Latin American Consensus for the Evaluation and Treatment of Patients With Metastatic/Locally Advanced Urothelial Carcinoma

Ray Manneh Kopp, MD, MS[1]; Fernando Galanternik, MD, MS[2]; Fabio A. Schutz, MD[3]; Fabio Kater, MD[3]; Allan Ramos-Esquivel, MD, PhD[4]; Silvia Neciosup, MD, MS, PhD[5]; Nora Sobrevilla-Moreno, MD[6]; Laura Bernal Vaca, MD[7]; Linda Ibatá-Bernal, MD, MS[8]; Susan Martínez-Rojas, MD, MS[8]; and Maria T. Bourlon, MD, MS[9]

DOI https://doi.org/10.1200/GO.23.00244

ABSTRACT

PURPOSE Urothelial cancer accounts for approximately 3% of new cancer cases worldwide, with a high burden of disease in countries with medium and low human development indexes where its incidence and mortality are increasing. The purpose of this consensus is to develop statements on the evaluation and treatment of locally advanced and metastatic urothelial carcinoma that would further guide the clinical practice in Latin America.

METHODS A systematic review of the literature was conducted by an independent team of methodologists. Then, a modified Delphi method was developed with clinical specialists from different Latin American countries.

RESULTS Forty-two consensus statements, based on evidence, were developed to address the staging, the evaluation (suitability for chemotherapy, risk assessment, and biomarkers), and systemic treatment (first-line and subsequent therapies) of locally advanced or metastatic urothelial carcinoma. The statements made in this consensus are suggested practice recommendations in the Latin American context; however, the importance of a complete and individualized patient evaluation as a guide for therapeutic selection is highlighted. The availability and affordability of support tools for the evaluation of the disease, as well as specific therapies, may limit the application of the best practices suggested.

RECOMMENDATIONS Therapeutic decisions need to be tailored to the context-specific clinical setting and availability of resources. Local research is promoted to improve outcomes for patients with this challenging cancer in Latin America.

ACCOMPANYING CONTENT

Appendix

Data Supplement

Accepted November 7, 2023
Published January 25, 2024

JCO Global Oncol 10:e2300244

INTRODUCTION

Urothelial cancer represents 3% of new cancer cases worldwide, ranking eleventh in incidence, with 573,000 new cases each year.[1] This disease is four times more common in men than in women,[2,3] and 90% of diagnoses are made in people age 55 years or older. Although most cases are reported in countries with high and very high human development index, the burden of this disease is more significant in countries with medium and low human development index, where there is an increase in incidence and mortality from this cause.[4] It is estimated that in Latin America and the Caribbean countries, there are 33,840 new cases and 13,100 deaths from this cause each year.[2]

Within the clinical spectrum of urothelial cancer, the greatest burden of morbidity and mortality is associated with muscle-invasive disease (MIBC). At the time of diagnosis, approximately 25% of bladder cancers are MIBC without extra bladder extension, while 5% of cases correspond to a locally advanced tumor involving nearby tissues or spread to nonregional lymph nodes or distant organs.[5] Nearly 50% of patients with MIBC who undergo treatment with curative intent will eventually relapse and develop metastatic disease.[5] Patients with MIBC have a poor prognosis, with a 5-year survival without treatment of approximately 5%.[6]

Advanced metastatic involvement in urothelial cancer requires a therapeutic approach focused on maintaining the quality of life and prolonging survival. Currently, most of the clinical practice guidelines available on the evaluation and systemic treatment of patients with locally advanced and metastatic urothelial carcinoma come from developed countries in Asia,[7] Europe,[8-10] and North America.[11]

However, there are few recommendations on this for developing countries, such as Latin America, specifically considering the limited resources and significant barriers to access for timely diagnosis and treatment.[12]

Given this, the purpose of this consensus is to develop statements on the evaluation and treatment of locally advanced and metastatic urothelial carcinoma that would further guide the clinical practice in Latin America. Considering the heterogeneity of this region in the ethnic, social, cultural, and economic aspects, the recommendations must be adapted to the reality of each country.

METHODS

Participants

A group of clinical oncologists, representatives of different Latin American countries, and an independent methodologic team developed this consensus. This panel was selected on the basis of their specific experience in urothelial cancer and their availability for the activities of review of evidence and discussions for the construction and validation of recommendations. Detailed information about the participants and their declarations of interest, made preliminarily in the consensus process, are described in the Data Supplement.

Evidence Search and Formulation

All members of the panel formulated the scope of the consensus in a session. The target population was defined as adults with locally advanced unresectable urothelial carcinoma and/or metastatic disease. The contents were classified into staging, evaluation (aptitude for chemotherapy, risk assessment, and biomarkers), and systemic treatment (first-line and subsequent therapies).

A systematic review of the literature was performed. The literature search was carried out in April 2022 in databases of compiling agencies and developers of clinical practice guidelines, with strategies adapted to each database, with the free terms: "bladder" AND "cancer OR neoplasia OR tumor" AND "guideline." Clinical practice guidelines, evidence-based recommendations documents, systematic literature reviews, clinical trials, and observational studies were eligible for inclusion. Only documents available as a complete publication, in English and Spanish, published in the past 7 years, were considered. Previous versions of guidelines were excluded. Additional material was searched in relevant international scientific societies and electronic databases (PubMed and Latin American and Caribbean Health Sciences Literature [LILACS]).

For the selection of the identified references, two reviewers independently evaluated the documents under the eligibility criteria, initially screening the references by title and abstract and then reviewing the full text of the articles. Disagreements about the inclusion criteria were solved by discussion. The search specifications and evidence selection are detailed in the Data Supplement.

The quality of the clinical practice guidelines was evaluated using the AGREE-II tool. The recommendations and statements were extracted from the highest-quality evidence in a preset format according to the predefined thematic matrix. The missing information was completed with targeted searches.

Delphi Process

The consensus process was developed with a modified Delphi method. The questionnaire items were organized in sections according to the predefined topics. The panel of experts reviewed them to determine the need to make adjustments, deletions, or additions. The final version of the questionnaire included 80 items distributed in five thematic blocks: staging, aptitude for chemotherapy, risk assessment, biomarkers, and systemic treatment. The questionnaire was sent to all panel members in the first round. A 5-point Likert-type scale was used to evaluate the statements, according to the *appropriateness method* developed by the RAND Corporation and the University of California at Los Angeles (UCLA).[13] In a second round with the panel, anonymous voting results were shown, and items without consensus were revisited and voted on again. Final recommendations were reformulated and defined. The specifications of the Delphi process for assessment and definition of consensus, as well as the clinical questions, can be found in the Data Supplement.

Cost-effectiveness and access to therapies were considered to contextualize the recommendations in a region with limited resources.

RESULTS

General Considerations

The statements made from this consensus are suggested practice recommendations without constituting a limiting care guideline, particularly in the Latin American context, where it is essential to consider therapeutic decisions in light of the realities of the specific clinical setting and the availability of resources.

Managing patients in advanced stages of the oncologic disease can be challenging. Providing clear and comprehensive information to patients about all the possible benefits and side effects of each therapy facilitates shared decision making.

