2024 CUA-GUMOC Expert Report: Management of unresectable locally advanced and metastatic urothelial carcinoma

Carlos E. Stecca*[1], Deepro Chowdhury*[1], Normand Blais[2], Nimira Alimohamed[3], Lori Wood[4], Christina M. Canil[5], Bernie Eigl[6], Girish S. Kulkarni[7], Peter C. Black[8], Wassim Kassouf[9], Peter Chung[10], Scott North[11], Di Maria Jiang[1], Srikala S. Sridhar[1]

[1]Division of Hematology and Medical Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [2]Division of Medical Oncology/Hematology, Centre Hospitalier de l' Université de Montréal, Montreal, QC, Canada; [3]Department of Medicine, Division of Medical Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [4]Division of Medical Oncology, QEII Health Sciences Center, Halifax, NS, Canada; [5]The Ottawa Hospital Cancer Center, Ottawa, ON Canada; Ottawa Hospital Research Institute, Ottawa, ON, Canada; [6]BC Cancer, Vancouver, BC, Canada; [7]Divisions of Urology and Surgical Oncology, Department of Surgery, University Health Network, University of Toronto, Toronto, ON, Canada; [8]Department of Urological Sciences, University of British Columbia, Vancouver, BC, Canada; [9]Department of Surgery, McGill University Health Center, Montreal, QC, Canada; [10]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [11]Department of Medical Oncology, Cross Cancer Institute, Edmonton, AB, Canada

*Co-first authors

REVIEWERS:
Dominick Bossé, Ottawa Cancer Centre, Ottawa, ON, Canada
Rodney H. Breau, University of Ottawa, Ottawa, ON, Canada
Henry Conter, London Regional Cancer Program, London, ON, Canada

Cite as: Stecca CE, Chowdhury D, Blais N, et al. 2024 CUA-GUMOC Expert Report: Management of unresectable locally advanced and metastatic urothelial carcinoma. *Can Urol Assoc J* 2024;18(12):379-90. http://dx.doi.org/10.5489/cuaj.8946

See related commentary on page 391

INTRODUCTION

Urothelial cancer (UC) ranks as the fifth most common cancer in Canada, with an estimated 13 400 new cases and 2600 deaths in 2023.[1] Although these cancers can develop anywhere along the urinary tract, they most commonly arise from the urinary bladder. At diagnosis, 70% of patients will have non-muscle invasive disease (NMIBC), 25% muscle-invasive disease (MIBC), and 5% will have incurable locally advanced (LA) or metastatic UC (mUC). Treatment outcomes for UC remain suboptimal, with up to 40–50% of patients with MIBC relapsing despite definitive treatment, and real-world contemporary evidence suggesting a median overall survival (mOS) of only 20 months (mos) for patients with mUC.[2-5]

Since the 2019 publication of the previous Genitourinary Medical Oncologists of Canada (GUMOC) consensus statement on the management of mUC,[6] the field has witnessed significant therapeutic advances, marked by the introduction of several new treatment modalities, including immunotherapy (IO), novel antibody drug conjugates (ADC), and targeted therapies. This updated Expert Report aims to incorporate recent data from randomized controlled trials (RCTs) into evidence-based recommendations to guide management of patients with mUC in Canada.

METHODS

We conducted a comprehensive literature review evaluating studies of mUC, with an emphasis on RCTs published since the 2019 publication. A search of PubMed, Medline, and Embase, in addition to other published guidelines and abstract presentations at major conferences, were used to identify relevant studies. Wherever possible we sought to align our treatment recommendations with those of international organizations such as American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO) and European Association of Urology (EAU); however, full alignment may be limited by differences in clinical practice standards, regional variations, and the availability of approved therapies in Canada.

Draft recommendations on various aspects of mUC management, based on best available evidence, were initially developed by the co-first and senior authors. These recommendations were shared with all co-authors via email for input, and revisions were made based on this email discussion. Through this process, consensus was reached by incorporating and addressing all the feedback points, ensuring alignment among the authors.

Authorship in this consensus is composed of experts and key opinion leaders in genitourinary medical oncology, uro-oncology, and radiation oncology across Canada. These experts were selected based on their significant clinical experience, academic contributions, and leadership in clinical practice guidelines.

A multidisciplinary approach is emphasized, particularly in the setting of locally advanced disease (defined here as cT4b and/or cN1-N3), oligometastatic, or oligoprogressive disease (OPD). Statements pertaining to aspects of management are intended to provide general guidance regarding treatment decision making, however, are not meant to supersede clinical judgement of individual scenarios.

SYSTEMIC THERAPY FOR PATIENTS WITH 1A/mUC (TABLE 1)

First-line treatment

Recently published data has changed the treatment landscape of 1a/mUC.

■ STATEMENT 1

The preferred first-line (1L) treatment is the combination of enfortumab vedotin (EV) with pembrolizumab (EV + P).

Enfortumab vedotin and pembrolizumab

The results of two large, randomized, phase 3 studies — EV-302[7] and Checkmate 9018 — have significantly changed the treatment landscape for patients with mUC.

The EV-302 study randomized 886 patients with untreated mUC and estimated glomerular filtration rate (eGFR) >30 ml/min to receive the combination of EV, an ADC that targets nectin-4, combined with the immune checkpoint inhibitor (ICI), pembrolizumab (P) vs. platinum-based chemotherapy (PBC). In the experimental arm, while EV was administered until disease progression, P was allowed for a maximum of 35 cycles. EV + P was shown to be superior to PBC: the mOS was 31.5 vs. 16.1 mos (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.38–0.58, p<0.00001); progression-free survival (PFS) 12.5 vs. 6.3 mos (HR 0.45, 95% CI 0.38–0.54, p<0.00001); objective response rate (ORR) 68% vs. 44%; with complete response (CR) rates of 29.1% vs. 12.5% and duration of response not reached, but at least 20.2 mos (20.2–NE) vs. 7 mos (6.2–10.2). Importantly, benefits were seen across all subgroups and regardless of cisplatin eligibility.

Although only one-third of patients in the PBC arm received subsequent maintenance ICI, which is the current standard of care for patients not progressing on PBC, this actually reflects real-world data regarding the uptake of maintenance avelumab. Despite this small potential limitation, the results of EV + P remain

Table 1. Approved regimens in metastatic urothelial cancer (mUC)

Treatment type	Agent(s) (abbreviation)	Dose	Route	Schedule	Cycle length	ORR (%)	mPFS (mos)	mOS (mos)	Adverse effects
Combination chemotherapy	Cisplatin-gemcitabine (GC)	21 days (growth factor support optional)	49.4	7.7	14	Myelosuppression, peripheral neuropathy, acute kidney injury			
	Cisplatin	70 mg/m^2	IV	D1					
		35 mg/m^2	IV	D1 + D8					
	Gemcitabine	1000 mg/m^2	IV	D1 + D8					
	Carboplatin-gemitabine (GCarbo)	21 days	41.2	5.8	9.3	Myelosuppression, peripheral neuropathy			
	Carboplatin	AUC 5-6	IV	D1					
	Gemcitabine	1000 mg/m^2	IV	D1 + D8					
	Dose-dense MVAC (ddMVAC)	14 days (requires growth factor support)	64	9.5	15.1	Myelosuppression, mucositis, peripheral neuropathy, acute kidney injury			
	Methotrexate	30 mg/m^2	IV	D1					
	Vinblastine	3 mg/m^2	IV	D2					
	Doxorubicin	30 mg/m^2	IV	D2					
	Cisplatin	70 mg/m^2	IV	D2					

ADC: antibody drug conjugate; D: day; HFS: hand-foot syndrome; iRAEs: immunotherapy-related adverse events; IV: intravenous: mPFS: median progression-free survival; mOS: median overall survival; ORR: objective response rate; PO: orally.

outstanding and practice-changing, with benefits seen across all subgroups and regardless of cisplatin eligibility.[9-11] EV + P was generally well-tolerated, without detriment to patients' global health status/quality of life or functioning;[12] however EV + P does have a different toxicity profile compared to chemotherapy. The most common adverse events (AE), primarily associated with EV, were skin reactions (66.8%), peripheral neuropathy (63.2%), ocular disorders (primarily dry eyes [21.4%]), and hyperglycemia (13.0%). These occurred in addition to the immune-related AEs (IRAE) typically expected with P and will require careful monitoring and management, including dose adjustments, as this treatment becomes adopted into routine practice.

