Ontario Health
Cancer Care Ontario

Guideline Endorsement 3-25

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

Ontario Health (Cancer Care Ontario) Endorsement of ASCO Rapid Recommendation on 177Lutetium-Prostate-Specific Membrane Antigen-617 (PSMA-617) for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Report Date: November 10, 2023

This document describes the Ontario Health (Cancer Care Ontario)-Genitourinary Disease Site Group endorsement of the **2022 Systemic Therapy Update on ^{177}Lutetium-Prostate-Specific-Membrane Antigen-617 (PSMA-617) for Metastatic Castration-Resistant Prostate Cancer: ASCO Rapid Recommendation.** The original publication is available at https://ascopubs.org/doi/abs/10.1200/JCO.22.01865?role=tab

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Section 1: Guideline Endorsement

GUIDELINE OBJECTIVES

The objectives of this guideline are to provide guidance for the most contemporary management for men with metastatic castration-resistant prostate cancer (mCRPC) and optimize treatment.

TARGET POPULATION

Patients with prostate cancer who are eligible for treatment with ^{177}Lutetium-prostate-specific membrane antigen-617 (^{177}Lutetium-PSMA-617).

INTENDED USERS

This guideline is targeted for clinicians involved in the care of patients with prostate cancer who are eligible for treatment with ^{177}Lutetium-PSMA-617.

ENDORSEMENT

The Genitourinary Disease Site Group of Ontario Health (Cancer Care Ontario) endorses two of the three recommendations of Systemic Therapy Update on ^{177}Lutetium-PSMA-617 for mCRPC, published by the American Society of Clinical Oncology (ASCO) [1], available at https://ascopubs.org/doi/abs/10.1200/JCO.22.01865?role=tab.

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1. The panel recommends the use of ^{177}Lu-PSMA-617 IV once every six weeks for four to six cycles as a treatment option in patients with PSMA positron emission tomography (PET)/computed tomography-positive mCRPC who have progressed on one prior line of androgen receptor pathway inhibitor and at least one line of prior chemotherapy (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong)

2. The panel recommends that patients should be selected with PSMA PET (Type: Evidence-based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).

3. The third recommendation (either Ga-68 PSMA-11 or F-18 piflufolastat be used as radiotracers to determine eligibility currently) was not endorsed by the Working Group because of practical considerations of available evidence. The evidence supporting this topic area is rapidly changing. Although Ga-68 PSMA-11 was the radiopharmaceutical used in the VISION trial [2], the Working Group recognizes that other PSMA targeted radiopharmaceuticals are being used effectively to select patients for PSMA targeted therapy and believes that more will be made available on this topic in the future.

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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

Prostate cancer is the third most common cancer and the fifth leading cause of death due to cancer in Canada [3]. The 2023 Canadian cancer estimates projects that approximately 21% of men will develop prostate cancer and 10% will die in 2023. Although prostate cancer is less aggressive than other cancers, approximately 30% of prostate cancer cases are/or become advanced [4]. In the metastatic incurable stage, prostate cancer can be castration resistant or non-castration resistant. mCRPC has a high expression of PSMA. Since ^{177}Lutetium-PSMA-617, a radioligand therapy, is indicated for the treatment of adults with PSMA-positive mCRPC, a guideline specific to Ontario clinicians involved in the care of patients with prostate cancer is needed. Therefore, the objective of this document is to provide the most contemporary management strategy for men in Ontario with mCRPC by endorsing the ASCO rapid recommendations on Systemic Therapy Update on ^{177}Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer [1].