Regardless of the specific regimen used, patients receiving chemotherapy should be reassessed every three to four cycles. Treatment must be continued until disease progression or unacceptable toxicity.

All patients should be referred early to palliative care for simultaneous management, with benefits that include reduction of disease-related symptoms, improvement in functional status, increase in quality of life, and reduction in the use of systemic treatments at the end of life.[14]

Staging

Images of the chest, abdomen, and pelvis allow the characterization of the primary tumor and the identification of metastatic lesions (Table 1). At the pulmonary level, metastases typically present as multiple and bilateral pulmonary nodules that are well defined, not calcified, and predominantly basal and peripheral in location.[15,16] Most lymph node metastases that originate in urogenital cancer are located in the retroperitoneum, and the risk of malignancy is strongly associated with the size of the nodules, with nodules larger than 1 cm (on their short axis) highly suspicious of metastatic disease.[16,17]

Computed tomography (CT) and magnetic resonance imaging (MRI) are the standard imaging techniques for assessing local and distant disease.[16,18] Bone scans remain the most widely used imaging technique for detecting and monitoring osteoblastic lesions.[16] On the other hand, diagnostic ureteroscopy is helpful in cases of suspected upper urinary tract involvement.[19]

Fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) has proven to be a good alternative to identify lung, liver, and bone metastases. It has a sensitivity of 96% and a specificity of 88% for lung metastases and has been described as effective as MRI and CT in detecting liver metastases.[16] In identifying bone metastases, the sensitivity and specificity reported are 94% and 76%, respectively.[20] Along with a standard CT scan, FDG-PET-CT provides a further improvement in the staging of urothelial carcinoma.[21-24] However, it does not perform well in the evaluation of urinary tract lesions because of the FDG being excreted in urine,[25] The higher cost of FDG-PET may limit its access, so it is recommended only in selected patients.[22]

Regarding the feasibility of implementing these interventions, the experts recognize the limitations of access to some studies, such as FDG-PET-CT in certain Latin American countries, so the recommendations are subject to the availability and affordability of these support strategies in the different territories and health systems of the region.

TABLE 1. Staging of Advanced Metastatic Urothelial Carcinoma in Latin America

Staging in Advanced Metastatic Urothelial Cancer	Agreement, %
Perform chest tomography with or without contrast (preferred) for staging the disease.	100
If not performed in the initial evaluation, perform tomography or magnetic resonance imaging of the abdomen and pelvis with intravenous contrast.	100
Consider FDG-PET-CT in selected patients with muscle-invasive bladder cancer, including those with low glomerular filtration rate, allergy to contrast media, or in whom imaging is inconclusive.	89
If upper tract lesions are suspected, perform ureteroscopy and consider biopsy only when additional information can modify treatment decisions.	100
Perform brain MRI with and without intravenous contrast only in symptomatic or selected high-risk patients (eg, small cell histology).	89
Consider brain tomography with intravenous contrast only when symptomatic patients cannot undergo MRI (incompatible cardiac pacemaker, implant, or foreign body).	78
Perform bone scans in symptomatic patients or patients with elevated alkaline phosphatase.	89
Consider node biopsy if evidence of spread is limited to regional nodes and biopsy is technically feasible.	89
Perform a complete blood count with differential, electrolytes, kidney and liver function tests, and alkaline phosphatase within 2 weeks before the start of chemotherapy. Consider screening for hepatitis B and HIV in patients starting systemic chemotherapy.	100

Abbreviations: FDG-PET-CT, fluorodeoxyglucose positron emission tomography-computed tomography; MRI, magnetic resonance imaging.

Assessment of Fitness for Chemotherapy, Risk Stratification, and Biomarkers

Table 2.

Assessment of Suitability for Chemotherapy With Cisplatin

Cisplatin constitutes a fundamental pillar in the chemotherapeutic treatment of patients with locally advanced and metastatic urothelial carcinoma.[26] However, the excretion of cisplatin by the kidneys can cause tubulointerstitial injury, the risk of which increases due to decreased blood flow in the renal vasculature, usually because of dehydration and hypotension.[27] This cisplatin-induced nephrotoxicity is dose-dependent and produces reduced renal clearance, hypomagnesemia, and hypokalemia.[27] In addition, the use of cisplatin-based chemotherapy in patients with urothelial cancer also has been limited by other toxicities, particularly in patients with comorbidities.[26] The overall proportion of patients ineligible for cisplatin-based chemotherapy varies in different populations and can reach more than 40%.[28]

Although experts report taking into account Galsky's criteria[29] to determine the eligibility for cisplatin, they consider that it must be evaluated individually. The essential attributes to define chemotherapy fitness are functional status and creatinine clearance. Experts also consider using *split-dose* cisplatin feasible in patients with creatinine clearance between 50 and 60 mL/min.[30]

TABLE 2. Evaluation of Advanced Metastatic Urothelial Carcinoma in Latin America

Suitability for Chemotherapy With Cisplatin	Agreement, %
To assess the patient's eligibility for cisplatin, the Galsky criteria are generally considered, which include at least one of the following: ECOG 2 or Karnofsky performance status <60%-70%, creatinine clearance <60 ml/min, NYHA class III heart failure, grade ≥2 hearing loss, and/or grade ≥2 peripheral neuropathy (CTCAE v4). *In patients with creatinine clearance of 50-60 ml/min, consider using split-dose cisplatin regimens.	100
To assess the patient's eligibility for cisplatin, an estimated GFR must be obtained. For patients with equivocal GFR results, a 24-hour urine collection or glomerular filtration scan may be considered to determine eligibility for cisplatin treatment.	100
Risk assessment	
Consider the Bajorin criteria (presence of Karnofsky functional status <80% and/or visceral metastases to lung, liver, or bone) as prognostic factors in the survival of patients with urothelial cell carcinoma.	89
In patients receiving first- or second-line treatment, consider the Bellmunt criteria (presence of liver metastases, poor performance status [ECOG > 0], and hemoglobin level <10 g/dL) as predictors of a worse prognosis in terms of OS.	100
For the prognostic classification in patients undergoing second-line treatment, in addition to the Bellmunt criteria, the time since the last chemotherapy could be considered. The time since the previous chemotherapy that best discriminates patients with the worst prognosis is 3 months when they received chemotherapy for metastatic disease and 10 months when the chemotherapy was perioperative.	89
In patients with advanced urothelial carcinoma unresponsive to platinum chemotherapy, albumin below the lower limit of normal is considered a poor prognostic factor for OS in addition to time since previous chemotherapy, hemoglobin, functional status, and visceral metastases.	89
Molecular/genomic tests	
Molecular/genomic testing should only be performed in laboratories qualified to perform highly complex molecular pathology tests.	100
FGFR alteration testing should be considered, depending on the availability of the test and the patient's condition. This will help plan future lines of therapy.	100
Molecular/genomic testing should be performed early, ideally at the time of advanced bladder cancer diagnosis, to facilitate treatment decisions and to avoid delays in starting subsequent lines of therapy.	100
In addition to determining eligibility for specific therapies in clinical practice, molecular/genomic testing can be used to assess eligibility for clinical trials.	
Genomic tests (on the basis of PCR or NGS) should be used to detect *FGFR 2/3* mutations and fusions.	100
Identifying PD-L1 expression helps select patients for monotherapy with immune checkpoint inhibitors in the context of advanced disease in patients not eligible for chemotherapy and without previous treatment.	63

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FGFR, fibroblast growth factor receptor; GFR, glomerular filtration rate; NGS, next-generation sequencing; NYHA, New York Heart Association Heart Failure Rating Scale; OS, overall survival; PCR, polymerase chain reaction.