Gemcitabine-cisplatin + nivolumab

The phase 3 CheckMate 901 (CM901) trial was the first trial in mUC to demonstrate a survival benefit of cisplatin-based chemotherapy combined with an ICI;[13] however, it is important to note that, unlike prior combination trials with the same design, such as Keynote-361[14] and IMvigor-130,[15] CM901 only enrolled cisplatin-eligible patients. In the gemcitabine + cisplatin + nivolumab (GC + Nivo) arm compared to the GC arm, mOS was 21.7 vs. 18.9 mos (HR 0.78, 95% CI 0.63–0.96, p=0.02) and mPFS was 7.9 vs. 7.6 mos (HR 0.72, 95% CI 0.59–0.88, p=0.0012). These curves separated at around eight months, accounting for the significant difference between arms despite numerically similar PFS. The ORR was 57.6% (CR 21.7%) vs. 43.8% (CR 11.8%), and notably, the duration of CR was three times longer (37.1 vs. 13.2 mos) in the GC + Nivo arm,

Table 1 (cont'd). Approved regimens in metastatic urothelial cancer (mUC)

Treatment type	Agent(s) (abbreviation)	Dose	Route	Schedule	Cycle length	ORR (%)	mPFS (mos)	mOS (mos)	Adverse effects
Switch-maintenance	Avelumab (if CR/PR/SD on frontline platinum chemotherapy)	10 mg/kg	IV	D1	14 days	N/A	5.5	23.8	iRAEs
ADC + immunotherapy	Enfortumab vedotin	1.25 mg/kg	IV	D1 + 8	21 days	68.0	12.5	31.5	Neutropenia, diarrhea, peripheral neuropathy, hyperglycemia, rash, iRAEs
	Pembrolizumab	200 mg	IV	D1					
Chemotherapy + immunotherapy	Nivolumab	360 mg	IV	D1	21 days	58	7.9	21.7	Myelosuppression, peripheral neuropathy, acute kidney injury, iRAEs
	Cisplatin	70 mg/m^2	IV	D1					
	Gemcitabine	1000 mg/m^2	IV	D1 + 8					
Second-line immunotherapy	Pembrolizumab	200 mg	IV	D1	21 days	21.1	2.1	10.3	iRAEs
ADC	Enfortumab vedotin (EV)	1.25 mg/kg	IV	D1, 8, 15	28 days	40.5	5.5	13	Neutropenia, diarrhea, peripheral neuropathy, hyperglycemia, rash
	Sacituzumanb govitecan (SG)	10 mg/kg	IV	D1, 8	21 days	27	5.4	10.9	Diarrhea, nausea, neutropenia, anemia, leukopenia
Targeted therapy	Erdafitinib	8 mg (to 9 mg if tolerated)	PO	Daily	Continuous	46	5.6	12.1	Hyperphosphatemia, hyponatremia, HFS, stomatitis, onycholysis, central serous retinopathy

ADC: antibody drug conjugate; D: day; HFS: hand-foot syndrome; iRAEs: immunotherapy-related adverse events; IV: intravenous: mPFS: median progression-free survival; mOS: median overall survival; ORR: objective response rate; PO: orally.

despite the fact that the maximum duration of treatment was only 24 mos. A recent exploratory analysis identified that patients with lymph node-only mUC were more likely to achieve a CR and that in this subgroup of patients, GC + Nivo induced durable disease control and higher OS and PFS vs. GC alone.[16]

While EV + P and GC + Nivo have not been formally compared, given the increased magnitude of benefit seen with EV + P over chemotherapy regardless of cisplatin-eligibility, it is recommended that patients should preferentially receive EV + P if available and eligible. It is important to note that this recommendation reflects the team's opinion and is based on data from separate trials, which limits direct comparisons. If EV + P is not available, GC + Nivo is an alternative option for patients eligible for cisplatin. If a patient is not a candidate for EV + P or GC + Nivo, but eligible for carboplatin, then gemcitabine-carboplatin (GCa) followed with maintenance avelumab, if no progression on chemotherapy, is another option.[9]

Special consideration

Defining the optimal 1L treatment has become increasingly challenging, not only because of the novel treatment options available in this setting, but also because of the approval of adjuvant nivolumab or similar such agents for patients with resected UC.[17] In patients with high risk of recurrence, nivolumab may be delivered for up to one year. Although a formal approach for these patients has not been established, it seems reasonable that in patients who have had prior neoadjuvant PBC and disease progression during or shortly after completion of adjuvant ICI, the next line of therapy could be EV. A suggested approach based on expert opinion, and pending data clarification, would be the following:

■ STATEMENT 2

If progression occurs within one year of PBC and during adjuvant ICI, single-agent EV appears to be a reasonable next option.

■ STATEMENT 3

For patients who experience progressive disease within six months of completing adjuvant ICI, single-agent EV is a reasonable next option.

■ STATEMENT 4

In cases where progression occurs more than six months after completing adjuvant ICI therapy, the treatment options may include EV + P, GC + Nivo, or if EV + P not available and patient is cisplatin-ineligible, GCa followed by maintenance avelumab.

Other first-line options

■ STATEMENT 5

In platinum-eligible patients, treatment with either GC or GCa followed by maintenance avelumab in those without disease progression remains a reasonable alternative treatment. For platinum-ineligible patients, treatment with pembrolizumab, single-agent chemotherapy, or EV may be discussed.

Chemotherapy followed by maintenance immunotherapy

Cisplatin-based regimens are generally preferred over carboplatin for eligible patients, as they generally yield higher ORR and CR rates.[18-21] Jiang and colleagues recently revisited the classic cisplatin eligibility criteria and suggested an algorithm for assessing cisplatin eligibility, emphasizing a multidisciplinary, individualized, and patient-centered approach aiming to avoid inappropriate exclusion of patients from cisplatin (Figure 1).[22,23] GC has been adopted as the standard of care in the mUC setting and used as the comparator arm in all contemporary mUC trials.[8,9,24]

Patients who receive at least four cycles of PBC without disease progression should be offered maintenance avelumab based on the phase 3 JAVELIN Bladder 100 trial.[23] This trial randomized patients who had either stable disease (SD), partial response (PR) or CR after 4–6 cycles of PBC to maintenance avelumab or best supportive care (BSC) every two weeks until disease progression. This trial met its primary endpoint of improved OS.[9]

An updated OS analysis confirms an ongoing benefit of maintenance avelumab in this population regardless of initial platinum-based agent. mOS was 25.1 vs. 17.5 mos, and 20.8 vs. 13 mos for patients receiving cisplatin or carboplatin, respectively, compared to BSC.[25] Benefit was also seen regardless of degree of response (SD, PR, or CR) to chemotherapy.

Whether this switch-maintenance strategy can be beneficial in patients who have previously progressed on or after adjuvant nivolumab or after 1L EV + P remains uncertain. Given the potential for serious AEs with immunotherapy, sequencing ICIs in patients known to be refractory to them is not recommended until further data on efficacy becomes available (Figure 1).

Eligibility for immunotherapy

Unlike cisplatin, there are no formal eligibility criteria for use of ICIs.

