Ontario Health
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Guideline Endorsement 3-23 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

An Endorsement of the 2021 Guideline on the Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

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This publication is a OH (CCO) initial management of prostate cancer Guideline Development Group endorsement of the 2021 Guideline on initial management of noncastrate advanced, recurrent, or metastatic prostate cancer. The original publication is available at:
https://ascopubs.org/doi/full/10.1200/JCO.20.03256

An assessment conducted in January 2025 indicated that Guideline 3-23 REQUIRES UPDATING. It is still appropriate for this document to be available while this process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

You can access the full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/70561

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For information about the PEBC and the most current version of all reports, please visit the OH (CCO) website at https://www.cancercareontario.ca/en/guidelines-advice or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Section 1: Guideline Endorsement

GUIDELINE OBJECTIVES

The objectives of this guideline are to assess the optimal initial treatments for men with noncastrate advanced, recurrent, or metastatic prostate cancer. Our recommendations are based on the 2021 guideline on the Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update [1].

TARGET POPULATION

Men with noncastrate advanced, recurrent, or metastatic prostate cancer.

INTENDED USERS

The guideline document will support providers in recommending the most optimal initial treatments for men with noncastrate advanced, recurrent, or metastatic prostate cancer.

ENDORSEMENT

The Initial Management of Prostate Cancer Guideline Development Group of Ontario Health (Cancer Care Ontario) endorses the majority of the American Society of Clinical Oncology (ASCO) recommendations of Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update modified by the endorsement process described in this document. They were reprinted with the permission of Wolters Kluwer Health, Inc. and Copyright Clearance Center.

Thirteen of the 15 Recommendations were endorsed without modifications. Two recommendations (R2.1, R2.2) were not endorsed (with explanation) as listed in Table 1-1.

Table 1-1. Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

Recommendations (see Virgo et al., 2021 [1] for complete recommendations)	Assessment
Clinical Question 1: What are the standard initial treatment options for metastatic noncastrate prostate cancer?	
R 1.0. Docetaxel, abiraterone, enzalutamide, or apalutamide, each when administered with androgen deprivation therapy (ADT), represent four separate standards of care for noncastrate metastatic prostate cancer. The use of any of these agents in any particular combination or in any particular series cannot yet be recommended.	**ENDORSED**
ADT plus Docetaxel	
R 1.1. For men with metastatic noncastrate prostate cancer with high-volume disease as defined per CHAARTED [2] who are candidates for treatment with chemotherapy, the addition of docetaxel to ADT should be offered.	**ENDORSED**
R 1.2. For patients with low-volume metastatic disease as defined per CHAARTED [2] who are candidates for chemotherapy, docetaxel plus ADT should not be offered.	**ENDORSED**
R 1.3. The recommended regimen of docetaxel for men with metastatic noncastrate prostate cancer is six doses administered at three-week intervals at 75 mg/m^2 either alone (per CHAARTED [2]) or with prednisolone (per Systemic	**ENDORSED**