Risk Assessment

Despite the introduction of cisplatin-based chemotherapy regimens, the outcome of patients with advanced urothelial carcinoma is widely variable according to the stage of the disease, the conditions of the patients, and the therapies administered. For this reason, it is necessary to implement criteria and risk scales to identify those patients with a worse prognosis to better stratify patient's treatments and for patient counseling and follow-up. The first prognostic model for urothelial carcinoma was developed by Bajorin et al[31] and included assessing the functional status and visceral metastases as independent predictors of overall survival (OS).[32] The median survival times for patients with zero, one, or two risk factors (Karnofsky functional status <80% and/or presence of metastases in the lung, liver, or bone) were 33, 13.4, and 9.3 months, respectively (P = .0001).[31] The Bellmunt score was developed in patients who progressed after first-line platinum-based chemotherapy. It was determined that visceral metastases, specifically liver metastases, poor functional status, and anemia with hemoglobin level <10 g/dL were associated with a worse prognosis.[33] These two scores were developed in cohorts that received cytotoxic chemotherapy (first and second line, respectively), and although they have been used in recent clinical trials, there are new models that include other prognostic parameters, such as the albumin,[34,35] and C-reactive protein levels,[36] as well as the time since the last chemotherapy.[37] Risk assessment criteria allow the stratification of patients in clinical trials and provide prognostic information. The panel of experts recommends a closer follow-up in patients identified with a worse prognosis.

Molecular/Genomic Tests

Complete genomic profiling studies using validated sequencing platforms on the basis of hybrid capture have identified multiple potentially clinically relevant genetic alterations in patients with advanced metastatic urothelial carcinoma.[38] These genetic alterations are potential predictors of the therapeutic response of target-specific drugs. In a single-arm phase II clinical trial, erdafitinib was shown to induce an objective tumor response in up to 40% of patients with locally advanced and unresectable urothelial carcinoma with genetic alterations (mutations and fusions) in the fibroblast growth factor receptor (*FGFR*).[39]

Likewise, independent data monitoring committee analysis of the phase III KEYNOTE-361[40] and IMVIGOR-130[41] clinical trials found that patients whose tumors had low PD-L1 expression who were randomly assigned to the monotherapy arms (pembrolizumab and atezolizumab, respectively) had reduced survival compared with patients receiving cisplatin or carboplatin-based chemotherapy. Therefore, the studies for pembrolizumab and atezolizumab suspended the accrual of patients whose tumors had low expression of PD-L1 in the monotherapy arms with these molecules.[42]

In the Latin American context, there are limitations to access to molecular and genomic tests; however, as stated in the recommendations, it is ideal to have these tests to support therapy planning. The identification of PD-L1 is not routinely performed in practice. However, if the patient is not eligible for platinum-based chemotherapy, the determination of PD-L1 can be helpful in determining eligibility for immunotherapy. No expert panel consensus was reached regarding the utility of PD-L1 in the first-line treatment of patients with advanced disease not eligible for chemotherapy with cisplatin. There is insufficient clinical evidence or randomized phase III clinical trials to make this therapeutic decision.

First-Line Systemic Therapy in Patients Eligible for Cisplatin Chemotherapy

A meta-analysis[43] that compared the efficacy on clinical outcomes of cisplatin versus carboplatin-based chemotherapy demonstrated a significantly greater likelihood of achieving an objective response and, in particular, a complete response, with cisplatin versus carboplatin-based therapy as first-line treatment in carcinoma locally advanced and metastatic urothelial. Cisplatin-based chemotherapy was associated with a significantly higher probability of achieving a complete response (relative risk [RR], 3.54 [95% CI, 1.48 to 8.49]; P = .005) and an overall response (RR, 1.34 [95% CI, 1.04 to 1.71]; P = .02). These findings support current practice guidelines that recommend cisplatin-based combination chemotherapy as standard first-line treatment for cisplatin-eligible patients with metastatic urothelial carcinoma (Table 3).

TABLE 3. First-Line Systemic Therapy in Advanced Metastatic Urothelial Carcinoma in Patients Eligible for Chemotherapy With Cisplatin

First-Line Systemic Therapy in Patients Eligible for Cisplatin Chemotherapy	Agreement, %
The preferred regimen for treating patients eligible for cisplatin chemotherapy is the combination of gemcitabine and cisplatin.* The recommended duration of treatment is four to six cycles with imaging evaluation intervals every three or four cycles or according to clinical criteria. In case of complete response, partial response, or stable disease, continue maintenance therapy with avelumab until disease progression or unacceptable toxicity Remarks: *Standard dosage: cisplatin 70 mg/m^2 once on day 1, and gemcitabine 1,250 mg/m^2 once on days 1 and 8 in cycles of 21 days, or once on days 1, 8, and 15 in cycles of 28 days Avelumab maintenance therapy: standard dosage 800 mg IV once on day 1 in 14-day cycles	100
An alternative regimen for treating patients eligible for cisplatin chemotherapy is the combination of ddMVAC* with growth factor support. The recommended duration of treatment is four to six cycles of platinum-based chemotherapy with imaging evaluation intervals every four or six cycles or according to clinical criteria. In case of complete response, partial response, or stable disease, continue maintenance therapy with avelumab until disease progression or unacceptable toxicity Remarks: *The standard dosage for ddMVAC is methotrexate 30 mg/m^2 once on day 1, cisplatin 70 mg/m^2 once on day 2, vinblastine 3 mg/m^2 once on day 2, and doxorubicin 30 mg/m^2 once on day 2 in cycles of 14 days (with granulocyte colony-stimulating factor)	100

Abbreviations: ddMVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; IV, intravenous route.

It has been shown that the number of chemotherapy cycles and the sites of metastasis affect the survival of patients with metastatic urothelial carcinoma; therefore, in highly selected patients, a multimodal approach that includes metastasectomy could contribute to long-term disease control, although there is no evidence from controlled clinical trials regarding the effectiveness of this intervention.[44]

Experts recommend a treatment duration of four to six cycles of platinum-based chemotherapy with imaging evaluation intervals every three to four treatment cycles or earlier, in the phase of induction chemotherapy, depending on clinical criteria. Barriers to access to specialized care in some countries in Latin America may limit the frequency of clinical imaging, so clinical criteria can be considered a tool to define the benefit of treatment.