■ STATEMENT 6

Although ICIs have been traditionally contraindicated in patients with active autoimmune disorders, chronic immunosuppression, organ dysfunction, and patients who underwent solid organ or hematopoietic stem cell transplant, ICI treatment in these challenging populations may still be possible following a multidisciplinary discussion and careful ongoing assessments for toxicity.

With the widespread use of immunotherapy across the spectrum of mUC, discussions around eligibility for ICIs have become increasingly important. Clinical trials traditionally excluded patients with autoimmune disease and patients who underwent solid organ or hematologic stem cell transplant due to the risk of disease reactivation, transplant rejection, and graft-versus-host disease. Moreover, patients on chronic immunosuppression are often considered ineligible to receive ICIs because immunosuppressive states may hinder response to immunotherapy. Finally, patients with organ dysfunction were mainly excluded from studies presumably due to challenges in characterizing safety signals.

Although high-quality studies are still lacking to support the use of ICIs in traditionally trial-ineligible patients, retrospective data suggests that they may have acceptable safety profiles in selected patients.[26,27] Informed discussions should be guided by balancing the risk of IRAEs with potential benefits of treatment, and a multidisciplinary approach is imperative in these challenging circumstances.

Immunotherapy, chemotherapy, and enfortumab-vedotin

Based on expert consensus, patients with creatinine clearance (CrCl) <30 mL/min, Eastern Cooperative Oncology Group (ECOG) >2, grade 2 or worse peripheral neuropathy, and NYHA class III or worse heart failure are not suitable for PBC.[28] Single-agent immunotherapy may be an alternative for these patients[29,30] but despite pembrolizumab's Health Canada approval in this setting for patients who express PDL1 (combined positive score [CPS] ≥10), it is not universally funded across all jurisdictions in Canada. In certain cases, access to pembrolizumab may be obtained through special funding mechanisms, regardless of PD-L1 or CPS scoring. Single-agent chemotherapy may also be considered in this setting, including taxanes and gemcitabine,[13,31-33] as previously discussed in the 2019 consensus statement.

More recently, the EV-103 cohort K included platinum-ineligible patients with an ECOG performance status of 0–2. EV + P and EV monotherapy were deemed safe for these patients as well, with response rates of 64.5% and 45.2%, respectively, although not formally powered to compared these two regimens. mOS was also reported to be 21.7 mos and 22.3 mos, respectively, with low primary progressive disease rates.[34] Based on these results and the encouraging long-term data, EV + P can be considered on an individual basis once available in Canada. For patients deemed unfit for any of the above options, BSC is the preferred approach.

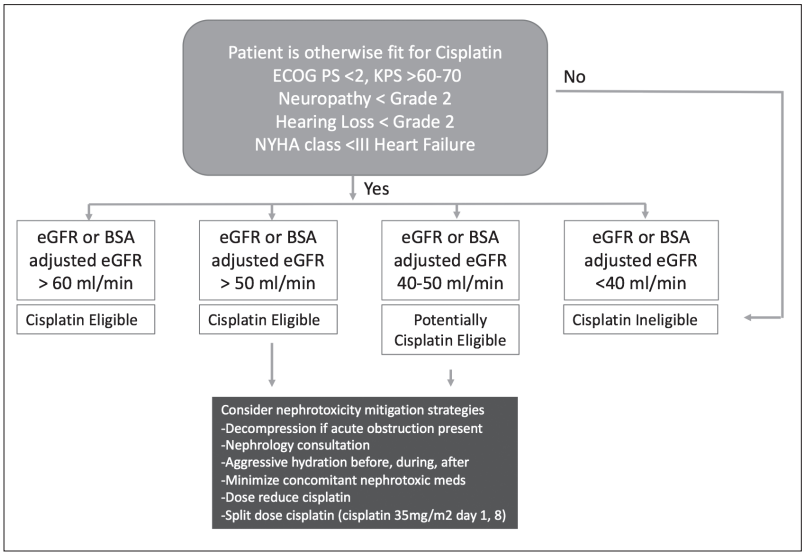

Figure 1. Determining cisplatin-eligibility in patients with metastatic urothelial carcinoma (adapted with permission from Jiang et al. *Nat Rev Urology* 2021;18:104-14). BSA: body surface area; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eGFR: estimated glomerular filtration rate.

Second and later lines of systemic therapy

Disease progression after enfortumab + vedotin plus pembrolizumab

■ STATEMENT 7

For patients with disease progression after treatment with EV + P in the 1L setting, options for second and later lines of systemic therapy include PBC, erdafitinib, or taxanes.

Platinum-based chemotherapy

As use of EV + P in the 1L becomes widespread, an increasing number of patients with mUC will remain platinum-naive by the time they require second-line (2L) treatment. Although there is currently no evidence from RCTs guiding treatment in the post-EV + P setting, PBC remains the preferred option in eligible

patients. In the EV + P arm of EV-302 study, 78.6% of patients who received subsequent 2L therapy received PBC. Whenever possible, cisplatin is normally preferred over carboplatin, as already discussed.

Erdafitinib

Fibroblast growth factor receptors (FGFR) comprises a family of five protein receptors involved in regulating cell proliferation, differentiation, and angiogenesis. FGFR2/3 alterations, including both fusions and mutations, are identified in about 15–20% of mUC patients and may portend a worse prognosis.[35] Notably, FGFR3 alterations are more commonly observed in upper tract urothelial carcinoma, highlighting the importance of FGFR testing in this subgroup, where the pre-test probability may be higher.[36]

Erdafitinib is an oral pan-FGFR inhibitor that showed an ORR of 40% in FGFR2/3-altered mUC in the phase 2 BLC-2001 trial, a single-arm trial that included patients who had disease progression after PBC but also allowed prior immunotherapy exposure.[35] The confirmatory phase 3 THOR trial cohort 1 showed superiority of erdafitinib over investigators' choice of chemotherapy (docetaxel or vinflunine) in patients who had one or two prior lines of treatment, including an ICI in all patients. With a median followup of 15.9 mos, mOS was 12.1 vs. 7.8 mos favoring erdafitinib (HR 0.64, 95% CI 0.47–0.88, p=0.005), with an ORR of 45.6% compared to 11.5%.[36] Common side effects of erdafitinib include hyperphosphatemia, diarrhea, stomatitis, dry mouth, and palmar-plantar erythrodysesthesia and onycholysis.

Cohort 2 of this trial, however, failed to show superiority of erdafitinib over pembrolizumab in terms of OS or PFS, despite the ORR of erdafitinib being double that of pembrolizumab (40.0% vs. 21.6%). Given these findings, aligned with more durable responses and better tolerability of ICI, erdafitinib is normally offered to patients with susceptible FGFR2/3 alterations who have already progressed on an ICI. It is reasonable to consider erdafitinib prior to ICI for patients in whom an objective response is urgently needed, such as in patients with symptomatic visceral disease or impending obstruction.

Non-platinum chemotherapy

Chemotherapy remains an option in later lines for those who can tolerate it, with the understanding that response rates are generally under 25%. Prior to the introduction of ICIs, taxane-based regimens were the most used in the 2L setting. Paclitaxel and docetaxel are generally well-tolerated and are the most commonly used agents in later lines, with response rates of 15–25%.[37-40] In this setting, doublet chemotherapy regimens are associated with slightly higher response rates, but their greater toxicity and failure to meaningfully impact OS has limited their use.[41] Participation in clinical trials is recommended whenever possible for eligible patients, while BSC is a reasonable alternative for those who are not candidates for any treatment.

Disease progression after chemotherapy and immunotherapy

■ STATEMENT 8

For patients presenting with disease progression after PBC and immunotherapy — either concurrent cisplatin, gemcitabine and nivolumab or platinum, gemcitabine and maintenance avelumab — treatment options for second and later lines include EV, erdafinitib if FGFR2/3 alteration is found, and taxane single-agent and platinum rechallenge in selected cases.

