Ontario Health
Cancer Care Ontario

Guideline Endorsement 3-24 REQUIRES UPDATING

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

Systemic Therapy for Metastatic Urothelial Cancer: An Endorsement of a Portion of the European Association of Urology Guideline on Muscle-Invasive and Metastatic Bladder Cancer

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This publication is a OH (CCO) Systemic Therapy for Metastatic Urothelial Cancer Guideline Development Group Endorsement of the 2021 European Association of Urology Guideline on muscle-invasive and metastatic bladder cancer The original publication is available at:
https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/

An assessment conducted in January 2025 indicated that Guideline 3-24 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/72401

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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 systemic therapy for metastatic urothelial cancer. Our recommendations are based on a portion of the 2021 European Association of Urology (EAU) guideline on Muscle-Invasive and Metastatic Bladder Cancer https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/.

TARGET POPULATION

The target population is patients with metastatic urothelial cancer.

INTENDED USERS

The intended users of this guideline are clinicians involved in the care of patients with metastatic urothelial cancer.

ENDORSEMENT

Six recommendations in the EAU guideline specific to systemic therapy for metastatic urothelial cancer are in Section 7.7 of the Muscle-invasive and Metastatic Bladder Cancer guideline. The Systemic Therapy for Metastatic Urothelial Cancer Guideline Development Group (GDG) of Ontario Health (Cancer Care Ontario) endorses five of the six recommendations in Section 7.7. They were reprinted with the permission of the EAU Guidelines Office.

Two of the six recommendations (7.7.1, 7.7.3) are endorsed as is and three are endorsed with comments (7.7.2, 7.7.4, 7.7.5) using the endorsement process described in this document. One recommendation is not endorsed (7.7.6). A summary is listed in Table 1-1.

Table 1-1. Portion of the European Association of Urology Guideline on Muscle-Invasive and Metastatic Bladder Cancer (Section 7.7 – recommendations specific to systemic therapy for metastatic urothelial cancer)

Recommendations	Assessment
First-line treatment for platinum-fit patients	
7.7.1 Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	**Endorsed**
7.7.2 In patients unfit for cisplatin but fit for carboplatin use the combination of carboplatin and gemcitabine. **Comments** Although some uncertainty and controversy exists to define the cisplatin-"unfit" patient, we choose to define this population according to the Galsky criteria [2] which has been further stratified based on the EAU flowchart (Figure 7.2) whereby platinum-ineligible patients consist of one of the following: 1. PS 2 AND GFR <60 mL/min 2. PS >2 3. GFR <30 mL/min 4. Grade 2 or above audiometric hearing loss 5. Grade 2 or above peripheral neuropathy 6. NYHA class III heart failure	**Endorsed**

The authors note in suitable patients with creatinine clearance from 50-59, providers may offer split dosing of cisplatin (35 mg/m^2 on day 1 and day 8) or eGFR, allowing more patients the opportunity to receive this combination. Regarding second-line therapies, erdafitinib in patients who are FGFR positive in 2L setting post platinum is an acceptable treatment.	
7.7.3 In patients achieving stable disease, or better, after first-line platinum-based chemotherapy use maintenance treatment with PD-L1 inhibitor avelumab.	**Endorsed**
First-line treatment in patients unfit for platinum-based chemotherapy	
7.7.4 Consider checkpoint inhibitors pembrolizumab or atezolizumab. **Comments** We agree with the "weak" rating of this recommendation but one may consider pembrolizumab an option in patients who cannot receive chemotherapy based on single-arm studies [3,4], notwithstanding access/reimbursement limitations. Atezolizumab is no longer accessible for bladder cancer in this setting in Canada.	**Endorsed**
Second-line treatment	
7.7.5 Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease. If this is not possible, offer atezolizumab, nivolumab (EMA, FDA approved); avelumab or durvalumab (FDA approved). **Comments** In Canada, only pembrolizumab is approved, funded, and available in patients with metastatic urothelial carcinoma. As such, the second sentence is not applicable to the Canadian setting.	**Endorsed**
Further treatment after platinum- and immunotherapy	
7.7.6 Offer treatment in clinical trials testing novel antibody drug conjugates (enfortumab vedotin, sacituzumab govitecan); or in case of patients with FGFR3 alterations, FGFR tyrosine kinase inhibitors. **Comments** This recommendation is no longer up to date. Offering clinical trials is of the utmost priority and importance, but these should not be limited to investigation of ADC and/or FGFR inhibitors. Furthermore, we suggest considering EV in patients who have previously received chemotherapy and checkpoint inhibitors based on EV-301 [5], a phase 3 trial showing significantly prolonged survival compared to chemotherapy (median OS: 12.88 vs. 8.97 months; HR for death 0.70; 95% CI, 0.51 to 0.75; P<0.001) [5]. Lastly, we suggest consideration of erdafitinib in previously treated patients with locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations based on an objective tumour response in 40% in a recent phase 2 study leading to its approval by Health Canada [6].	**Not Endorsed**
ADC = antibody drug conjugates; CI = confidence interval; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; EV = enfortumab vedotin; FDA = United States Food and Drug Administration; FGFR = fibroblast growth factor receptor; GC = gemcitabine plus cisplatin; GFR = glomerular filtration rate; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; HR = hazard ratio; NYHA = New York Heart Association; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression free survival; PS = performance status	