First-Line Systemic Therapy in Patients Ineligible for Cisplatin Chemotherapy

Different therapeutic alternatives have been proposed for patients not eligible for first-line therapy with cisplatin (Table 4). The preferred regimen is a combination of gemcitabine and carboplatin. The phase II/III clinical trial comparing methotrexate/carboplatin/vinblastine (M-CAVI) and carboplatin/gemcitabine (GC) in cisplatin-unfit patients reported an objective response rate (ORR) of 42% for GC versus 30% for M-CAVI. Severe acute toxicity was lower in the GC (13.6% *v* 23%). Limited benefit of combined therapy was observed in patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥2 and impaired renal function.[45]

Other combinations, such as gemcitabine and paclitaxel, have been studied as first- and second-line treatments. Generally, this combination is well tolerated and produces response rates between 38% and 60% in both lines.[46,47] Experts consider gemcitabine, alone or in combination with paclitaxel, to be first-line treatment alternatives in some patients, especially those who do not tolerate carboplatin and who are not candidates for immunotherapy.[46-49]

For patients showing stable disease or response throughout first-line chemotherapy treatment with platinum, maintenance treatment with avelumab is recommended. This recommendation is based on the results of the phase III randomized clinical trial JAVELIN Bladder 100, where it was observed that the OS in patients treated with avelumab was higher compared with the best supportive treatment (median OS of 21.4 *v* 14.3 months; hazard ratio [HR], 0.69 [95% CI, 0.56 to 0.86]; P = .001).[50] The OS benefit was observed in

TABLE 4. First-Line Systemic Therapy in Advanced Metastatic Urothelial Carcinoma in Patients Not Eligible for Chemotherapy With Cisplatin

First-Line Systemic Therapy in Patients Ineligible for Cisplatin Chemotherapy	Agreement, %
The preferred regimen for treating patients ineligible for cisplatin is the combination of gemcitabine and carboplatin.* In case of complete response, partial response, or stable disease, continue maintenance therapy with avelumab until disease progression or unacceptable toxicity. Remarks: *Standard dosage: carboplatin AUC5 day 1, and gemcitabine 1,000 mg/m^2 once on days 1 and 8 in cycles of 21 days or once on days 1, 8, and 15 in cycles of 28 days Avelumab maintenance therapy: standard dosage 800 mg IV once on day 1 in 14-day cycles	100
Pembrolizumab alone is a first-line option for platin-ineligible patients whose tumors express PD-L1. Remarks: *Standard dosage for pembrolizumab: 2 mg/kg to a maximum of 200mg IV once per day in 21-day cycles or fixed dose: 200 mg once every 3 weeks or 400 mg once every 6 weeks	80
Pembrolizumab alone is an option in patients who are not eligible for platinum chemotherapy regardless of PD-L1 expression, especially in patients without other treatment options. Remarks: *Standard dosage for pembrolizumab: 2 mg/kg to a maximum of 200mg IV once per day in 21-day cycles or fixed dose: 200 mg once every 3 weeks or 400 mg once every 6 week	60
Highly selected patients with oligometastatic disease who do not have evidence of rapid progression may benefit from metastasectomy or local ablative therapy after response to systemic therapy.	100

Abbreviation: IV, intravenous route.

all prespecified subgroups. Regarding safety, adverse events ≥grade 3 related to the treatment were reported in 16.6% of the patients treated with avelumab versus 0% of those treated with the best supportive treatment.

In recent years, the use of first-line immunotherapy has been approved in some patients. The single-arm, phase II KEYNOTE-052 trial evaluated pembrolizumab as a first-line treatment in these patients and reported an ORR of 24%, with 5% of patients achieving a complete response. Grade 3 or higher treatment-related adverse events occurred in 16% of patients treated with pembrolizumab at the time of data cutoff.[51] The long-term results were consistent with the initial analysis, with an ORR of 28.6% and a median OS of 11.3 months.[52] Additionally, the phase III KEYNOTE-361 trial[40] showed, after a median follow-up of 31.7 months, that the addition of pembrolizumab to chemotherapy did not significantly prolong the median progression-free survival (PFS) or OS compared with chemotherapy alone (8.3 *v* 7.1 months for PFS; $P = .0033$; and 17.0 *v* 14.3 months for OS; $P = .0407$). However, the phase II IMvigor210 multicenter trial evaluated atezolizumab in patients ineligible for cisplatin and reported an ORR of 23%, with 9% of patients showing a complete response. The median OS was 15.9 months. Grade 3 or 4 treatment-related adverse events occurred in 16% of patients.[53]

In May 2018, the US Food and Drug Administration issued a safety alert for the use of pembrolizumab and atezolizumab in the first line, as data from clinical trials showed a decrease in survival of patients receiving pembrolizumab or atezolizumab as first-line monotherapy compared with those receiving a therapy based on cisplatin or carboplatin, so the indication of these two drugs was modified, restricting it to patients who were not eligible for any platinum chemotherapy regardless of PD-L1, and those not eligible for cisplatin whose tumors overexpress PD-L1.[42] On November 2022, the manufacturer of atezolizumab withdrew the US indication for locally advanced or metastatic urothelial carcinoma in adults not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This decision was related to the results of OS in the IMvigor130 trial in the first-line treatment of patients with previously untreated advanced bladder cancer.

On the basis of the available evidence, the expert panel concluded that pembrolizumab alone may be considered in the first-line for platin-ineligible patients whose tumors overexpress PD-L1. A consensus was not reached that pembrolizumab in monotherapy is an option in patients who are not eligible for platinum chemotherapy, regardless of PD-L1 expression, because of the low response rate in PD-L1–negative patients, and the availability of other cost-effective therapeutic options for this subgroup of patients.

Regarding the use of pembrolizumab in resource-limited settings, the cost of pembrolizumab therapy could be reduced by adopting the dose of 4 mg/kg once every 6 weeks. In addition to the favorable cost implications, dosing adjustments in these settings could decrease the number of patient visits to outpatient centers and facilitate treatment adherence.[54]

Additionally, it has been proposed that the surgical approach with metastasectomy could benefit highly selected patients, reaching up to 33% survival at 5 years after surgery with a mean time to recurrence after metastasectomy of 14.25 months and OS from the moment of metastasectomy from 2 to 60 months.[55,56] This suggests that resection of metastatic disease is feasible and can contribute to long-term disease control, always in combination with systemic therapy. However, it is important to clarify that there are no randomized studies that support this intervention.

Systemic Therapy in Disease Progression After First-Line Therapy

Patients with disease progression after platinum-based chemotherapy have a worse prognosis.[57] Multiple therapeutic options have been developed to treat these patients.