Enfortumab vedotin

The phase 3 EV-301 trial randomized patients with la/mUC who had disease progression following both a platinum doublet chemotherapy and an ICI to receive either EV monotherapy or investigator's choice of cytotoxic chemotherapy (docetaxel, paclitaxel, or vinflunine).[42] In an updated long-term survival analysis, EV301 confirmed an OS advantage of EV compared to chemotherapy (12.9 vs. 8.9 mos).[43] This study led to Health Canada approval of EV for patients with mUC with disease progression post-PBC and ICI, including treatment settings beyond third line (3L). The proportion of patients who have not received EV in the first-line setting is expected to decrease as use of front-line EV + P becomes more widespread.

Disease progression after PBC

■ STATEMENT 9

For patients who did not receive immunotherapy in 1L/maintenance, pembrolizumab is the preferred 2L treatment.

Immune checkpoint inhibitors

Patients experiencing disease progression on or within one year after PBC who did not receive ICI in 1L/maintenance setting should be offered 2L pembrolizumab. Five ICIs have been tested in the 2L setting,[44-49] including two in randomized phase 3 stud-

ies, but only pembrolizumab has demonstrated an improvement in OS.[45,46]

Keynote-045 was a randomized, phase 3 study comparing pembrolizumab to investigators' choice of single-agent paclitaxel, docetaxel, or vinflunine in 542 patients with progressive disease during or within 12 mos after PBC. mOS was 10.3 mos with pembrolizumab vs 7.4 mos with chemotherapy (HR 0.73, 95% CI 0.59–0.91, p=0.002).[46]. Grade 3–5 toxicity was seen in 15% of patients on pembrolizumab compared to 49% on chemotherapy. Benefit was seen irrespective of the choice of chemotherapy or PD-L1 status. While ORR is relatively low, durable responses are seen in responders to pembrolizumab. Long-term followup, with a median of 62.9 mos, has shown a 48-month OS rate of 16.7% with pembrolizumab compared to 10.1% with chemotherapy, with a median duration of response (DOR) of 29.7 mos with pembrolizumab vs. only 4.4 mos with chemotherapy.[50]

Durable responses have been seen with other immune ICIs in this setting; however, none demonstrated an OS benefit over conventional chemotherapy, likely due to issues with trial design and the imperfect reliability of PD-L1 status for predicting response to ICIs in mUC.[45,51] The percentage of immunotherapy-naive patients in second or later lines of therapy is expected to decrease with the widespread use of nivolumab in the adjuvant setting after radical cystectomy and with eventual adoption of EV + P and GC + Nivo in the 1L setting.

Emerging later-line options

Sacituzumab govitecan

Sacituzumab govitecan (SG) is an ADC consisting of sacituzumab, a Trop-2 antibody linked to SN-38, the active metabolite of the topoisomerase inhibitor irinotecan.[52] The phase 2 TROPHY-U-01 trial demonstrated efficacy of this ADC in patients with mUC who had progressed on PBC and an ICI, with response rates of 27%, mDOR of 7.2 mos, and mPFS and OS of 5.4 mos and 10.9 mos, respectively.[52] Patients in the TROPHY-U-01 trial were also allowed to have received prior treatment with EV and erdafitinib, though only a small number had done so (9% of patients with EV and 2% with erdafitinib).[52] A confirmatory phase 3 trial (TROPiCS-04) has recently been completed, with a press release suggesting SG was not superior to 2L chemotherapy, but the formal results are not yet available.

Although not formally compared to EV, SG seems to have lower overall response rates, shorter OS, more toxicity, and a higher number of deaths related to neutropenic complications. Given multiple phase 3 trials showing the efficacy of EV over standard-of-care, if SG becomes available in UC, its use will have to be associated with granulocyte-colony stimulating factor (G-CSF) and will most likely be reserved for patients who have already received prior EV.

HER-2-directed therapy

Urothelial cancers have been reported to exhibit the third highest rate of *HER-2* overexpression among solid tumors, making them likely to respond to ADCs targeting this marker.[53] Disitamab vedotin, a humanized anti-*HER-2* antibody linked to MMAE, has showed encouraging ORR of 50.5%, with disease control rate of 82.2% in *HER-2*-positive patients.[54]

When given in combination with toripalimab, a PD-1 inhibitor, it has demonstrated an impressive ORR of 80% and a disease control rate of 90% in eligible patients.[55] Furthermore, in the recently published Destiny-Pan Tumor02 phase 2 trial, trastuzumab deruxtecan (T-DXd) demonstrated durable responses and promising survival outcomes across different tumor types expressing HER2. Specifically, in the mUC cohort, ORR, mPFS, and mOS in patients with IHC3+ were 56.3%, 7.4 mos, and 13.4 mos, respectively.[56]

Drug-related AEs were reported in 92.7% of patients, with the most common being nausea (51.2%), diarrhea (31.7%), and anemia (29.3%). Grade ≥ 3 AEs occurred in 41.5% of patients, leading to drug discontinuation in 9.8% of cases. Although this medication is not yet available in Canada, it has already been granted FDA accelerated approval for *HER2*-positive (IHC3+) solid tumors that have received prior systemic therapy and have no effective treatment options left.

Special situations

Patients with non-metastatic locally advanced/unresectable disease

■ STATEMENT 10

Patients with locally advanced/unresectable disease (cT4b and/or cN1–3) represent a unique subset that can be managed with either purely palliative or potentially curative-intent therapy, depending on the extent of disease, patient fitness, goals of care, and response to 1L chemotherapy. Discussion of such cases in a multidisciplinary tumor board should always be considered to optimize patient outcomes.

Clinical T4b disease is defined as a tumor that invades the pelvic wall, abdominal wall, or adjacent bowel/rectum, and is often unresectable unless significant downstaging can be achieved. Clinical N1–2 disease consists of lymph node involvement in the true pelvis, whereas N3 consists of common iliac lymph node involvement. Importantly, patients with cN1–2 stage disease, and a small proportion of patients with clinically involved lymph nodes, are found postoperatively to have pN0, implying false-positive clinical staging.[57]

Evidence defining the optimal treatment of cT4b and cN1–3 disease is limited to retrospective series, as these patients have been routinely excluded from neoadjuvant chemotherapy trials. In the Advanced Bladder Cancer meta-analysis of neoadjuvant chemotherapy, they represented only 1% and 4% of cases, respectively.[58] Likewise, these patients have generally been excluded from chemo-radiotherapy studies.[59] Consequently, the optimal management of this subgroup is not well-defined.

Treatment options for those with N1–3 or T4b disease that becomes resectable after neoadjuvant systemic therapy include consolidative radical therapy (cystectomy or [chemo]radiotherapy) or alternatively PBC followed by maintenance avelumab or EV + P once it becomes available. The option of local therapy following a few months of systemic therapy should be assessed, given its potential for long-term disease control of the pelvis.