Table 1-1. Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

Recommendations (see Virgo et al., 2021 [1] for complete recommendations)	Assessment
Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) [3].	
ADT plus Abiraterone	
R 1.4. For men with high-risk de novo metastatic noncastrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE [4].	**ENDORSED**
R 1.5. For men with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE [5].	**ENDORSED**
R 1.6. The recommended regimen for men with metastatic noncastrate prostate cancer is abiraterone 1000 mg with either prednisolone or prednisone 5 mg once daily until progressive disease is documented.	**ENDORSED**
ADT Plus Enzalutamide	
R 1.7. ADT plus enzalutamide should be offered to men with metastatic noncastrate prostate cancer including both those with de novo metastatic disease and those who have received prior therapies, such as radical prostatectomy (RP) or radiotherapy (RT) for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (prostate-specific antigen [PSA] progression-free, clinical progression-free, and overall) when compared with ADT alone for men with metastatic noncastrate prostate cancer as a group per ENZAMET [6].	**ENDORSED**
R 1.8. The recommended regimen for men with metastatic noncastrate prostate cancer is enzalutamide (160 mg per day) with ADT.	**ENDORSED**
ADT Plus Apalutamide	
R 1.9. ADT plus apalutamide should also be offered to men with metastatic noncastrate prostate cancer, including those with de novo metastatic disease or those who have received prior therapy, such as RP or RT for localized disease per TITAN [7].	**ENDORSED**
R 1.95. The recommended regimen for men with metastatic noncastrate prostate cancer is apalutamide (240 mg per day) with ADT.	**ENDORSED**
CLINICAL QUESTION 2: Are combination therapies such as combined androgen blockade (castration plus a nonsteroidal antiandrogen) better than castration alone for men with noncastrate locally advanced nonmetastatic prostate cancer?	
R 2.1. ADT plus abiraterone and prednisolone should be considered for men with noncastrate locally advanced nonmetastatic prostate cancer, rather than castration monotherapy, because of the failure-free survival benefit per STAMPEDE [5]. RT to the primary was mandated in STAMPEDE [5] for patients with newly diagnosed node-negative, nonmetastatic disease and encouraged in patients with newly diagnosed node-positive, nonmetastatic disease. Failure-free survival (time to the earliest of biochemical failure, disease progression, or death) was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone, although ADT plus abiraterone was administered for two or less years to men with nonmetastatic disease. **Explanation:** In the STAMPEDE trial [5], for patients with nonmetastatic disease, there was no significant survival difference between groups treated with ADT plus abiraterone versus ADT alone (hazard ratio, 0.75; 95% confidence interval, 0.48 to 1.18). The nonmetastatic group in this trial was a subgroup of a secondary outcome and consisted of both radiated and non-radiated patients. While there may be benefit to addition of abiraterone to castration in cN0 patients, we believe the level of evidence is overestimated and the balance of benefit to harm is not defined. The	**Not ENDORSED (with explanation)**

Table 1-1. Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

Recommendations (see Virgo et al., 2021 [1] for complete recommendations)	Assessment
rationale and evidence for abiraterone, enzalutamide, or apalutamide in cN1 patients is stronger based on LATITUDE [4], ENZAMET [6], and TITAN [7] trials.	
R 2.2. In resource-constrained settings where drugs such as abiraterone may not be available, combined androgen blockade using ADT plus a first-generation antiandrogen, such as flutamide, nilutamide, or bicalutamide, may be offered to men with locally advanced nonmetastatic prostate cancer, rather than castration monotherapy based on recent meta-analyses. **Explanation:** Although locally advanced, non-metastatic patients were included in one [8] of the two [9] meta-analyses, outcomes for this group of patients were not explicitly studied or reported in subgroup analyses. As a result, data to support this recommendation are lacking.	**Not ENDORSED (with explanation)**
CLINICAL QUESTION 3: Does early (immediate) androgen deprivation therapy improve outcomes over deferred therapy for men with noncastrate locally advanced nonmetastatic disease?	
R 3.1. Early (immediate) ADT may be offered to men who initially present with noncastrate locally advanced nonmetastatic disease who have not undergone previous local treatment and are unwilling or unable to undergo RT based on evidence in one meta-analysis of a modest, but statistically significant benefit in terms of both overall survival and cancer-specific survival among the larger population of men with locally advanced nonmetastatic disease.	**ENDORSED**
CLINICAL QUESTION 4: Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy for men with biochemically recurrent nonmetastatic disease?	
R 4.1. Intermittent therapy may be offered to men with high-risk biochemically recurrent nonmetastatic prostate cancer after RP and/or RT based on evidence in meta-analyses of the noninferiority of intermittent androgen deprivation therapy when compared with continuous androgen deprivation therapy with respect to overall survival [10]. This is further supported by evidence from four meta-analyses [11-14] testing superiority. Low-risk biochemical recurrence after RP is defined as a PSA doubling time >1 year and pathologic Gleason score <8. Low-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence >18 months and clinical Gleason score <8. High-risk biochemical recurrence after RP is defined as a PSA doubling time <1 year or a pathologic Gleason score of 8-10. High-risk biochemical recurrence after RT is defined as an interval to biochemical recurrence <18 months or a clinical Gleason score of 8-10 [15]. Active surveillance may be offered to men with low-risk biochemically recurrent nonmetastatic prostate cancer.	**ENDORSED**
ASCO = American Society of Clinical Oncology; CHAARTED = Chemo hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer	