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Section 2: Endorsement Methods Overview and Process

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 a contemporary EAU guideline that was recommended by the Genitourinary (GU) advisory committee as a product that should be considered for endorsement/adoption (2021 – Muscle-Invasive and Metastatic Bladder Cancer). We are primarily interested in Section 7.7 of the guideline, which focuses on systemic therapy for metastatic bladder cancer.

The following research question was considered when choosing the guideline: "what are the optimal systemic therapies for metastatic urothelial cancer" (interventions: systemic chemotherapy treatment; comparators: alternate systemic chemotherapy treatments)?

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Systemic Therapy for Metastatic Urothelial Cancer GDG, which was convened at the request of the Disease Pathway Management, GU Cancers Advisory Committee, and Systemic Treatment Program. The project was led by a small Working Group of the GDG, which was responsible for reviewing the evidence base and recommendations in the disease management portion focusing on systemic therapy for metastatic urothelial cancer (Section 7.7) of the EAU's "Muscle-Invasive and Metastatic Bladder Cancer" 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 have expertise in medical oncology. Other members of the Systemic Therapy for Metastatic Urothelial 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 OH (CCO)'s Guideline Endorsement Protocol [7]. This process includes selection of a guideline, assessment of the recommendations (if applicable), drafting the endorsement document by the Working Group, and internal and external review by content and methodology experts.

The PEBC assesses the quality of guidelines using the AGREE II tool [8]. 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 Disease Pathway Management, GU Cancers Advisory Committee, and the Systemic Treatment Program discovered a contemporary EAU guideline they deemed as high quality and recommended it as a product that should be considered for endorsement/adoption. The EAU evidence-based guideline on muscle-invasive and metastatic bladder cancer was later reviewed in detail and subsequently accepted as potentially useful and relevant to guide practice in Ontario and presented to the PEBC to be endorsed.

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 "5" by all three appraisers (on a scale from 1 to 7). Two of the three 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 30% for scope and purpose, 87% for stakeholder involvement, 62% for rigour of development, 72% for clarity of presentation, 29% for applicability, and 83% for editorial independence.

DESCRIPTION OF ENDORSED GUIDELINE(S)

The EAU originally published a guideline on bladder cancer in 2000 covering both non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). In 2004, the document was split into two and MIBC was given its own guideline. The 2021 version of the document is an update of a 2020 version.

The EAU guideline on muscle-invasive and metastatic bladder cancer covers the following areas: epidemiology, aretiology and pathology; staging and classification systems; diagnostic evaluation; markers; disease management; and follow-up.

Our focus was on the disease management section (Section 7) of the document, which contained the following eight topics: 1) neoadjuvant therapy; 2) pre-and post-operative radiotherapy in MIBC; 3) radical surgery and urinary diversion; 4) unresectable tumours; 5) bladder-sparing treatments for localised disease; 6) adjuvant therapy; 7) metastatic disease; and 8) quality of life. Since our original area of interest was systemic therapy for metastatic urothelial cancer, we focused on section 7.7 of the document focusing on metastatic disease.

ENDORSEMENT PROCESS

The Working Group assessed Section 7.7 of the 2021 EAU Guideline in detail and reviewed each recommendation to determine whether it could be endorsed, endorsed with modifications, or rejected. There are six recommendations in section 7.7 (metastatic disease) of the guideline. 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 and MODIFICATIONS

Six recommendations in the EAU guideline specific to systemic therapy for metastatic urothelial cancer are in Section 7.7 of the Muscle-invasive and Metastatic Bladder Cancer guideline. The Systemic Therapy for Metastatic Urothelial Cancer Guideline Development Group (GDG) of OH (CCO) endorses five of the six recommendations in Section 7.7. They were reprinted with the permission of the EAU Guidelines Office.