In a retrospective study of 3753 patients with la/mUC treated in the pre-immunotherapy era, Seisen and colleagues found that patients who received high-intensity local therapy (LT, defined as either radical cystectomy or >50 Gy of radiation) had a longer mOS than patients treated with "conservative" LT (defined as either no LT, transurethral resection of bladder tumor [TURBT] alone, or <50 Gy of bladder radiation therapy) (mOS 14.9 [9.8–30.7] mos vs. 10.0 (5.3–17.1) mos, p< 0.001).[60] Adjuvant immunotherapy in patients with ypT2+ or ypTN+ disease may further improve disease-free survival and cure rates based on randomized phase 3 data that showed disease-free survival and OS benefits in operable patients.[61,62]

A commonly used treatment paradigm in published series of multiple different tumor types, including urothelial, colorectal, lung, etc., has consisted of four cycles of chemotherapy followed by local consolidation where possible.[63-76] Both, GC and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) can be considered in locally advanced UC, but it is important to note that patients with T4b or node-positive disease were excluded from the pivotal trial comparing these strategies.[77]

In general, outcomes are better in patients showing a response to initial systemic chemotherapy, though a proportion of patients with SD may also derive benefit from subsequent definitive local therapy.[67,68] For la/mUC, results from the studies above demonstrate the potential for prolonged disease control or cure, with reported five-year cancer-specific survival (CSS)/OS rates of around 30%, and higher rates in patients who had a pathologic complete response (pCR) to induction therapy. On this basis, it is also reasonable to endorse the above treatment strategy for patients who receive either switch-maintenance therapy with avelumab or EV + P and have excellent responses and disease stability after several months of systemic treatment. The choice of surgery or (chemo)radiation should be made on a case-by-case basis, based on response to systemic treatment, restaging, multidisciplinary discussion, and fully informed shared decision-making with the patient.

Patients with distant metastatic disease who have excellent response to initial systemic therapy

■ STATEMENT 11

For patients who have significant tumor regression and/or low-volume residual metastatic disease after starting systemic palliative 1L treatment, we encourage multidisciplinary discussion to determine whether definitive local management or treatment of oligometastatic disease is warranted.

In the EV-302 trial, the CR rate for EV + P was an impressive 29.1% (the CR rate in the PBC arm was 12.5%).[7] Even if patients do not achieve a CR, a substantial proportion of them will still have a significant PR, resulting in only residual low-volume disease. While prospective randomized data are lacking, promising results have already been observed in small retrospective studies assessing patients with low-volume metastatic disease, documenting durable PFS interval following metastasectomy and consolidative radiotherapy post-chemotherapy.[72,73]

A systematic review and meta-analysis of six studies involving 158 patients evaluated the effectiveness of metastasis-directed radiotherapy (MDRT) with consolidative intent in oligometastatic UC patients. The results demonstrated a local control rate of 57–100%, a mPFS of 2.9–10.1 months, and a mOS of 14.9–51 months.[78] Radical cystectomy or bladder radiation can also be considered on a palliative basis to lower the risk

of symptomatic progression, such as pain or bleeding, in the pelvis.[79]

Prospective randomized trials in this setting are urgently needed, especially since this population of patients is expected to increase substantially given the improved response rates in patients receiving EV + P compared to conventional PBC. For now, discussion of these complex cases in multidisciplinary tumor boards is strongly encouraged, not only to determine the feasibility of a consolidation approach, but also to discuss the optimal timing for intervention.

Patients with oligoprogressive disease on systemic therapy

■ STATEMENT 12

In patients with OPD on systemic therapy, a multidisciplinary discussion with radiation and surgical oncology may be needed to determine whether local management can be employed so the current line of systemic therapy can be continued.

Oligoprogressive disease arises in the context of polymetastatic disease, manifesting after an initial positive response to systemic treatment, with disease progression confined to a limited number of sites. As a result of extensive therapeutic advances, OPD is being observed more frequently in clinical settings, and can be related to the formation of drug-resistant subclones.[74] Recognizing and treating patients with OPD could be helpful, as it may eliminate the resistant sites, slow or halt the progression of resistance, and extend the effectiveness of current systemic therapy. Local therapy for oligoprogressive lesions, while maintaining systemic treatment, has shown benefits across different cancer types.[75,79] Although evidence for specifically targeting OPD in UC may be limited, retrospective studies suggest that it may be feasible and effective.[53,80] Therefore, multidisciplinary discussions regarding metastasis-directed therapy in such patients may be important.

UPCOMING CHALLENGES AND FUTURE DIRECTIONS

As the treatment landscape of UC widens, with exciting new systemic options both in localized and metastatic settings, the treatment algorithm becomes more complex, imposing challenges in treatment sequencing, as showed in Figures 2 and 3.

Precision medicine in medical oncology is a continuously evolving field, and like in many other tumor sites, the development of targeted therapies and biomarkers for patients with mUC has become one of the most important topics of research. Efforts towards a more personalized approach may not only improve the chances of successful treatment but also enhance patients' quality of life.

The identification of predictive and prognostic biomarkers is another area of growing interest when it comes to research in mUC. PD-L1 has been extensively studied in clinical trials, but its role remains largely imperfect for use in treatment decisions.[32,51,81]

Another important tool that is being investigated with promising results across multiple tumor types, including UC, is the use of circulating tumor DNA (ctDNA). A recent update from the phase 3 IMvigor010 trial reaffirmed that ctDNA positivity, compared to negativity, was linked to shorter OS (HR 6.3, 95% CI 4.3–9.3) in the control arm. Additionally, it

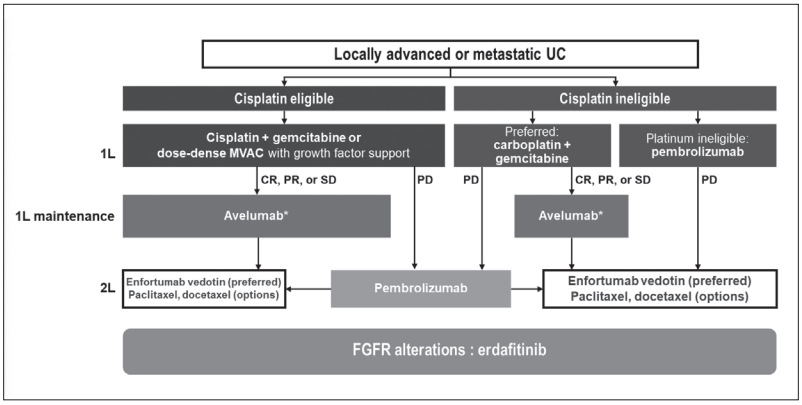

Figure 2. Treatment algorithm before the EV-302 and CM-901data. CR: complete response; FGFR: fibroblast growth factor receptors; MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin; PR: partial response; SD: stable disease; UC: urothelial carcinoma.

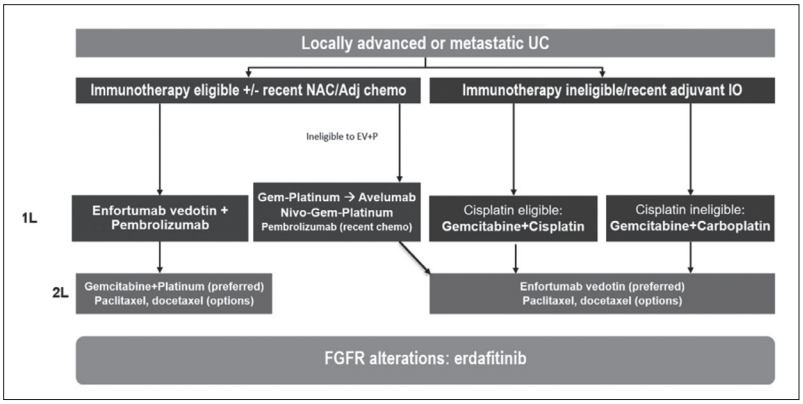

Figure 3. Proposed treatment algorithm after EV-302 and CM-901 availability. CR: complete response; EV + P: enfortumab vedotin + pembrolizumab; FGFR: fibroblast growth factor receptors; NAC: neoadjuvant chemotherapy; UC: urothelial carcinoma; 1L: first-line; 2L: second-line.

underscored the predictive value of ctDNA, as ctDNA-positive patients presented with significant OS advantage when receiving atezolizumab vs. observation (HR 0.59, 95% CI 0.42–0.83).[82] At this time, measurement of ctDNA levels cannot be recommended outside the context of a clinical trial, especially within the context of advanced disease.