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the ^{177}Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer Guideline Development Group (GDG), which was convened at the request of the Genitourinary Disease Site Group (GU DSG). The project was led by a small Working Group responsible for reviewing the evidence base and recommendations in the selected guidance document 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 radiation oncology, medical oncology, urologic oncology, nuclear medicine, and health research methodology. Other members of the 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 OH (CCO)'s Guideline Endorsement Protocol [5]. This process includes selection of a guideline, assessment of the recommendations, 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 [6,7]. 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. The AGREE II assessment is summarized in Appendix 2

Selection and Assessment of Guidelines

The ASCO guideline was identified for endorsement by the GU DSG based on the relevance of the topic and the AGREE II assessment result. A search for existing guidelines was undertaken on June 16, 2023, with the search term(s), '^{177}Lutetium AND metastatic castration-resistant prostate cancer' to determine whether any other guideline could be endorsed. The following sources were searched: Canadian Urological Association (CUA), National Institute for Health and Care Excellence (NICE) Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, ASCO, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki, MEDLINE and EMBASE. In addition to the already identified ASCO guideline, two existing guidelines from the Canadian Uro-Oncology Group and European Society for Medical Oncology were found [8,9]. One guideline from NICE is currently under development with expected publication date of November 2023.

DESCRIPTION OF ENDORSED GUIDELINE(S)

The 2022 rapid recommendation on ^{177}Lutetium-PSMA-617 was an update of the 2014 ASCO guideline on systemic therapy in men with mCRPC. This update was necessitated by the US Food and Drug Administration approval of the ^{177}Lutetium-PSMA-617 for the treatment of patients with PSMA-positive mCRPC in 2022. A targeted search for evidence identified five randomized controlled trials and five prospective studies with very low to moderate quality of evidence. Three recommendations were made by a panel of experts based on the available evidence. In accordance with the ASCO Conflict of Interest Policy, most of the experts declared no conflict.

ENDORSEMENT PROCESS

The Working Group reviewed **the** 2022 Systemic Therapy Update on ^{177}Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer [1] in detail and reviewed each recommendation of that guideline to determine whether it could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group with the interpretation of the available evidence presented in the guideline, and whether the recommendation was applicable and acceptable to the Ontario context, whether it was feasible for implementation, and whether new evidence reported since the guideline was developed might change any of the recommendations.

ENDORSEMENT REVIEW AND APPROVAL

Internal and External Reviews

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 voted, 75% must approve the document. The Expert Panel may specify that approval is conditional pending incorporation of suggested modifications.

For 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. However, this Endorsement project did not undergo external review because the Working Group agrees that ASCO external review processes was comprehensive enough.

Expert Panel Review and Approval

Prior to the review of the draft document, 24 members of the GU-DSG provided their conflict of interest declaration. Of the 24 members, 20 (83%) members voted in September 2023, and four did not respond. Among the 20 that voted, 18 (90%) approved the document and two gave conditional approval. The main comments from the Expert Panel and the Working Group responses are summarized in Table 2-1.

Table 2-1. Summary of the Working Group's responses to comments from the Expert Panel.

Expert panel Comments	Working Group Responses
1. Other important points in patient selection that need to be addressed are the correlates of PSMA avidity of the disease and discordant disease (fluorodeoxyglucose positive/PSMA negative or anatomically non-PSMA-avid disease)	We acknowledge that correlates such as PSMA avidity of the disease play a role in patient selection and likelihood of response but at this point we do not have sufficient data to specifically comment on the avidity outside of what has been reported in the studies.

2. Why does the wording not endorse Ga-68 PSMA-11 in the selection of patients but acknowledge that other tracers (PyL or 1007) would be acceptable PSMA tracers for radioligand therapy? 3. If the sentence were changed to "Gallium or fluorinated-based PSMA radiotracers to determine eligibility (evidence quality: low)" that would better reflect the variability of tracer use in the Ontario context and also the consensus guidelines that generally regard them to be all acceptable for clinical use. 4. I would hope that any recommendations on tracer selection be phrased to increase flexibility in adopting agents rather than limiting choices at the outset.	All PSMA targeted PET radiotracers are considered useful for patient selection prior to PSMA targeted therapy, until the availability of strong evidence that shows otherwise. Given there are variabilities in terms of accessibility, and with approvals currently underway, a broad approach to accessibility of any PSMA tracer is supported. However, differences in radiotracers biodistribution require due diligence be taken to ensure correct image interpretation and patient selection criteria.