Two of the six recommendations (7.7.1, 7.7.3) are endorsed as is and three are endorsed with comments (7.7.2, 7.7.4, 7.7.5) using the endorsement process described in this document. One recommendation is not endorsed (7.7.6). A summary is listed in Table 2-1.

Table 2-1. Portion of the European Association of Urology Guideline on Muscle-Invasive and Metastatic Bladder Cancer (Section 7.7 – recommendations specific to systemic therapy for metastatic urothelial cancer)

Recommendations	Assessment
First-line treatment for platinum-fit patients	
7.7.1 Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	**Endorsed**
7.7.2 In patients unfit for cisplatin but fit for carboplatin use the combination of carboplatin and gemcitabine. **Comments** Although some uncertainty and controversy exists to define the cisplatin "unfit" patient, we choose to define this population according to the Galsky criteria [2] which has been further stratified based on the EAU flowchart (Figure 7.2)whereby platinum-ineligible patients consist of one of the following: 1. PS 2 AND GFR <60 mL/min 2. PS >2 3. GFR <30 mL/min 4. Grade 2 or above audiometric hearing loss 5. Grade 2 or above peripheral neuropathy 6. NYHA class III heart failure The authors note in suitable patients with creatinine clearance from 50-59, providers may offer split dosing of cisplatin (35mg/m2 on day 1 and day 8) or eGFR, allowing more patients the opportunity to receive this combination. Regarding second-line therapies, erdafitinib in patients who are FGFR positive in 2L setting post platinum is an acceptable treatment.	**Endorsed**
7.7.3 In patients achieving stable disease, or better, after first-line platinum-based chemotherapy use maintenance treatment with PD-L1 inhibitor avelumab.	**Endorsed**
First-line treatment in patients unfit for platinum-based chemotherapy	
7.7.4 Consider checkpoint inhibitors pembrolizumab or atezolizumab. **Comments** We agree with the "weak" rating of this recommendation but one may consider pembrolizumab an option in patients who cannot receive chemotherapy based on single-arm studies [3,4], notwithstanding access/reimbursement limitations. Atezolizumab is no longer accessible for bladder cancer in this setting in Canada.	**Endorsed**
Second-line treatment	
7.7.5 Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease. If this is not possible, offer atezolizumab, nivolumab (EMA, FDA approved); avelumab or durvalumab (FDA approved). **Comments**	**Endorsed**

In Canada, only pembrolizumab is approved, funded, and available in patients with metastatic urothelial carcinoma. As such, the second sentence is not applicable to the Canadian setting.	
Further treatment after platinum- and immunotherapy	
7.7.6 Offer treatment in clinical trials testing novel antibody drug conjugates (enfortumab vedotin, sacituzumab govitecan); or in case of patients with FGFR3 alterations, FGFR tyrosine kinase inhibitors. **Comments** This recommendation is no longer up to date. Offering clinical trials is of the utmost priority and importance, but these should not be limited to investigation of ADC and/or FGFR inhibitors. Furthermore, we suggest considering EV in patients who have previously received chemotherapy and checkpoint inhibitors based on EV-301 [5], a phase 3 trial showing significantly prolonged survival compared to chemotherapy (median OS: 12.88 vs. 8.97 months; HR for death 0.70; 95% CI, 0.51 to 0.75; P<0.001) [5]. Lastly, we suggest consideration of erdafitinib in previously treated patients with locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations based on an objective tumour response in 40% in a recent phase 2 study leading to its approval by Health Canada [6].	**Not Endorsed**
ADC = antibody drug conjugates; CI = confidence interval; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; EV = enfortumab vedotin; FDA = United States Food and Drug Administration; FGFR = fibroblast growth factor receptor; GC = gemcitabine plus cisplatin; GFR = glomerular filtration rate; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; HR = hazard ratio; NYHA = New York Heart Association; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression free survival; PS = performance status	

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.