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Section 2: Endorsement Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR GUIDELINE

There is currently no established guideline, specific to Ontario, in this area; other jurisdictions are reviewing the evidence for management of noncastrate advanced, recurrent, or metastatic prostate cancer. It is of interest to our clinicians such that we can alter our care if the evidence supports it.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Initial Management of Prostate Cancer Guideline Development Group (GDG), which was convened at the request of the Ontario Genitourinary (GU) Cancers Advisory Committee (CAC). The project was led by a small Working Group of the GDG, which was responsible for reviewing the evidence base and recommendations in the "Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update" [1] in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in urology and surgery. Other members of the Initial Management of Prostate Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

ENDORSEMENT METHODS

The PEBC endorses guidelines using the process outlined in the OH (CCO) Guideline Endorsement Protocol [16]. This process includes selection of a guideline, assessment of the recommendations (if applicable), drafting the endorsement document by the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC assesses the quality of guidelines using the AGREE II tool [17]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations may be provided along with the recommendations for information purposes.

Selection of Guidelines

The Ontario GU CAC reviewed the ASCO evidence-based guideline on the initial management of noncastrate advanced, recurrent, or metastatic prostate cancer and accepted it as potentially useful and relevant to guide practice in Ontario.

Assessment of Guideline(s)

Details of the AGREE II assessment can be found in Appendix 2. The overall quality of the guideline was rated as "6" by one appraiser and "7" by the other (on a scale from 1 to 7). Both appraisers stated that they would recommend this guideline for use. The AGREE II quality ratings for the individual domains were varied; they were assessed at 97% for scope and purpose, 86% for stakeholder involvement, 89% for rigour of development, 89% for clarity of presentation, 92% for applicability, and 92% for editorial independence.

DESCRIPTION OF ENDORSED GUIDELINE(S)

The ASCO guideline updates all preceding ASCO guidelines on the initial management of noncastrate advanced, recurrent, or metastatic prostate cancer. The guideline addressed four clinical questions on the optimal evidence-based treatments for men with noncastrate advanced, recurrent, or metastatic prostate cancer. The authors based all recommendations on a systematic review of the literature and all recommendations were approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee. The recommendations were informed by four clinical practice guidelines, one clinical practice guidelines endorsement, 19 systematic reviews with or without meta-analyses, 47 phase III randomized controlled trials, nine cohort studies, and two review papers [1].

ENDORSEMENT PROCESS

The Working Group assessed the 2021 ASCO Guideline in detail and reviewed each recommendation of the guideline to determine whether it could be endorsed, endorsed with modifications, or rejected (not endorsed). There are 15 recommendations based on four research questions. The Working Group considered the following issues for each of the recommendations:

1) Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2) Are modifications required to align with the Ontario context?
3) Is it likely there is new, unidentified evidence that would call into question the recommendation?
4) Are statements of qualification/clarification to the recommendation required?

ENDORSEMENT REVIEW AND APPROVAL

Internal Review

For the endorsement document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. The Expert Panel may specify that approval is conditional, and that changes to the document are required (see Section 3 for results of the internal review).

External Review

Feedback on the approved draft endorsement document is obtained from content experts through Professional Consultation. Relevant care providers and other potential users of

the endorsement document are contacted and asked to provide feedback on the recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners (see Section 3 for results of the external review).

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the OH (CCO) website. The Professional Consultation of the External Review is intended to facilitate the dissemination of the endorsement document to Ontario practitioners. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

UPDATING THE ENDORSEMENT

OH (CCO)/PEBC will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ENDORSEMENT and MODIFICATIONS

Thirteen of the 15 Recommendations were endorsed without modifications or comments. Two recommendations (R2.1, R2.2) were not endorsed (with explanation) as listed in Table 2-1 (see Table 1-1 for a complete list of recommendations).