TABLE 5. Systemic Therapy in Disease Progression in Patients Treated With Platinum-Based Chemotherapy

Statement	Agreement, %
The inclusion in clinical trials of patients requiring second-line and subsequent treatment is recommended since information in this context is scarce.	100
Systemic therapy in disease progression after platinum chemotherapy.	
If progression-free survival was greater than 1 year after treatment with a platinum-containing regimen, platinum re-treatment might be considered.	100
Whether the disease progresses during or after platinum-based chemotherapy in patients who have not received a checkpoint inhibitor as maintenance therapy or within 12 months of platinum-containing adjuvant or neoadjuvant chemotherapy, regardless of expression levels of PD-L1, the preferred regimen as second-line therapy is pembrolizumab. Remarks: *Standard dosage for pembrolizumab: 2 mg/kg to a maximum of 200 mg IV once per day in 21-day cycles or fixed dose: 200 mg once every 3 weeks or 400 mg once every 6 weeks	100
Pembrolizumab is NOT indicated for patients who have progressed with avelumab maintenance therapy.	100
Whether the disease progresses during or after platinum-based chemotherapy in patients who have not received a checkpoint inhibitor as maintenance therapy or within 12 months of platinum-containing adjuvant or neoadjuvant chemotherapy, regardless of expression levels of PD-L1, nivolumab and avelumab are alternative regimens as second-line therapy. Remarks: *Standard dosage for nivolumab: 240 mg once every 2 weeks or 480 mg once every 4 weeks, for avelumab: 800 mg once every 2 weeks	100
Atezolizumab and durvalumab are not treatment options for patients with metastatic urothelial carcinoma in the postplatinum setting.	100
In the platinum-refractory setting, *FGFR*-targeted therapy (erdafitinib) is a therapeutic option in patients with alterations of the *FGFR* gene (*FGFR2* or *FGFR3* mutations, or *FGFR3* fusions). Remarks: *Standard dosage for erdafitinib: 8 mg orally once daily with a dose increase to 9 mg once daily if criteria are met	100
Other regimens that may be helpful in those who have not previously used them include ifosfamide, doxorubicin and gemcitabine, gemcitabine and paclitaxel, gemcitabine and cisplatin, and G-CSF–supported ddMVAC.	100

Abbreviations: ddMVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; FGFR, fibroblast growth factor receptor; G-CSF, granulocyte colony-stimulating factor; IV, intravenous route.

The choice of the second line of treatment depends on the treatment offered in the first line (Table 5).

If PFS was greater than 1 year after treatment with a platinum-containing regimen, platinum retreatment might be considered. This recommendation is based on the results of observational studies comparing subsequent platinum-based versus non–platinum-based chemotherapy in patients who had previously received platinum-based chemotherapy. OS was higher in the platinum chemotherapy group (median 7.9 *v* 5.5 months). No difference was observed in PFS.[58]

If the disease progresses during or after platinum chemotherapy in patients who have not received a checkpoint inhibitor as maintenance therapy or within 12 months of neoadjuvant or adjuvant chemotherapy containing platinum, regardless of the expression levels of PD-L1, pembrolizumab is recommended. This is supported by the results of a phase III KEYNOTE-045 multicenter clinical trial that compared pembrolizumab against other chemotherapy options (paclitaxel, docetaxel, or vinflunine) in patients with recurrent or progressing metastatic urothelial carcinoma after platinum-based chemotherapy. This study found a median OS of 10.3 months (95% CI, 8.0 to 11.8) in the pembrolizumab group compared with 7.4 months (95% CI, 6.1 to 8.3) in the chemotherapy group (HR for death, 0.73 [95% CI, 0.59 to 0.91]; $P = .002$). Furthermore, there were fewer treatment-related adverse events of any grade in the pembrolizumab group than in the chemotherapy group (60.9% *v* 90.2%).[57] The long-term results confirmed these findings.[59] Information regarding treatment with pembrolizumab in patients with progression after initial treatment with a checkpoint inhibitor is insufficient; therefore, its use is not recommended.[60]

Nivolumab and avelumab are alternative regimens in patients with progression after platinum-based chemotherapy. In a phase II trial in these patients, a median OS of 8.74 months (95% CI, 6.05 to not reached) and an ORR of 19.6% (95% CI, 15.0 to 24.9) were reported after nivolumab treatment regardless of the PD-L1 status of the tumor.[61] Grade 3 or 4 treatment-related adverse events were reported in 18% of patients.[63] However, a phase Ib study that evaluated the use of avelumab in this population reported a median PFS of 11.6 weeks (95% CI, 6.1 to 17.4 weeks), a median OS of 13.7 months (95% CI, 8.5 to not estimable), and a 12-month OS rate of 54.3% (95% CI, 37.9 to 68.1). Additionally, the most frequent treatment-related adverse events were fatigue/asthenia (31.8%), infusion-related reaction (20.5%), and nausea (11.4%). This indicates good tolerance, durable responses, and prolonged survival in patients with metastatic urothelial carcinoma after progression on platinum-based chemotherapy.[63]

Atezolizumab and durvalumab are not indicated in this population because clinical trials have not shown a benefit from the use of these therapies compared with chemotherapy.[64-66]

However, erdafitinib has shown activity and an acceptable safety profile in patients with progression after platinum chemotherapy. In an open-label phase II trial (BLC-2001) in patients with at least one *FGFR3* mutation or *FGFR* 2/3 fusion and a history of disease progression during or after at least one cycle of chemotherapy or within 12 months after neoadjuvant chemotherapy or adjuvant therapy, there was an objective response rate of 40% (95% CI, 30 to 49), a median PFS of 5.5 months, and a median OS of 13.8 months. Grade 3

TABLE 6. Systemic Therapy in Disease Progression in Patients Treated With Checkpoint Inhibitors

Statement	Agreement, %
Systemic therapy in disease progression after checkpoint inhibitors or other non–platinum-based therapies.	
In patients eligible for cisplatin, treated with first-line checkpoint inhibitors, without previous chemotherapy, and who have progressed, the preferred regimens are gemcitabine and cisplatin, or ddMVAC with growth factor support.	100
In patients ineligible for cisplatin, treated with first-line checkpoint inhibitors, without previous chemotherapy, and who have progressed, the preferred regimen is gemcitabine/carboplatin.	100
In patients treated with first-line checkpoint inhibitors or other treatments and who have progressed, *FGFR*-targeted therapy (erdafitinib) is a therapeutic option in patients with alterations of the *FGFR* gene (*FGFR2* or *FGFR3* mutations, or *FGFR3* fusions).	100
In patients who have progressed after platinum-based chemotherapy and first-line, maintenance, or second-line immunotherapy, the use of enfortumab vedotin is indicated until disease progression or unacceptable toxicity. Remarks: *Standard dosage for enfortumab vedotin: 1.25 mg/kg IV once on days 1, 8, and 15 in 28-day cycles	100
In patients who have progressed after platinum-based chemotherapy and first-line, maintenance, or second-line immunotherapy, and other therapies, treatment with taxanes (docetaxel or paclitaxel) may be considered as a single agent or vinflunine.	100
Other regimens that may be useful in certain circumstances after the other lines of treatment are ifosfamide, doxorubicin, pemetrexed, and sacituzumab govitecan.	100
Chemotherapy may be considered instead of the best supportive treatment, if clinically appropriate.	100

Abbreviations: ddMVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; FGFR, fibroblast growth factor receptor; IV, intravenous route.

or higher treatment-related adverse events were reported in 46% of patients.[67]

Regarding the use of other regimens, a randomized phase II clinical trial compared two regimens of gemcitabine and paclitaxel with different frequencies of administration, and it was observed that this combination is an effective second-line regimen in patients with disease progression after platinum-based chemotherapy. They showed good tolerance to treatment and superiority of the 3-week scheme. The latter achieved an overall objective response of 44% (12 of 27), with eight complete remissions and four partial remissions. In addition, the median time to progression was 11 (3-41) months.[68] In clinical trials of single-agent second-line chemotherapy for advanced urothelial carcinoma in which agents such as docetaxel, gemcitabine, pemetrexed, and vinflunine, among others, have been evaluated, survival ranges from 5 to 13 months, with a response rate between 0% and 29%.[69,70]

In those patients in whom a first-line checkpoint inhibitor was administered and have disease progression, the preferred second-line options include platinum-based chemotherapy (in those patients who had not previously received it), enfortumab vedotin, or erdafitinib. Other regimens may also be appropriate in the second-line setting, such as taxanes, vinflunine, and when all therapeutic lines are exhausted, ifosfamide, doxorubicin, and pemetrexed, among others (Table 6).