ACKNOWLEDGEMENTS

The Systemic Therapy for Metastatic Urothelial Cancer GDG would like to thank the following individuals for their assistance in developing this report:

- Sheila McNair, Jonathan Sussman, Xiaomei Yao, Norma Varela, Fulvia Baldassarre

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Section 3: Internal and External Review

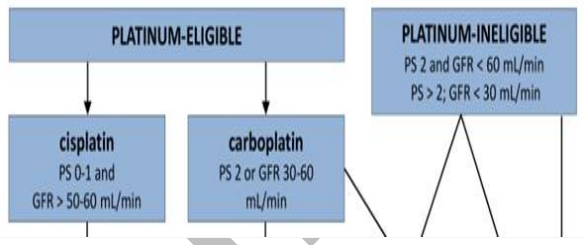
INTERNAL REVIEW

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

All of the nine members of the GDG Expert Panel members voted for a total of 100% response in April of 2022. Of those who voted, all nine approved the document (100%). 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
Regarding recommendation 7.7.2. "The relation between comorbidities, treatment efficacy, and treatment-related toxic effects is complex and has not been adequately explored in patients with advanced UC." A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. [Galsky et al. Lancet Oncol 2011 Mar;12(3):211-4] The Galsky criteria are very acceptable in clinical practice but can be further stratified based on **Figure 7.2: Flow chart for the management of metastatic urothelial cancer***  Thus, fitness for platinum can be re-defined as cisplatin versus carboplatin fitness. Here, according to the EAU algorithm, we see that cisplatin eligibility is defined as performance status (PS) 0-1 AND glomerular filtration rate (GFR) >50 mL/min Carboplatin is offered if PS 2 or GFR >30 mL/min. Based on provider judgment, split dose cisplatin could also be considered	We agree and have added the following comment to 7.7.2: Although some uncertainty and controversy exists to define the cisplatin "unfit" patient, we choose to define this population according to the Galsky criteria [2] which has been further stratified based on the EAU flowchart (Figure 7.2) whereby platinum-ineligible patients consist of one of the following: 1. PS 2 AND GFR <60 mL/min 2. PS >2 3. GFR <30 mL/min 4. Grade 2 or above audiometric hearing loss 5. Grade 2 or above peripheral neuropathy 6. NYHA class III heart failure

Platinum-ineligible is strictly defined as in the right-sided box above. **Therefore, to summarize, would add a comment regarding use of Galsky criteria reconciled with EAU flow chart whereby platinum-ineligible patients consist of one of the following:** **1. PS 2 AND GFR <60 mL/min** **2. PS >2** **3. GFR <30 mL/min** **4. Grade 2 or above audiometric hearing loss** **5. Grade 2 or above peripheral neuropathy** **6. New York Heart Association (NYHA) class III heart failure**	
Regarding comment portion of 7.7.2. Should also include estimated glomerular filtration rate (eGFR) here, some evidence suggest eGFR may be more accurate; https://www.nature.com/articles/s41585-020-00404-6 Should we also include Shilpa Gupta's work on defining platinum (carbo) eligibility? https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.7_suppl.451 Regarding second line treatment in general… What about erdafitinib in patients who are fibroblast growth factor receptor (FGFR) positive in 2L setting post platinum? Technically pembro is not the only 2L option for these pts.	We have added "eGFR" to the second paragraph of the comment portion of 7.7.2. We feel Shilpa Gupta's work is outside the scope of this work. We have added the following to the comment portion of 7.7.2: "Regarding second-line treatment, erdafitinib in patients who are FGFR positive in 2L setting post platinum is an acceptable treatment."
Regarding comment portion of 7.7.1. I would delete this comment as I don't think we have enough data to say that 'GC is preferable to ddMVAC...especially in the young patients. The progression-free survival (PFS) and response rates were reported. PFS results reported in 2021 In ESMO. In the group that received neoadjuvant chemotherapy, ddMVAC was actually better. Regarding recommendation 7.7.4. I thought atezolizumab is no longer accessible for bladder cancer in this setting in Canada?	We agree and have deleted the comment portion of 7.7.1. We have added the following to the comment portion of 7.7.4: "Atezolizumab is no longer accessible for bladder cancer in this setting in Canada."
ADA's are noted for Antibody Drug Conjugates - I would suggest making this antibody drug conjugates (ADCs) to remain consistent with commonly used terminology.	We have changed ADA to ADC in the document.

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 GU oncologists in the PEBC database were contacted by email to inform them of the survey (n=88). Eight (9%) 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 the eight physicians 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.