Table 2-1: Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

Recommendations (see Virgo et al., 2021 [1] for complete recommendations)	Assessment
R 2.1. ADT plus abiraterone and prednisolone should be considered for men with noncastrate locally advanced nonmetastatic prostate cancer, rather than castration monotherapy, because of the failure-free survival benefit per STAMPEDE [5]. RT to the primary was mandated in STAMPEDE [5] for patients with newly diagnosed node-negative, nonmetastatic disease and encouraged in patients with newly diagnosed node-positive, nonmetastatic disease. Failure-free survival (time to the earliest of biochemical failure, disease progression, or death) was significantly improved for patients with nonmetastatic disease treated with ADT plus abiraterone and prednisolone compared with those treated with ADT alone, although ADT plus abiraterone was administered for two or less years to men with nonmetastatic disease. **Explanation:** In the STAMPEDE trial [5], for patients with nonmetastatic disease, there was no significant survival difference between groups treated with ADT plus abiraterone versus ADT alone (hazard ratio, 0.75; 95% confidence interval, 0.48 to 1.18). The nonmetastatic group in this trial was a subgroup of a secondary outcome and consisted of both radiated and non-radiated patients. While there may be benefit to addition of abiraterone to castration in cN0 patients, we believe the level of evidence is overestimated and the balance of benefit to harm is not defined. The rationale and evidence for abiraterone, enzalutamide, or apalutamide in cN1 patients is stronger based on LATITUDE [4], ENZAMET [6], and TITAN [7] trials.	**Not ENDORSED (with explanation)**
R 2.2. In resource-constrained settings where drugs such as abiraterone may not be available, combined androgen blockade using ADT plus a first-generation antiandrogen, such as flutamide, nilutamide, or bicalutamide, may be offered to men with locally advanced nonmetastatic prostate cancer, rather than castration monotherapy based on recent meta-analyses. **Explanation:**	**Not ENDORSED (with explanation)**

Table 2-1: Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

Although locally advanced, non-metastatic patients were included in one [8] of the two [9] meta-analyses, outcomes for this group of patients were not explicitly studied or reported in subgroup analyses. As a result, data to support this recommendation are lacking.	
ASCO = American Society of Clinical Oncology	

ACKNOWLEDGEMENTS

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- Jonathan Sussman and Sheila McNair for providing feedback on draft versions.
- Sara Miller for copyediting

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Section 3: Internal and External Review

INTERNAL REVIEW

The endorsement was evaluated by the GDG Expert Panel (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Following the formulation of the first draft, the recommendation endorsement was reviewed by the Director and Assistant Director of the PEBC and the Working Group was responsible for ensuring the necessary changes were made. An Expert Panel of clinical content experts (members of the GU community) reviewed the draft endorsement document, provided feedback, and approved the final version (See Appendix 1 for a list of Expert Panel members and conflict of interest declarations).

Of the nine members of the GDG Expert Panel, eight members voted, for a total of 89% response in July 2021. Of those eight who voted, six approved the document (75%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 3-1.

Table 3-1. Summary of the Working Group's responses to comments from the Expert Panel

Comments	Responses
I disagree with the decision to not endorse question 2.1. I agree that the original endorsement was based on intermediate outcomes, but a 79% benefit in failure-free survival with a hazard ratio of 0.21 is an impressive difference. There so far have been very few overall survival events in this group and it will be years before it will be possible to determine the magnitude of any overall survival advantage. Given the known survival benefits of adding ADT to RT for locally advanced non-metastatic disease, and with adding abiraterone+prednisone to ADT and RT for nodal metastatic disease, it is not much of a leap to expect a survival advantage to eventually follow this impressive failure-free survival benefit. I think the authors are being overly rigid in their interpretation of the data. Otherwise, I agree with their recommendations.	We do not agree with the argument to endorse 2.1. The phrase "it is not much of a leap to expect a survival advantage to eventually follow" speaks for itself and is not supported by the evidence supporting Recommendation 2.1.
Overall, the document is fine, but I have the following important caveats. In particular, I would not approve unless point 1, below, is adopted. Recommendation 2.2 states '*R 2.2*. In resource-constrained settings where drugs such as abiraterone may not be available, combined	We have no issue with using the suggested phrasing for bicalutamide; then if not available, the others. For the reviewer's second point, our goal is to determine whether to approve or not approve the