Recently, therapeutic regimens have been studied for patients ineligible for cisplatin, previously treated with checkpoint inhibitors and presenting recurrence or progression, as well as for those treated with platinum and immunotherapy or more lines of treatment. Enfortumab vedotin, an antibody-drug conjugate targeting nectin-4, in a single-arm phase II clinical trial showed results in patients not eligible for cisplatin-treated with anti–PD-1 or anti–PD-L1, with an objective response of 52% (95% CI, 41 to 62), 20% of complete response and, 31% partial response.[71] The median PFS was 5.8 months (95% CI, 5.03 to 8.28) and the median OS was 14.7 months (95% CI, 10.51 to 18.20). Grade ≥3 treatment-related adverse events were reported in 55% of patients, and 13% of patients discontinued treatment due to adverse events.[71]

Some agents, such as paclitaxel or vinflunine, have shown more modest objective response rates of 10% and 18%, respectively, when used as single agents. However, modifications of these molecules, such as paclitaxel bound to albumin in nanoparticles, can increase their objective response rate by up to 27.7%.[72]

Another monoclonal antibody, sacituzumab govitecan, was evaluated in a phase II clinical trial in patients who had progressed after previous therapy with checkpoint inhibitors and platinum-based chemotherapy with an overall response rate of 27% (95% CI, 19.5 to 36.6) and a decrease in measurable disease in 77% of the participants. The median PFS was 5.4 months (95% CI, 3.5 to 7.2) and the median OS was 10.9 months (95% CI, 9.0 to 13.8). Six percent of the patients in the study discontinued treatment as a result of treatment-related adverse events.

A treatment algorithm is presented on Figure 1.

Future Treatment Perspectives

Recently, defective DNA damage response and repair have been identified in a higher proportion of patients with MIBC,[73,74] and a strong association between DNA damage response gene mutation and sensitivity to cisplatin-based chemotherapy and to immunotherapy.[75,76] These observations have led to the initiation of trials involving selected patients to explore the effectiveness of poly(ADP-ribose) polymerase (PARP) inhibitors. There are three phase II trials investigating the efficacy of durvalumab plus olaparib, rucaparib, and niraparib, respectively.

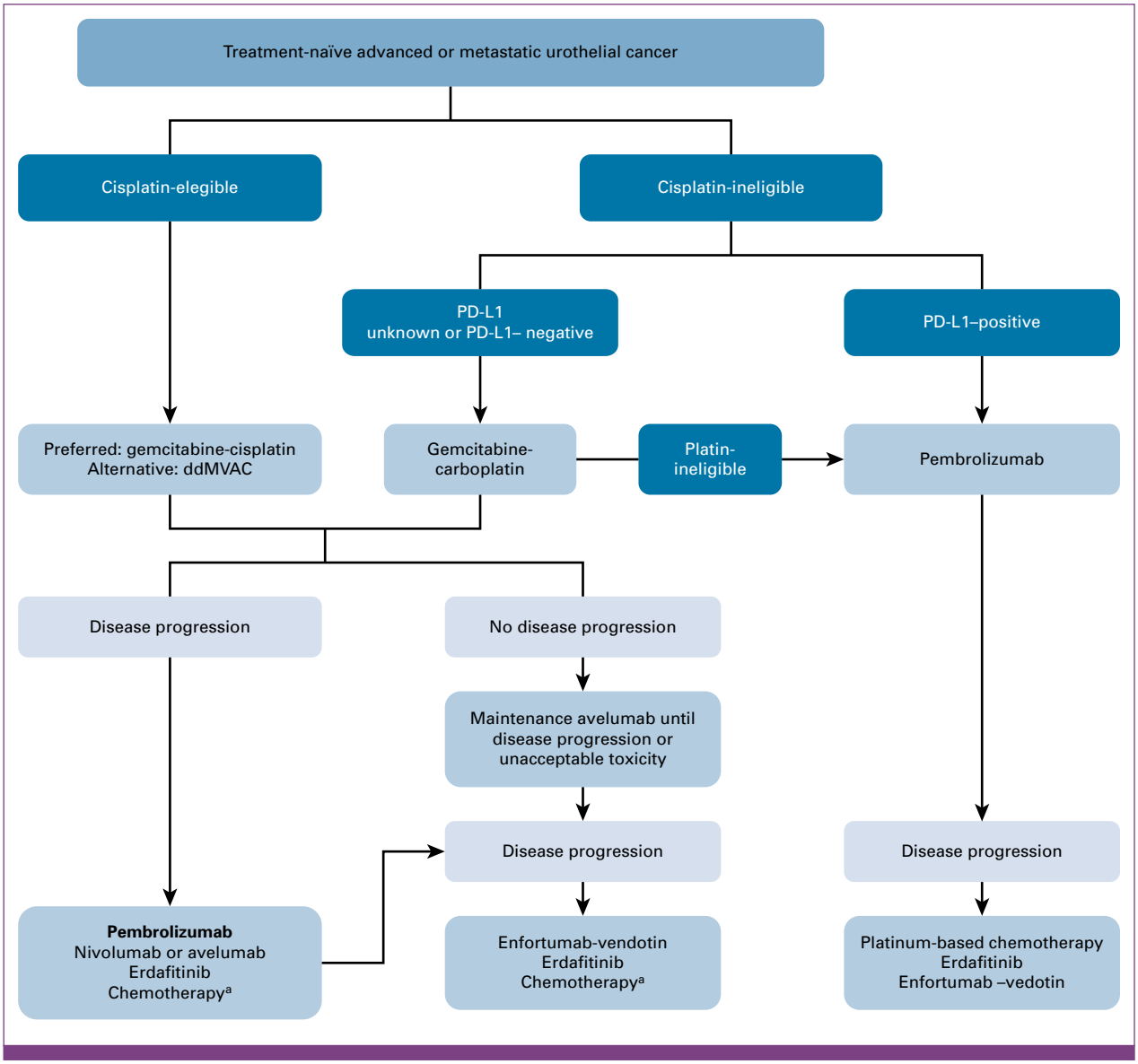

FIG 1. Treatment algorithm. [a]Other regimens that may be helpful in those who have not previously used them include ifosfamide, doxorubicin and gemcitabine, gemcitabine and paclitaxel, gemcitabine and cisplatin, and G-CSF–supported ddMVAC. In patients who have progressed after platinum-based chemotherapy and first-line, maintenance, or second-line immunotherapy, and other therapies, treatment with taxanes (docetaxel or paclitaxel) may be considered as a single agent or vinflunine. Other regimens that may be useful in certain circumstances after the other lines of treatment are ifosfamide, doxorubicin, pemetrexed, and sacituzumab govitecan. ddMVAC, methotrexate, vinblastine, doxorubicin, and cisplatin. Modified from Powles et al.[8]