	N=8 (9%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1	4	3
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1			3	4
3. I would recommend this guideline for use in practice.			1	2	5
4. What are the barriers or enablers to the implementation of this guideline report?	Firstly, I am a Radiation Oncologist so wouldn't directly make use of this guideline. In my opinion, the adoption of a portion of an existing guideline THEN adding in a number of provisos and comments and not endorsing one part of the portion of the guideline really leads me to question how enthusiastic is the endorsement and how well aligned are the ESMO guidelines with expert opinion around Canadian practice. Is there another guideline with better alignment that could be adopted or perhaps the GU PEBC should do a guideline from scratch. Barriers - Drug access, access to timely imaging Enablers - regular imaging follow-up Availability of some of the medications in Canada. As a radiologist this is outside my usual spectrum of expertise. Would be nice to have a section on imaging follow-up (frequency, type, e.g., computed tomography (CT) abdomen/pelvis vs CT urogram). barrier: availability I do not see there would not be barriers to the implementation of these guidelines Funding and availability of drugs Dissemination should include urologic community. It is concise and easy to understand, so useful.				

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

Comments	Responses
1. Be sure to include urologists in the dissemination	No response needed

CONCLUSION

The final endorsed recommendations contained in Section 1 reflect the integration of feedback obtained through the 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 Systemic Therapy for Metastatic Urothelial Cancer GDG 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
Christina Canil	The Ottawa Hospital Cancer Centre, Ottawa ON.	See below [a]
Sebastien Hotte	Oncology, Faculty of Health Sciences, McMaster University, Hamilton, ON.	See below [b]
Aly-Khan Lalani	Oncology, Faculty of Health Sciences, McMaster University, Hamilton, ON.	See below [c]
Srikala Sridhar	Cancer Clinical Research Unit (CCRU), Princess Margaret Cancer Centre, Toronto, ON.	See below [d]
Expert Panel and Members of the Guideline Development Group		
Nimira Alimohamed	Tom Baker Cancer Centre The University of Calgary Calgary, AB.	See below [e]
Anupam Batra	Grand River Hospital Kitchener Waterloo, ON	See below [f]
Dominick Bosse	The Ottawa Hospital Department of Medical Oncology Ottawa, ON	See below [g]
Rodney Breau	Department of Surgery, University of Ottawa Ottawa, ON.	See below [h]
Naz Fallah-Rad	University Health Network, Princess Margaret Cancer Centre Toronto, ON.	See below [i]
Neil Fleshner	Division of Urology, University of Toronto Toronto, ON	See below [j]
Di Maria Jiang	University Health Network, Princess Margaret Cancer Centre Toronto, ON.	See below [k]
Wassim Kassouf	Department of Surgery Division of Urology McGill University Montreal, QC	See below [l]
Som Mukherjee	Department of Medical Oncology, Hamilton Regional Cancer Centre Hamilton, ON	See below [m]

[a] $500 or more consulting capacity Janssen, Astra Zeneca, BMS, Bayer, Eisai, Pfizer, Ipsen, Roche, Astellas, Merck, Amgen, Ferring, Seattle Genetics; Other financial or material support Pfizer, Sanofi Genzyme.
[b] $500 or more consulting capacity Consultant/advisory board: BMS, Janssen, Merck, SeaGen.
[c] $500 or more consulting capacity Ad hoc honoraria for advisory meetings: AbbVie, Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, Novartis, Pfizer, Roche, TerSera; Grants or other research support BioCanRx, BMS, Novartis, Roche, Ipsen, EMD Serono [all funds directed to institution].