androgen blockade using ADT plus a first-generation antiandrogen, such as flutamide, nilutamide, or bicalutamide'. These three anti-androgens should not be described as equivalent. Bicalutamide has fewer side effects, is dosed 1/day, and is a more effective anti-androgen based on a randomized phase III study showing a mortality benefit (Akaza H, Hinotsu S, Usami M, Arai Y, Kanetake H, Naito S, Hirao Y; Study Group for the Combined Androgen Blockade Therapy of Prostate Cancer. Cancer Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. 2009 Aug 1;115(15):3437-45) and several other publications (Klotz L, Schellhammer P. Combined androgen blockade: the case for bicalutamide. Clin Prostate Cancer. 2005 Mar;3(4):215-9) There is a reason why bicalutamide is used in lieu of the other two drugs by almost all clinicians. In my opinion it is the second-generation antiandrogen, and should not be lumped with the earlier two drugs. Regardless, I would suggest the wording be changed to '…..ADT plus bicalutamide, or if this is not available, the earlier first-generation antiandrogens, such as flutamide, nilutamide' There is a major unmet need to provide guidance about sequencing of the androgen receptor-axis-targeted therapies. The guideline does not do this. Based on recent data including the Canadian-led study from Khalaf DJ et al. *Lancet Oncol*. 2019;20:1730-9, the guideline should indicate that evidence suggests abiraterone before enzalutamide provides a more prolonged time to progression than enzalutamide before abiraterone.	guideline, not to add to it. Thus, this point on sequencing is out of scope.
Re: R 1.2 I am not sure we should be so definitive about low-volume metastatic castration-sensitive prostate cancer and docetaxel. STAMPEDE showed a benefit for docetaxel even in the low-volume patients 10.1093/annonc/mdz396 The comment in the ASCO guidelines that the analysis in STAMPEDE was not powered to show a difference is confusing because that would be an argument if the STAMPEDE analysis, did not show a difference, but it did. Meaning that there is some effect present here and it was detected. This I would err on the saying there is lack of consensus and decisions could be made on a case-by-case basis…if that is possible to do in these guidelines.	As far as sequencing androgen receptor-axis-targeted therapies, I don't think we can ADD to the guideline during the endorsement process. For that to be the case, we would have to go through the systematic review process, etc. I think we can leave 1.2 alone.

Overall, the piece is well written and I fully endorse the content. The tables are potentially overwhelming for the less-experienced reader seeking guidance. Suggest a bit more user-friendly formatting geared to indicate how the table is organised. For example, in row 3 of the first page, I suggest replacing "ADT plus Doxetaxel" with "Standard of Care 1: ADT plus Doxetaxel (in bold font)" and so on. Patient selection is critical for application of the recommendations. Therefore, I find cross-referencing eligibility criteria and definitions (MVD, LVD) to the RCT of interest too cryptic for a summary table (i.e., this strategy forces the reader to pull up additional documentation to understand the patient context/apply the recommendations). Would recommend a footnote after "as defined per CHAARTED" and elsewhere (e.g., LATITUDE) then add an additional row to the end of the section with the footnote summarizing the definitions. Or an alternative strategy that embeds the definitions into the summary table in some other way.	We have incorporated these stylistic edits into the document, where feasible.

EXTERNAL REVIEW

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the endorsement document. All urologists and GU oncologists in the PEBC database were contacted by email to inform them of the survey (n=90). Thirteen (14.4%) responses were received. Four stated that they did not have interest in this area or were unavailable to review this endorsement document at the time. The results of the feedback survey from 13 clinicans are summarized in Table 3-2. The main comments from the consultation and the Working Group's responses are summarized in Table 3-3.

Table 3-2. Responses to four items on the professional consultation survey.

	13 (14.4%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				5	8
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1	3	9
3. I would recommend this guideline for use in practice.				2	11
4. What are the barriers or enablers to the implementation of this guideline report?	• Barriers and enablers both have to do with the willingness of the treating physician to prescribe these medications. The guideline is clear however if a physician is reluctant to				

	prescribe these agents because of concerns over side effects and drug, drug interactions, they will not use the guideline. In and of itself the guideline is clear and straightforward in its recommendations. It will serve as a good tool for those interested in treating. • Funding • Drug access situation is complex and changing. The noncastrate metastatic prostate cancer field is rapidly evolving. The different treatments available these days might be overwhelming for heath care providers only seeing limited number of patients. • None identified once funding arrangements in place • The recommendations are specific and unambiguous. The different options for management are clearly presented. • Enablers: Clearly written. Clinically relevant questions. Barriers: Presentation could include a decision flowchart, which many physicians are accustomed to using. • Possibly in an isolated area with no access to the Internet and low laboratory access would be a barrier but this is almost easily discredited. Then, provided that the clinician does have access to the various medications, the report could be easily implemented • Accessibility • None