Preliminary results have shown an increased PFS and OS with PARP inhibitors in homologous recombination repair mutation patients. Further studies are necessary to confirm these observations.[77]

Other new therapies being explored for use in bladder cancer are drugs targeting the androgen receptor (AR), which through different pathways has been linked to the progression and response of this type of cancer. Preclinical studies have shown that AR inhibition in monotherapy can successfully inhibit the growth of urothelial carcinoma and it has a synergistic effect with cisplatin-based chemotherapy. Currently available clinical data include a phase I/Ib study in which the safety and efficacy of enzalutamide (80 and 160 mg once daily) in combination with cisplatin and gemcitabine (six standard dose cycles) was investigated in 10 patients with metastatic urothelial cancer (ClinicalTrials.gov identifier: NCT02300610). The results showed complete response in one patient with strong positive AR expression, partial response in four patients, and stable disease in two patients. No dose-limiting toxicities were observed. The results of the combination are promising and should be corroborated in future investigations in urothelial cancer.[78,79]

RECOMMENDATION

In conclusion, the results of this consensus in the evaluation and systemic treatment of patients with advanced metastatic urothelial carcinoma reflect a need for the management of the disease in Latin American countries and aim to facilitate the incorporation of the best and most recent evidence available to populations with different characteristics, with barriers and limited resources for health care. The importance of patients' complete and individualized evaluation is highlighted as a guide for therapeutic selection. The availability and affordability of support tools for the evaluation of the disease, as well as specific therapies, may limit the application of the best practices suggested, so these aspects should be considered in the context of clinical decisions. Similarly, the generation of local research is promoted to expand knowledge regarding locally advanced unresectable urothelial carcinoma and/or metastatic disease in our patients.

AFFILIATIONS

[1]Sociedad de Oncología y Hematología del Cesar, Valledupar, Colombia
[2]Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" (CEMIC), Buenos Aires, Argentina
[3]Beneficência Portuguesa de São Paulo, Sao Paulo, SP, Brazil
[4]Hospital San Juan de Dios, Caja Costarricense de Seguro Social, San José, Costa Rica
[5]Instituto Nacional del Enfermedades Neoplásicas, Lima, Perú
[6]Instituto Nacional de Cancerología, Clínica de Tumores Genitourinarios, Ciudad de México, México
[7]Clínica Universitaria Colombia y Clínica de Marly, Bogotá, Colombia
[8]InValue Health Solutions, Bogotá, Colombia
[9]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, México

CORRESPONDING AUTHOR

Maria T. Bourlon, MD, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Belisario Domínguez Secc 16, Tlalpan, Ciudad de México, 14080, México;
e-mail: maitebourlon@gmail.com.

SUPPORT

Supported by Janssen Pharmaceutical. The funder had no participation in the design or development of the consensus and had no influence whatsoever in the preparation of this manuscript.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: Fernando Galanternik
Administrative support: Fernando Galanternik
Provision of study materials or patients: Ray Manneh Kopp, Fabio Kater
Collection and assembly of data: Linda Ibatá-Bernal, Susan Martínez-Rojas
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Ray Manneh Kopp
Honoraria: Astellas Scientific and Medical Affairs Inc, Janssen-Cilag, Bayer, Merck Sharp & Dohme, Roche, Bristol Myers Squibb, Sanofi, AstraZeneca, Pfizer, Lilly, Ipsen
Consulting or Advisory Role: Astellas Pharma, Janssen-Cilag, Roche, Merck Serono, Merck Sharp & Dohme, AstraZeneca, Sanofi, Pfizer, Bayer, Ipsen, Tecnofarma
Speakers' Bureau: San Jorge Foundation, Asociación Colombiana de Hematoligía y Oncología (ACHO)
Research Funding: Pfizer, Merck Sharp & Dohme, Novartis, Amgen, Bristol Myers Squibb/Celgene
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Roche/Genentech, Pfizer, Bayer

Fernando Galanternik
Consulting or Advisory Role: Janssen Oncology

Fabio A. Schutz
Employment: Sanofi, Janssen medical Affairs
Consulting or Advisory Role: Janssen Oncology, Merck Sharp & Dohme, Bristol Myers Squibb, Pfizer, Astellas Pharma, AstraZeneca, Adium Pharma, Bayer
Speakers' Bureau: Janssen Oncology, Astellas Pharma, Bayer, Pfizer, Bristol Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Adium Pharma, Merck Serono
Research Funding: Janssen Oncology (Inst), MSD Oncology (Inst), BMS Brazil (Inst)
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Roche, Bristol Myers Squibb, Astellas Pharma, Janssen-Cilag

Fabio Kater
Consulting or Advisory Role: Janssen-Cilag, Pfizer
Travel, Accommodations, Expenses: MSD Oncology, AstraZeneca

Allan Ramos-Esquivel
Honoraria: Pfizer, Roche, AstraZeneca, Bayer, Novartis, Janssen Oncology
Consulting or Advisory Role: Roche, Bayer, Novartis
Travel, Accommodations, Expenses: Bayer, Roche, Novartis, Johnson & Johnson

Nora Sobrevilla-Moreno
Honoraria: Bristol Myers Squibb (Mexico), MSD Oncology, Pfizer, Bayer, Ipsen, Janssen Oncology, Astellas Pharma, Merck/Pfizer
Consulting or Advisory Role: Pfizer, MSD Oncology, Bayer, AstraZeneca, Janssen Oncology, Astellas Pharma
Speakers' Bureau: Bayer
Travel, Accommodations, Expenses: MSD Oncology, Janssen Oncology, Ipsen, Merck Serono

Laura Bernal Vaca
Stock and Other Ownership Interests: Idime
Honoraria: Janssen, Bayer, Bristol Myers Squibb, MSD, AstraZeneca, Pfizer, Tecnofarma, Merck, Novartis, Ipsen, Astellas Pharma
Consulting or Advisory Role: Janssen, Bayer, Ipsen, Pfizer, AstraZeneca, MSD
Speakers' Bureau: Janssen, Bayer, MSD, AstraZeneca, Bristol Myers Squibb, Ipsen
Research Funding: MSD, GlaxoSmithKline
Travel, Accommodations, Expenses: Bayer, Janssen, MSD, AstraZeneca, Amgen, Pfizer

Linda Ibatá-Bernal
Honoraria: Astellas Pharma

Maria T. Bourlon
Leadership: BMS
Honoraria: Tecnofarma, BMS
Consulting or Advisory Role: Bristol Myers Squibb, Asofarma, Eisai, MSD Oncology, Janssen Oncology, Novartis, Bayer, Ferring, Pfizer, MSD, Merck, Astellas Pharma, Gilead Sciences, Novartis
Speakers' Bureau: Asofarma, MSD Oncology, Bristol Myers Squibb, Bayer, Eisai, Janssen Oncology, Ipsen, Pfizer, Merck, Ferring, Tecnofarma, Medicamenta, AstraZeneca, Astellas Pharma
Research Funding: Pfizer, Janssen Oncology (Inst)
Expert Testimony: Asofarma
Travel, Accommodations, Expenses: Asofarma, Janssen-Cilag, MSD Oncology, Bristol Myers Squibb (Mexico), Pfizer
Other Relationship: Sanofi