Lastly, with the incorporation of EV + P into the treatment landscape of mUC, further research is needed to determine the optimal duration for administering the combination therapy. A deeper understanding of resistance mechanisms and investigation into biomarkers that predict the response to EV + P could be leveraged to de-intensify treatment and reduce toxicity.

CONCLUSIONS

Treatment of mUC has undergone significant transformation with the advent of ICIs, ADCs, and targeted therapy. While PBC followed by switch-maintenance avelumab remains standard-of-care for eligible patients (Figure 2), the results of EV-302 and CM-901 have introduced other possible options to the 1L setting, adding complexity to the treatment algorithm (Figure 3).

Ongoing efforts towards a more personalized approach will hopefully help improve patient outcomes and quality of life. Furthermore, it is essential that all patients are referred to support or advocacy groups, such as Bladder Cancer Canada or the Bladder Cancer Advocacy Network, to provide them with additional support and information needed to actively participate in their cancer care.

COMPETING INTERESTS: Dr. Blais has participated in clinical trials supported by Alethia, AstraZeneca, CCTG, and Pfizer. Dr. Alimohamed has been an advisor/consultant for AstraZeneca, Bayer, BMS, EMD Serono, Gilead, Merck, Pfizer, and Seagen. Dr. Canil has been an advisory board member for Advanced Accel, Bayer, BMS, Eisai, EMD Serono, Ipsen, Merck, Novartis, Pfizer, and Seagen; a speaker for EMD Serono and Pfizer; has received a grant from Janssen; and has participated in clinical trials supported by Eisai and Pfizer. Dr Eigl has received honoraria from Astellas, AstraZeneca, Bayer, EMD Serono, Janssen, Merck Pfizer, Roche, and Seagen; and as Director of the Provincial Clinical Trials Office, BC Cancer, has had potential interaction with all sponsors of cancer clinical trials conducted in BC. Dr. Kulkarni has been an advisory board member for Abbvie, Astellas, Astra Zeneca, Bayer, BMS, EMD Serono, enGene, Ferring, Johnson & Johnson, Novartis, Pfizer , Photocure, Theralase, and Tolmar; has received honoraria from Ferring, Johnson & Johnson, TerSera, Tolmar, and Verity; and has participated in clinical trials supported by AstraZeneca, BMS, Johnson & Johnson, Merck, Pfizer, Seagen, Theralase, and Verity. Dr. Black has been an advisory board member for AbbVie, Astellas, AstraZeneca, Bayer, BMS, EMD Serono, Ferring, Janssen, MDxHealth, Merck, Minogue, Nonagen, Nanology, Pfizer, Protara, QED, Roche, Sanofi, Sesen, STIMIT, Therelase, UroGen, and Verity; a speakers' bureau member for Bayer, BioSyent, Pfizer, Sanofi, and TerSera; owns a patent marketed by Veracyte; and has participated in a clinical trial supported by Roche. Dr. Kassouf has been participated as consultant on advisory boards for Abbvie, Astellas, Bayer, BMS, EMD Serono, Ferring, Janssen, Merck, Roche, and Sesen Bio; and has participated in clinical trials supported by Astra Zeneca, BMS, Janssen, Pfizer, Sesen Bio, and Theralase. Dr. Chung has received honoraria from AbbVie, Knight, Tersera, Tolmar, and Verity. Dr. Jiang has been an advisory board member for Astra Zeneca/Merck, Bayer, EMD Serono, Janssen, McKesson, Novartis AAA, Pfizer, and Seagen; a speakers' bureau member for Amgen, Astellas, AstraZeneca, Bayer, EMD Serono, Janssen, Medunik, Novartis AAA, Pfizer, and Seagen; has received honoraria from Amgen, Astellas, Bayer, Pfizer, and TerSera; and has participated in clinical trials supported by AstraZeneca, Eli Lilli, Merck, and PointBiopharma. Dr. Sridhar has held an advisory role with Astellas, AstraZeneca, Bayer, Bicycle Therapeutics, BMS, Daiichi Sankyo, Eisai, EMD Serono, Gilead, Ipsen, Janssen, Merck, and Pfizer. Dr. Bossé has received honoraria for educational talks and/or advisory board participation from AstraZeneca, Bayer, BMS, EMD Serono, Ipsen, Janssen, Knight Therapeutics, Merck, and Pfizer; and received a grant for a radiomics project from Ipsen. Dr. Conter received payment for a data-driven decision-making tool at Roche Canada. The remaining authors and reviewers do not report any competing personal or financial interests related to this work.

REFERENCES

1. Bladder Cancer Statistics, Canadian Cancer Society. Available at: https://cancer.ca/en/cancer-information/cancer-types/bladder/statistics. Accessed April 28, 20240N
2. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase 3 study. *J Clin Oncol* 2000;18:3068-77. https://doi.org/10.1200/JCO.2000.18.17.3068
3. American Cancer Society. Overview of bladder cancer. Available at: https://www.cancer.org/content/dam/CRC/PDF/Public/8557.00.pdf. Accessed April 29, 2024.
4. Hassler MR, Moedlagl V, Hindinger H, et al. Treatment patterns and real-world outcomes for locally advanced or metastatic urothelial cancer in the era of immunotherapy. *Eur Urol Focus* 2023; Epub ahead of print. https://doi.org/10.1016/j.euf.2023.12.005
5. Barthelemy P, Loriot Y, Voog E, et al. Full analysis from AVENANCE: A real-world study of avelumab first-line (1L) maintenance treatment in patients (pts) with advanced urothelial carcinoma (aUC). *J Clin Oncol* 2023;41:471. https://doi.org/10.1200/JCO.2023.41.6_suppl.471
6. Warren M, Kolinsky M, Canil CM, et al. Canadian Urological Association/Genitourinary Medical Oncologists of Canada consensus statement: Management of unresectable locally advanced and metastatic urothelial carcinoma. *Can Urol Assoc J* 2019;13:318-27. https://doi.org/10.5489/cuaj.6015
7. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med* 2024;390:875-88. https://doi.org/10.1056/NEJMoa2312117
8. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. *N Engl J Med* 2023;389:1778-89. https://doi.org/10.1056/NEJMoa2309863
9. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med* 2020;383:1218-30. https://doi.org/10.1056/NEJMoa2002788
10. Mamtani R, Zhang H, Parikh RB, et al. Uptake of maintenance immunotherapy and changes in upstream treatment selection among patients with urothelial cancer. *JAMA Netw Open* 2023;6:e238395. https://doi.org/10.1001/jamanetworkopen.2023.8395
11. Li H, Herms L, Leong T, et al. US real-world first-line (1L) treatment patterns and outcomes for patients with metastatic urothelial carcinoma (mUC) following maintenance avelumab approval. *J Clin Oncol* 2023;41:Suppl:483. https://doi.org/10.1200/JCO.2023.41.6_suppl.483
12. Gupta S, Loriot Y, Van Der Heijden MS, et al. Patient-reported outcomes (PROs) from a randomized, phase 3 trial of enfortumab vedotin plus pembrolizumab (EV+P) versus platinum-based chemotherapy (PBC) in previously untreated locally advanced or metastatic urothelial cancer (la/mUC). *J Clin Oncol* 2024;42(16suppl):4502. https://doi.org/10.1200/JCO.2024.42.16_suppl.4502
13. Roth BJ, Dreicer R, Einhorn LH, et al. Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: A phase 2 trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1994;12:2264-70. https://doi.org/10.1200/JCO.1994.12.11.2264
14. Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy vs. chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): A randomized, open-label, phase 3 trial. *Lancet Oncol* 2021;22:931-45. https://doi.org/10.1016/S1470-2045(21)00152-2
15. Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): A multicenter, randomized, placebo-controlled phase 3 trial. *Lancet* 2020;395:1547-57. https://doi.org/10.1016/S0140-6736(20)30230-0