Table 3-3. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. No additional comments Well done	No response needed
2. No additional comments Well done	No response needed
3. I feel that this is a very thorough report and should be adopted.	No response needed

CONCLUSION

The final endorsed recommendation contained in Section 1 reflect the integration of feedback obtained through the internal and external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table 1: Members of the Initial Management of Prostate Cancer Guideline Development Group

Name	Affiliation	Conflict of Interest
Working Group		
Judy Brown	Health Research Methodologist McMaster University, Department of Oncology, Program in Evidence-Based Care, Hamilton, ON	None declared
Girish Kulkarni	Department of Surgery University of Toronto Toronto, ON	See below [a]
Chris Morash	Department of Surgery University of Ottawa Ottawa, ON	None declared
Rodney Breau	Department of Surgery, University of Ottawa Ottawa, ON	None declared
Expert Panel and Members of the Guideline Development Group		
Michael Brundage	Queens University School of Medicine, Department of Oncology	None declared
Christina Canil	The Ottawa Hospital Cancer Centre Ottawa ON	See below [b]
Charles Catton	Princess Margaret Cancer Centre 610 University Avenue Toronto, ON	See below [c]
Joseph Chin	London Health Sciences Centre, Victoria Hospital London, Ontario,	None declared
Raj Goel	Windsor Regional Hospital Department of Urology Windsor ON	See below [d]
Aaron Hansen	UHN Princess Margaret Cancer Centre Division of Medical Oncology & Hematology Toronto ON	None declared
Laurence Klotz	Sunnybrook Health Sciences Centre Toronto, ON	See below [e]
Jason Izard	Kingston Health Sciences Centre Department of Urology Kingston, ON	See below [f]
Andrew Loblaw	Sunnybrook Health Sciences Centre Toronto, ON	See below [g]

[a] Received $500 or more in a single year to act in a consulting capacity from Janssen, Astellas, Bayer, Ferring, Abbvie, TerSera, Theralase, Sanofi, Merck, Roche, Knight Therapeutics, Biosyent (honoraria for above listed companies would add to more than $1,000). Grant received from Biosyent.