[d] $500 or more consulting capacity Consultancy for Pfizer, Astra Zeneca, Roche, BMS, Merck, Seagen, Immunomedex, Janssen, Astellas, Bayer; Grants or other research Janssen, Bayer; Principal investigator in multiple trials across the field; Published editorial, commentary, opinion in multiple papers in the field.
[e] $500 or more consulting capacity Seagen, Pfizer,EMD, Serrano; principal investigator EV 302, MERCK 866, MERCK 905.
[f] $500 or more consulting capacity BMS, Pfizer, Janssen, Bayer, Novartis.
[g] $500 or more consulting capacity Bayer, AbbVie, Ipsen, Pfizer, BMS, AstraZeneca, AMGEN, Janssen; Other financial or material support Pfizer (cover cost of ESMO registration), Ipsen (cover cost of ASCO GU registration); Combined financial interests of over 1,000 COI declared in the categories above amount for more than 1000$.
[h] $500 or more consulting capacity Ferring Pharmaceuticals.
i $500 or more consulting capacity Bayer: Consultancy / Advisory Board, IPSEN: Consultancy / Advisory Board, Bristol Myers Squibb: Consultancy / Advisory Board, Pfizer: Consultancy / Advisory Board, Merck: Consultancy / Advisory Board.
[j] $500 or more consulting capacity Amgen, Janssen, Astellas, Bayer, Sanofi, Abbvie, Ferring; Chief medical officer for Verity pharmaceuticals and POINT Biopharma; Stock holdings in POINT Biopharma and Verity pharmaceuticals; Research grants (to the institution) from Janssen, Astellas, Bayer, Sanofi, Nucleix, Progenix, SpectraCure AB, Bavarian Nordic.
[k] $500 or more consulting capacity Janssen Canada, Ipsen, Bayer Canada, EMD Serono and Pfizer Alliance, Amgen; Pending agreement of an unrestricted education grant from Astellas, amount TBD; I am the site PI of the following trials currently enrolling patients:
- NASC 10183, single arm phase II CTEP trial of pembrolizumab plus tazmetostat in patients with mUC
- Capitello 281 (AZ): phase III trial for patients with mCSPC
- 70218902EDI1001 (Janssen): phase I trial for patients with mCRPC
- SPLASH (point biopharma): phase III trial for patients with mCRPC
I will be the site PI of the following trials currently pending trial activation:
- 81712917PCR2001 (Janssen): phase Ib trial for patients with mCRPC
- CA022-009 (BMS): phase II trial for patients with mCRPC
[l] $500 or more consulting capacity Merck, BMS, Pfizer-EMD Serono, Janssen, Sessen Bio, Ferring; Received grant support to conduct an investigator-initiated trial in bladder cancer by Roche; PI on CCTG BL13 trial for localized MIBC
[m] $500 or more consulting capacity Advisory Board Member - EMD Serono, Merck, Novartis; Local PI for AstraZeneca trials BAYOU, DANUBE (not national PI), IMMU-132; Published editorial https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6788915/

Appendix 2: AGREE II Score Sheet

Domain	Item	AGREE II Appraiser Ratings[1]		
		1	2	3
1) Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	5	4	5
	2. The health question(s) covered by the guideline is (are) specifically described.	2	1	2
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	3	1	2
Domain score[2] - (25-9/63-9) *100 = 16/54 *100 = .2962*100 = **29.6%**		Score 25		
2) Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7	6	5
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	6	7	6
	6. The target users of the guideline are clearly defined.	7	6	6
Domain score[2] - (56-9/63-9) *100 = 47/54 *100 = .8703*100 = **87.0%**		Score 56		
3) Rigor of development	7. Systematic methods were used to search for evidence.	6	5	6
	8. The criteria for selecting the evidence are clearly described.	4	2	2
	9. The strengths and limitations of the body of evidence are clearly described.	5	4	5
	10. The methods for formulating the recommendations are clearly described.	4	2	4
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	6	5	5
	12. There is an explicit link between the recommendations and the supporting evidence.	6	5	7
	13. The guideline has been externally reviewed by experts prior to its publication.	6	5	2
	14. A procedure for updating the guideline is provided.	7	6	4
Domain score[2] - (113-24/168-24) *100 = 89/144 *100 = .86180 *100 = **61.8%**		Score 113		
4) Clarity of presentation	15. The recommendations are specific and unambiguous.	6	4	5
	16. The different options for management of the condition or health issue are clearly presented.	5	4	5
	17. Key recommendations are easily identifiable.	6	6	7
Domain score[2] - (48-9/63-9) *100 = 39/54 *100 = .7222 *100 = **72.2%**		Score 48		
5) Applicability	18. The guideline describes facilitators and barriers to its application.	4	3	1
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	5	3	1
	20. The potential resource implications of applying the recommendations have been considered.	3	3	1
	21. The guideline presents monitoring and/ or auditing criteria.	5	3	1
Domain Score[2] - (33-12/84-12) *100 =21/72 *100 = .2917 *100 = **29.2%**		Score 33		

Domain	Item	AGREE II Appraiser Ratings[1]		
		1	2	3
6) **Editorial independence**	22. The views of the funding body have not influenced the content of the guideline.	6	6	7
	23. Competing interests of guideline development group members have been recorded and addressed.	6	6	5
Domain Score[2] - (36-6/42-6) *100 = 30/36 *100 = .8333 *100 = **83.3%**		Score 36		
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**5**	**5**	**5**
Overall Guideline Assessment	2. I would recommend this guideline for use.	**Yes**	**No**	**Yes**

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