therapy and progression to non-metastatic castrate-resistant prostate cancer. *Canadian Urological Association Journal.* 13(12):420-6. DOI: http://dx.doi.org/10.5489/cuaj.5600
4. PrAbiraterone Product Monograph. Updated Nov 2022 https://pdf.hres.ca/dpd_pm/00068066.PDF Accessed June 7, 2024.
5. Attard G. et al. (2022). Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two 2andomized controlled phase 3 trials of the STAMPEDE platform protocol. *The Lancet*. 399(10323):447-460. DOI: https://doi.org/10.1016/S0140-6736(21)02437-5

6. Cornford P. et al. (2024). EAU – EANM – ESTRO – ESUR – ISUP – SIOG Guidelines on Prostate Cancer. Prostate Cancer – Limited Update April 2024. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2024_2024-04-09-132035_ypmy_2024-04-16-122605_lqpk.pdf. Accessed June 7, 2024

7. Schaeffer EM. et al. (2024). NCCN Clinical Practice Guidelines in Oncology, Prostate Cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf Accessed Jun 7, 2024

8. Canada's Drug and Health Technology Agency. CADTH Reimbursement Recommendation: Abiraterone Acetate and Prednisone. https://www.cadth.ca/sites/default/files/DRR/2023/PX0291/Recommendation%20and%20Reasons.pdf Accessed June 7, 2024.