[b] Advisory Board - Sanofi-Genzyme, Pfizer, Eisai, Merck, EMD Serono, Novartis, Bayer, BMS, Astra Zeneca, Ipsen, Roche, Amgen, Ferring, Seattle Genetics Speaker at educational event - Bayer, Janssen, Astellas, Pfizer. Member of national genitourinary research consortium - Janssen
Member of medical advisory board - Kidney Cancer Canada (volunteer); Conference Travel - Sanofi-Genzyme, Amgen, Janssen, Pfizer; Local PI: Eisai, Janssen, Pfizer, Hoffman-La Roce, GSK (Funds to institution) Local Co-PI: Clovis, Astra Zeneca, Bayer; Member of the CCO GU Drug Advisory Committee
[c] Advisory boards for Abbvie, Astellas, Bayer, Knight
[d] Speaker honoraria for companies; observational research conducted using hormonal therapy in advanced prostate cancer
[e] Stock ownership Myovant; Investigator on the Prosper study (Apalutamide); Editorial on the Titan study, NEJM, 2020.
[f] Consulting fees for Janssen, Astellas, Bayer, Sanofi and AbbVie; Conference support travel from Janssen, Sanofi and Bayer; Co-investigator in the following clinical trials:
1.EMBARK Trial - A Phase III, Randomized, Efficacy and Safety Study of Enzalutamide Plus Leuprolide, Enzalutamide Monotherapy, and Placebo Plus Leuprolide in Men with High-Risk Non-Metastatic Prostate Cancer Progressing After Definitive Therapy
2.TITAN Trial - A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects With Metastatic Hormone-sensitive Prostate Cancer (mHSPC)
3.ARCHES Trial - A Multinational, Phase 3, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus ADT in Patients With Metastatic Hormone Sensitive Prostate Cancer (mHSPC)
4.ARAMIS Trial - A Multinational, Randomised, Double-blind, Placebo-controlled, Phase III Efficacy and Safety Study of Darolutamide (ODM-201) in Men With High-risk Non-metastatic Castration-resistant Prostate Cancer;
Principal Investigator for: Real time MRI fused to cone beam CT guided biopsies of the prostate: The safety and feasibility of a novel method of prostate biopsy (NCT04180592). Funded through Prostate Cancer Fight Foundation; Robinson AG, Izard JP, Vera-Badillo FE. Treatment and Patient Selection for Patients with Metastatic Castration-resistant Prostate After Progression on Docetaxel and Abiraterone/Enzalutamide: When to Play Your CARD and When to Do Your PARP. Eur Urol. 2021 Mar 25:S0302-2838(21)00172-X. doi: 10.1016/j.eururo.2021.03.001. Epub ahead of print. PMID: 33773874.
[g] Partner works for Genzyme; Consulting for AbbVie, Astellas, Bayer, Janssen, Sanofi, TerSera; Other finacial or material support for AbbVie, Astellas, Janssen, Sanofi, TerSera; Combined financial interests above 1,000; Provide adice or guidance to multiple news agencies about prostate cancer treatment and side effects; Had managerial responsibility for an organization or department that has received $5,000 or more in a single year (AbbVie, TerSera fellowship support to Sunnybrook; TerSera funding for trial to Prostate Cure Foundation) (I'm Director)

Appendix 2: Agree II Score Sheet

Domain	Item	AGREE II Appraiser Ratings[1]	
		1	2
1) Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	7
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	6	7
Domain score[2] - (41-6/42-6)*100 = 35/36 *100 = .9722 *100 = **97.2%**		Score 41	
2) Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	6	5
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	6
	6. The target users of the guideline are clearly defined.	7	7
Domain score[2] - (37-6/42-6)*100 = 31/36 *100 = .8611*100 = **86.1%**		Score 37	
3) Rigour of development	7. Systematic methods were used to search for evidence.	6	7
	8. The criteria for selecting the evidence are clearly described.	6	7
	9. The strengths and limitations of the body of evidence are clearly described.	6	5
	10. The methods for formulating the recommendations are clearly described.	6	7
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	5	7
	12. There is an explicit link between the recommendations and the supporting evidence.	6	7
	13. The guideline has been externally reviewed by experts prior to its publication.	7	7
	14. A procedure for updating the guideline is provided.	6	6
Domain score[2] - (101-16/112-16)*100 = 85/96 *100 = .8888 *100 = **88.8%**		Score 101	
4) Clarity of presentation	15. The recommendations are specific and unambiguous.	6	7
	16. The different options for management of the condition or health issue are clearly presented.	5	7
	17. Key recommendations are easily identifiable.	6	7
Domain score[2] - (38-6/42-6)*100 = 32/36 *100 = .8888 *100 = **88.9%**		Score 38	
5) Applicability	18. The guideline describes facilitators and barriers to its application.	5	6
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	5	6
	20. The potential resource implications of applying the recommendations have been considered.	5	6
	21. The guideline presents monitoring and/ or auditing criteria.	4	6
Domain Score[2] - (43-8/56-8)*100 =35/48 *100 = .9210 *100 = **92.1%**		Score 43	

Domain	Item	AGREE II Appraiser Ratings[1]	
		1	2
6) **Editorial independence**	22. The views of the funding body have not influenced the content of the guideline.	6	7
	23. Competing interests of guideline development group members have been recorded and addressed.	6	7
Domain Score[2] - (26-4/28-4)*100 = 22/24 *100 = .9167 *100 = **91.7%**		Score 26	
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**6**	**7**
Overall Guideline Assessment	2. I would recommend this guideline for use.	**Yes**	**Yes**

[1] Rated on a scale from 1 to 7, [2] Domain score = (Obtained score – Minimum possible score)/(Maximum possible score – Minimum possible score)