16. Galsky MD, Sonpavde GP, Powles T, et al. Characterization of complete responders to nivolumab + gemcitabine-cisplatin vs. gemcitabine-cisplatin alone and patients with lymph node-only metastatic urothelial carcinoma from the CheckMate 901 trial. *J Clin Oncol* 2024;42(16_suppl):4509. https://doi.org/10.1200/JCO.2024.42.16_suppl.4509
17. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma [published correction appears in *N Engl J Med* 2021;385:864]. *N Engl J Med* 2021;384:2102-14. https://doi.org/10.1056/NEJMoa2034442
18. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602-8. https://doi.org/10.1200/JCO.2005.07.757
19. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven-year update of an EORTC phase 3 trial of high-dose intensity M-VAC chemotherapy and G-CSF vs. classic M-VAC in advanced urothelial tract tumors. *Eur J Cancer* 2006;42:50-4. https://doi.org/10.1016/j.ejca.2005.08.032
20. De Santis M, Bellmunt J, Mead G, et al. Randomized phase 2/3 trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol* 2012;30:191-9. https://doi.org/10.1200/JCO.2011.37.3571
21. Galsky MD, Chen GJ, Oh WK, et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol* 2012;23:406-10. https://doi.org/10.1093/annonc/mdr156
22. Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. *J Clin Oncol* 2011;29:2432-8. https://doi.org/10.1200/JCO.2011.34.8433
23. Jiang DM, Gupta S, Kitchlu A, et al. Defining cisplatin eligibility in patients with muscle-invasive bladder cancer. *Nat Rev Urol* 2021;18:104-14. https://doi.org/10.1038/s41585-020-00404-6
24. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med* 2024;390:875-88. https://doi.org/10.1056/NEJMoa2312117
25. Sridhar SS, Powles T, Gupta S, et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Long-term follow-up from the JAVELIN Bladder 100 trial in subgroups defined by 1L chemotherapy regimen and analysis of overall survival (OS) from start of 1L chemotherapy. *J Clin Oncol* 2023;41:508. https://doi.org/10.1200/JCO.2023.41.6_suppl.508
26. Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol* 2016;2:234-40. https://doi.org/10.1001/jamaoncol.2015.4368
27. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* 2017;28:368-76. https://doi.org/10.1093/annonc/mdw443
28. Gupta S, Bellmunt J, Pimack ER, et al. Defining "platinum-ineligible" patients with metastatic urothelial cancer (mUC). *J Clin Oncol* 2022;40:4577. https://doi.org/10.1200/JCO.2022.40.16_suppl.4577
29. Vuky J, Balar AV, Castellano D, et al. Long-term outcomes in KEYNOTE-052: Phase 2 study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. *J Clin Oncol* 2020;38:2658-66. https://doi.org/10.1200/JCO.19.01213
30. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: A single-arm, multicenter, phase 2 trial [published correction appears in *Lancet* 2017;390:848]. *Lancet* 2017;389:67-76. https://doi.org/10.1016/S0140-6736(16)32455-2
31. de Wit R, Kruit WH, Stoter G, et al. Docetaxel (taxotere): An active agent in metastatic urothelial cancer; results of a phase 2 study in non-chemotherapy-pretreated patients. *Br J Cancer* 1998;78:1342-5. https://doi.org/10.1038/bjc.1998.681
32. Moore MJ, Tannock IF, Ernst DS, et al. Gemcitabine: A promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 1997;15:3441-5. https://doi.org/10.1200/JCO.1997.15.12.3441
33. Stadler WM, Kuzel T, Roth B, et al. Phase 2 study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 1997;15:3394-8. https://doi.org/10.1200/JCO.1997.15.11.3394
34. O'Donnell PH, Milowsky MI, Petrylak DP, et al. Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer. *J Clin Oncol* 2023;41:4107-17. https://doi.org/10.1200/JCO.22.02887
35. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med* 2019;381:338-48. https://doi.org/10.1056/NEJMoa1817323
36. Loriot Y, Matsubara N, Park SH, et al. Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. *N Engl J Med* 2023;389:1961-71. https://doi.org/10.1056/NEJMoa2308849
37. Vaughn DJ, Broome CM, Hussain M, et al. Phase 2 trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002;20:937-40. https://doi.org/10.1200/JCO.2002.20.4.937
38. McCaffrey JA, Hilton S, Mazumdar M, et al. Phase 2 trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997;15:1853-17. https://doi.org/10.1200/JCO.1997.15.5.1853
39. Ko YJ, Canil CM, Mukherjee SD, et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicenter, phase 2 study. *Lancet Oncol* 2013;14:769-76. https://doi.org/10.1016/S1470-2045(13)70162-1
40. Sridhar SS, Blais N, Tran B, et al. Efficacy and safety of nab-paclitaxel vs paclitaxel on survival in patients with platinum-refractory metastatic urothelial Cancer: The Canadian Cancer Trials Group BL.12 randomized clinical trial. *JAMA Oncol* 2020;6:1751-8. https://doi.org/10.1001/jamaoncol.2020.3927
41. Raggi D, Miceli R, Sonpavde G, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: A systematic review and meta-analysis. *Ann Oncol* 2016;27:49-61. https://doi.org/10.1093/annonc/mdv509
42. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 2021;384:1125-35. https://doi.org/10.1056/NEJMoa2035807
43. Rosenberg JE, Powles T, Sonpavde GP, et al. EV-301 long-term outcomes: 24-month findings from the phase 3 trial of enfortumab vedotin vs. chemotherapy in patients with previously treated advanced urothelial carcinoma. *Ann Oncol* 2023;34:1047-54. https://doi.org/10.1016/j.annonc.2023.08.016
44. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicenter, phase 2 trial. *Lancet* 2016;387:1909-20. https://doi.org/10.1016/S0140-6736(16)00561-4
45. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab vs. chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicenter, open-label, phase 3 randomized controlled trial [published correction appears in *Lancet* 2018;392:1402]. *Lancet* 2018;391:748-57. https://doi.org/10.1016/S0140-6736(17)33297-X
46. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376:1015-26. https://doi.org/10.1056/NEJMoa1613683
47. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicenter, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312-22. https://doi.org/10.1016/S1470-2045(17)30065-7
48. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: Updated results from a phase 1/2 open-label study. *JAMA Oncol* 2017;3:e172411. https://doi.org/10.1001/jamaoncol.2017.2411
49. Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): Pooled results from two expansion cohorts of an open-label, phase 1 trial [published correction appears in *Lancet Oncol* 2018;19:e335]. *Lancet Oncol* 2018;19:51-64. https://doi.org/10.1016/S1470-2045(17)30900-2
50. Balar AV, Castellano DE, Grivas P, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: Results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of followup. *Ann Oncol* 2023;34. https://doi.org/10.1016/j.annonc.2022.11.012
51. Di Nunno V, De Luca E, Buttigliero C, et al. Immune-checkpoint inhibitors in previously treated patients with advanced or metastatic urothelial carcinoma: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2018;129:124-32. https://doi.org/10.1016/j.critrevonc.2018.07.004
52. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A phase 2 open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. *J Clin Oncol* 2021;39:2474-85. https://doi.org/10.1200/JCO.20.03489
53. Franzese C, Francolini G, Nicosia L, et al. Stereotactic body radiation therapy in the management of oligometastatic and oligoprogressive bladder cancer and other urothelial malignancies. *Clin Oncol* 2021;33:50-6. https://doi.org/10.1016/j.clon.2020.07.008
54. Sheng X, He Z, Shi Y, et al. RC48-ADC for metastatic urothelial carcinoma with HER2-positive: Combined analysis of RC48-C005 and RC48-C009 trials. *J Clin Oncol* 2022;40:4520. https://doi.org/10.1200/JCO.2022.40.16_suppl.4520
55. Zhou L, et al. RC48-ADC combined with toripalimab, an anti-PD-1 monoclonal antibody (Ab), in patients with locally advanced or metastatic urothelial carcinoma (UC): Preliminary results of a phase 1b/2 study. *J Clin Oncol* 2021;39:4534. https://doi.org/10.1200/JCO.2021.39.15_suppl.4534

56. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with her2-expressing solid tumors: Primary results from the DESTINY-PanTumor02 phase 2 trial. *J Clin Oncol* 2024;42:47-58. https://doi.org/10.1200/JCO.23.02005
57. Hermans TJ, Fransen van de Putte EE, Horenblas S, et al. Pathological downstaging and survival after induction chemotherapy and radical cystectomy for clinically node-positive bladder cancer-Results of a nationwide population-based study. *Eur J Cancer* 2016;69:1-8. https://doi.org/10.1016/j.ejca.2016.09.015
58. Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis. *Lancet* 2003;361:1927-34. https://doi.org/10.1016/S0140-6736(03)13580-5
59. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012;366:1477-88. https://doi.org/10.1056/NEJMoa1106106
60. Seisen T, Sun M, Leow JJ, et al. Efficacy of high-intensity local treatment for metastatic urothelial carcinoma of the bladder: A propensity score-weighted analysis from the national cancer data base. *J Clin Oncol* 2016;34:3529-36. https://doi.org/10.1200/JCO.2016.66.7352
61. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab vs. placebo in muscle-invasive urothelial carcinoma [published correction appears in *N Engl J Med* 20216;385:864]. *N Engl J Med* 2021;384:2102-14. https://doi.org/10.1056/NEJMoa2034442
62. Apolo A, Ballman KV, Sonpavde GP, et al. AMBASSADOR Alliance A031501: Phase 3 randomized adjuvant study of pembrolizumab in muscle-invasive and locally advanced urothelial carcinoma (MIUC) vs. observation. *J Clin Oncol* 2024;42:LBA531. https://doi.org/10.1200/JCO.2024.42.4_suppl.LBA531
63. Als AB, Sengelov L, von der Maase H. Long-term survival after gemcitabine and cisplatin in patients with locally advanced transitional cell carcinoma of the bladder: Focus on supplementary treatment strategies. *Eur Urol* 2007;52:478-86. https://doi.org/10.1016/j.eururo.2007.03.016
64. Urakami S, Yuasa T, Yamamoto S, et al. Clinical response to induction chemotherapy predicts improved survival outcome in urothelial carcinoma with clinical lymph nodal metastasis treated by consolidative surgery. *Int J Clin Oncol* 2015;20:1171-8. https://doi.org/10.1007/s10147-015-0839-y
65. Ghadjar P, Burkhard FC, Gautschi O, et al. Induction chemotherapy for unresectable urothelial carcinoma of the bladder. *BJU Int* 2011;107:894-7. https://doi.org/10.1111/j.1464-410X.2010.09574.x
66. Herr HW, Donat SM, Bajorin DF. Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. *J Urol* 2001;165:811-4. https://doi.org/10.1016/S0022-5347(05)66533-0
67. Ho PL, Willis DL, Patil J, et al. Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: The MD Anderson Cancer Center Experience. *Urol Oncol* 2016;34:59.e1-598. https://doi.org/10.1016/j.urolonc.2015.08.012
68. Meijer RP, Mertens LS, van Rhijn BW, et al. Induction chemotherapy followed by surgery in node positive bladder cancer. *Urology* 2014;83:134-9. https://doi.org/10.1016/j.urology.2013.08.082
69. Powles T, Perez-Valderrama B, Gupta S, et al. EV-302/KEYNOTE-A39: Open-label, randomized phase 3 study of enfortumab vedotin in combination with pembrolizumab vs chemotherapy in previously untreated locally advanced or metastatic urothelial carcinoma. *Ann Oncol* 2023:S1254-1335. https://doi.org/10.1016/j.annonc.2023.10.106
70. Li R, Metcalfe M, Kukreja J, et al. Role of radical cystectomy in non-organ confined bladder cancer: A systematic review. *Bladder Cancer* 2018;4:31-40. https://doi.org/10.3233/BLC-170130
71. Han WS, Kim K, Park JS. Result of surgical resection for pulmonary metastasis from urothelial carcinoma. *Korean J Thorac Cardiovasc Surg* 2012;45:242-5. https://doi.org/10.5090/kjtcs.2012.45.4.242
72. Abe T, Minami K, Harabayashi T, et al. Prognostic impact of local radiotherapy on metastatic urothelial carcinoma patients receiving systemic chemotherapy [correction published in *Jpn J Clin Oncol* 2020;50:727]. *Jpn J Clin Oncol* 2020;50:206-13. https://doi.org/10.1093/jjco/hyz152
73. Aboudaram A, Chaltiel L, Pouessel D, et al. Consolidative radiotherapy for metastatic urothelial bladder cancer patients with no progression and with no more than five residual metastatic lesions following first-line systemic therapy: A retrospective analysis. *Cancers* 2023;15:1161. https://doi.org/10.3390/cancers15041161
74. Patel PH, Palma D, McDonald F, et al. The dandelion dilemma revisited for oligoprogression: Treat the whole lawn or weed selectively? *Clin Oncol* 2019;31:824-33. https://doi.org/10.1016/j.clon.2019.05.015
75. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: A multicenter, randomized, controlled, phase 2 study. *Lancet Oncol* 2016;17:1672-82. https://doi.org/10.1016/S1470-2045(16)30532-0
76. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver: A prognostic scoring system to improve case selection, based on 1568 patients. Cancer 1996;77:1254-62. https://doi.org/10.1002/(SICI)1097-0142(19960401)77:7<1254::AID-CNCR5>3.0.CO;2-I
77. Pfister C, Gravis G, Flechon A, et al. Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (VESPER): Survival endpoints at 5 years in an open-label, randomized, phase 3 study. *Lancet Oncol* 2024;25:255-64. https://doi.org/10.1016/S1470-2045(23)00587-9
78. Longo N, Celentano G, Napolitano L, et al. Metastasis-directed radiation therapy with consolidative intent for oligometastatic urothelial carcinoma: A systematic review and meta-analysis. *Cancers* 2022;14:2373. https://doi.org/10.3390/cancers14102373
79. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomized, phase 2, open-label trial. *Lancet* 2019;393:2051-8. https://doi.org/10.1016/S0140-6736(18)32487-5
80. Francolini G, Desideri I, Detti B, et al. Stereotactic radiotherapy in oligoprogressive and oligorecurrent urothelial cancer patients: A retrospective experience. *Cancer Treat Res Commun* 2019;19:100124. https://doi.org/10.1016/j.ctarc.2019.100124
81. Bamias A, Davis ID, Galsky MD, et al. Atezolizumab monotherapy vs. chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (IMvigor130): Final overall survival analysis from a randomized, controlled, phase 3 study. *Lancet Oncol* 2024;25:46-61. https://doi.org/10.1016/S1470-2045(23)00539-9
82. Powles T, Assaf ZJ, Degaonkar V, et al. Updated overall survival by circulating tumor DNA status from the phase 3 IMvigor010 trial: Adjuvant atezolizumab vs. observation in muscle-invasive urothelial carcinoma. *Eur Urol* 2024;85:114-22. https://doi.org/10.1016/j.eururo.2023.06.007

CORRESPONDENCE: Dr. Srikala S. Sridhar, Division of Hematology and Medical Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; Srikala.Sridhar@uhn.ca