DISSEMINATION AND IMPLEMENTATION

The endorsement document will be published on the OH (CCO) website. 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. Implementation of guidelines developed by the PEBC may be undertaken by GU-DSG.

UPDATING THE ENDORSEMENT

This Endorsement is valid until November 2026 or at which time the CCO GU-DSG will review the endorsement and determine if a new version of the endorsed guideline has been released. The GU-DSG may begin the update process before November 2026 if the PEBC annual assessment of this document identifies a need for immediate update.

ACKNOWLEDGEMENTS

The the ^{177}Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- Jonathan Sussman, Sheila MacNair for reviewing the drafts.
- Sara Miller for copyediting.

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Appendix 1: Members of the ^{177}Lutetium-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer Guideline Development Group

Name	**Affiliation**	**Conflict of Interest** Declaration[1]
Working Group		
Katherine Zukotynski	Hamilton Health Sciences	• President of the American College of Nuclear Medicine • Received honorarium from Fusion pharmaceuticals for consultation role. • Received honorarium from Novartis for speaker and advisory board roles. • Co-PI for PATRON clinical trial. • Contributed to the CADTH clinical narrative review for ^{177}Lu-PSMA.
Chika Arinze	McMaster University	None declared.
Kulkarni, Girish	University Health Network	• Program Director for the University of Toronto Urologic Oncology Fellowship program.
Sebastien Hotte	Hamilton Health Sciences	• Received honorarium from AAA/Novartis for consultation/advisory board role. • Received grant from AAA/Novartis for clinical trial funding (all funds to the institution).
Loblaw, Andrew	Sunnybrook Health Sciences Centre	None declared.
Expert Panel Member		
Alejandro Berlin	University Health Network	None declared.
Aly-Khan Lalani	Hamilton Health Sciences	• Received honorarium for consultation or advisory board role in more than one company. • Received grant for clinical trial funding (all funds to the institution) from more than one company. • Member of CCO GU DAC.
Andrew Feifer	Credit Valley Hospital	• Received Astellas educational grant for prostate cancer research. • PI for Janssen COSMIC study.
Antonio Finelli	University Health Network	None declared.
Anupam Batra	Grand River Hospital	• Received honorarium for consultation/advisory board role in more than one company.

[1] Some expert panel members have participated in various roles in more than one of the following companies: AbbVie, Amgen, Astellas, Astra Zeneca, Bayer, BMS, Clovis, Eisai, EMD Serono, IPSEN, Janssen, Knights Pharmaceutics, McKesson, Medison, Merck, NEED Inc, Novartis (AAA), Pfizer, POINT Biopharma Inc, Roche-Genentech, Tersera.

		• Received grant for clinical trial funding (all funds to the institution) from different companies.
Bobby Shayegan	McMaster University	• A co-Chair of national advisory board for AAA/Novartis and was on the Ontario advisory board prior to the national role.
Charles Catton	University Health Network	None declared.
Chris Morash	The Ottawa Hospital	• Received honorarium from AAA for advisory board role.
Christina Canil	The Ottawa Hospital	None declared.
Danny Vesprini	Sunnybrook Health Sciences	None declared.
David Laidley	St Joseph's Hospital	None declared.
Di Maria Jiang	University Health Network	• Received honorarium from different companies for consultation/advisory board role, travel support and speaker fees. • Received unrestricted educational grants from Amgen, Tersera, and Astellas • Site PI for the following trials: SPLASH, Capitello 281/280, JNJ-70218902, KEYNOTE-921, PC-BETS, PR21, ETCTN 10183.
Dominick Bosse	The Ottawa Hospital	• Received honorarium from different companies for consultation/advisory board role, travel support, and speaking fees.
Eugene Leung	Ottawa Civic Hospital	• Received honorarium from different companies for consultation/advisory board role.
Glenn Bauman	London Health Sciences Centre	• Participated in advisory boards role with AAA/Novartis • Has been a principal investigator for CCTG-PR21 study and received grants or other research support from OICR, CIHR. • Has publications on relevant topic and contributed to the CADTH clinical narrative review for ^{177}Lu-PSMA.
Jack Barkin	Humber River Regional Hospital	• Has shares in a relevant business.
John Srigley	Credit Valley Hospital	None declared.
Jonathan Romsa	London Health Sciences Centre	None declared.
Joseph Chin	London Health Sciences Centre	None declared.
Patrick Viet-Haibach	University Health Network	• Deputy Radiologist-in-Chief and Division Head for JDMI - Abdominal Imaging • Received editorial and speaker fees, from different organizations. • Received honorarium and travel support from German Cancer Center Centre for strategic panel advisory role.

		• Received grants from Siemens Healthineers.
Rodney Breau	The Ottawa Hospital	• Received honorarium from AAA/Novartis for consultation/advisory board role.
Scott Morgan	Ottawa Hospital Cancer Centre	• Received honorarium for consultation/advisory board role. • Received research grant as the PI from Knight Therapeutics to support a trial of radiotherapy in localized prostate cancer (all funds to institution)
Ur Metser	University Health Network	• Received grant as a PI and honorarium from POINT Biopharma for consultation. • Served as advisory panel member for PSMA PET in patient selection for ^{177}Lu-PSMA therapy and contributed to the CADTH clinical narrative review for ^{177}Lu-PSMA.
Urban Emmenegger	Sunnybrook Health Sciences Centre	• Received grant from different companies for the conduct of clinical trials (all funds to the institution) and honorarium for consultation/advisory board. • Has been a PI for VISION-PSMAddition.

Abbreviations: AAA: Advanced Accelerator Applications; CADTH: Canadian Agency for Drugs and Technologies in Health; CCO: Cancer Care Ontario; CIHR: Canadian Institutes of Health Research; DAC: Docetaxel-Doxorubicin-Cyclophosphamide; GU: Genitourinary; JDMI: Joint Department of Medical Imaging; OICR: Ontario Institute for Cancer Research; PI: Principal investigator.

Appendix 2: AGREE II Score Sheet

Domain	Item	AGREE II Rating		
		Appraiser 1	Appraiser 2	Domain Score
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	6	7	78%
	2. The health question(s) covered by the guideline is (are) specifically described.	3	7	
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	6	5	
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	5	5	36%
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	1	1	
	6. The target users of the guideline are clearly defined.	3	4	
Rigor of development	7. Systematic methods were used to search for evidence.	5	6	87%
	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	7	
	10. The methods for formulating the recommendations are clearly described.	4	5	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	6	7	
	12. There is an explicit link between the recommendations and the supporting evidence.	7	7	
	13. The guideline has been externally reviewed by experts prior to its publication.	6	6	
	14. A procedure for updating the guideline is provided.	7	7	
Clarity of presentation	15. The recommendations are specific and unambiguous.	7	7	100%
	16. The different options for management of the condition or health issue are clearly presented.	7	7	
	17. Key recommendations are easily identifiable.	7	7	
Applicability	18. The guideline describes facilitators and barriers to its application.	1	1	8%
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	1	1	
	20. The potential resource implications of applying the recommendations have been considered.	1	1	
	21. The guideline presents monitoring and/ or auditing criteria.	2	4	

Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	4	5	79%
	23. Competing interests of guideline development group members have been recorded and addressed.	7	7	
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**6**	**6**	**83%**
Overall Guideline Assessment	2. I would recommend this guideline for use.	*Yes*	*Yes*	

Overall Score

(Obtained score – Minimum possible score)
(Maximum possible score – Minimum possible score)

(243-46) / (322-46) = 0.713 X 100 = 71%