No other potential conflicts of interest were reported.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209-249, 2021
2. International Agency for Research on Cancer, World Health Organization. Bladder Source: Globocan, The Global Cancer Observatory, 2020. https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf
3. Saginala K, Barsouk A, Aluru JS, et al: Epidemiology of bladder cancer. Med Sci 8:15, 2020
4. Antoni S, Ferlay J, Soerjomataram I, et al: Bladder cancer incidence and mortality: A global overview and recent trends. Eur Urol 71:96-108, 2017
5. Stecca C, Abdeljalil O, Sridhar SS: Metastatic urothelial cancer: A rapidly changing treatment landscape. Ther Adv Med Oncol 13:175883592110473, 2021
6. Martini A, Sfakianos JP, Renström-Koskela L, et al: The natural history of untreated muscle-invasive bladder cancer. BJU Int 125:270-275, 2020
7. Matsumoto H, Shiraishi K, Azuma H, et al: Clinical Practice Guidelines for Bladder Cancer 2019 update by the Japanese Urological Association: Summary of the revision. Int J Urol 27:702-709, 2020
8. Powles T, Bellmunt J, Comperat E, et al: Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 33:244-258, 2022
9. Witjes JA, Bruins HM, Cathomas R, et al: European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2020 guidelines. Eur Urol 79:82-104, 2021
10. González Del Alba A, De Velasco G, Lainez N, et al: SEOM clinical guideline for treatment of muscle-invasive and metastatic urothelial bladder cancer (2018). Clin Transl Oncol 21:64-74, 2019
11. Flaig TW, Spiess PE, Agarwal N, et al: Bladder cancer, version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 18:329-354, 2020
12. Khauli R, Ferrigno R, Guimarães G, et al: Treatment of localized and locally advanced, high-risk prostate cancer: A report from the first prostate cancer consensus conference for developing countries. JCO Glob Oncol 10.1200/GO.20.00421
13. Holey EA, Feeley JL, Dixon J, et al: An exploration of the use of simple statistics to measure consensus and stability in Delphi studies. BMC Med Res Methodol 7:52, 2007
14. Mazzone E, Knipper S, Mistretta FA, et al: Trends and social barriers for inpatient palliative care in patients with metastatic bladder cancer receiving critical care therapies. J Natl Compr Cancer Netw 17:1344-1352, 2019
15. Girvin F, Ko JP: Pulmonary nodules: Detection, assessment, and CAD. AJR Am J Roentgenol 191:1057-1069, 2008
16. Heidenreich A, Albers P, Classen J, et al: Imaging studies in metastatic urogenital cancer patients undergoing systemic therapy: Recommendations of a Multidisciplinary Consensus Meeting of the Association of Urological Oncology of the German Cancer Society. Urol Int 85:1-10, 2010
17. Barrett T, Choyke PL, Kobayashi H: Imaging of the lymphatic system: New horizons. Contrast Media Mol Imaging 1:230-245, 2006
18. Kundra V, Silverman PM: Imaging in oncology from the University of Texas M. D. Anderson Cancer Center. Imaging in the diagnosis, staging, and follow-up of cancer of the urinary bladder. AJR Am J Roentgenol 180:1045-1054, 2003
19. Murahashi N, Abe T, Shinohara N, et al: Diagnostic outcome of ureteroscopy in urothelial carcinoma of the upper urinary tract: Incidence of later cancer detection and its risk factors after the first examination. BMC Urol 15:92, 2015
20. Schmidt GP, Schoenberg SO, Schmid R, et al: Screening for bone metastases: Whole-body MRI using a 32-channel system versus dual-modality PET-CT. Eur Radiol 17:939-949, 2007
21. Kibel AS, Dehdashti F, Katz MD, et al: Prospective study of [18F] fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. J Clin Oncol 27:4314-4320, 2009
22. Goodfellow H, Viney Z, Hughes P, et al: Role of fluorodeoxyglucose positron emission tomography (FDG PET)-computed tomography (CT) in the staging of bladder cancer. BJU Int 114:389-395, 2014
23. Kollberg P, Almquist H, Bläckberg M, et al: [18F] Fluorodeoxyglucose-positron emission tomography/computed tomography response evaluation can predict histological response at surgery after induction chemotherapy for oligometastatic bladder cancer. Scand J Urol 51:308-313, 2017
24. Lu Y-Y, Chen JH, Liang JA, et al: Clinical value of FDG PET or PET/CT in urinary bladder cancer: A systemic review and meta-analysis. Eur J Radiol 81:2411-2416, 2012
25. Zattoni F, Incerti E, Dal Moro F, et al: 18F-FDG PET/CT and urothelial carcinoma: Impact on management and prognosis-A multicenter retrospective study. Cancers (Basel) 11:700, 2019
26. Dietrich B, Siefker-Radtke AO, Srinivas S, et al: Systemic therapy for advanced urothelial carcinoma: Current standards and treatment considerations. Am Soc Clin Oncol Educ book 38:342-353, 2018
27. Jiang DM, Gupta S, Kitchlu A, et al: Defining cisplatin eligibility in patients with muscle-invasive bladder cancer. Nat Rev Urol 18:104-114, 2021
28. Dash A, Galsky MD, Vickers AJ, et al: Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 107:506-513, 2006
29. Galsky MD, Hahn NM, Rosenberg J, et al: A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol 12:211-214, 2011
30. Hussain SA, Palmer DH, Lloyd B, et al: A study of split-dose cisplatin-based neo-adjuvant chemotherapy in muscle-invasive bladder cancer. Oncol Lett 3:855-859, 2012
31. Bajorin DF, Dodd PM, Mazumdar M, et al: Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 17:3173-3181, 1999
32. Bellmunt J, Albanell J, Paz-Ares L, et al: Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer 95:751-757, 2002
33. Bellmunt J, Choueiri TK, Fougeray R, et al: Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 28:1850-1855, 2010
34. Apolo AB, Ostrovnaya I, Halabi S, et al: Prognostic model for predicting survival of patients with metastatic urothelial cancer treated with cisplatin-based chemotherapy. J Natl Cancer Inst 105: 499-503, 2013
35. Sonpavde G, Pond GR, Rosenberg JE, et al: Improved 5-factor prognostic classification of patients receiving salvage systemic therapy for advanced urothelial carcinoma. J Urol 195:277-282, 2016
36. Abuhelwa AY, Bellmunt J, Kichenadasse G, et al: Enhanced Bellmunt risk score for survival prediction in urothelial carcinoma treated with immunotherapy. Clin Genitourinary Cancer 20:132-138, 2022
37. Sonpavde G, Pond GR, Fougeray R, et al: Time from prior chemotherapy enhances prognostic risk grouping in the second-line setting of advanced urothelial carcinoma: A retrospective analysis of pooled, prospective phase 2 trials. Eur Urol 63:717-723, 2013
38. Ross JS, Wang K, Khaira D, et al: Comprehensive genomic profiling of 295 cases of clinically advanced urothelial carcinoma of the urinary bladder reveals a high frequency of clinically relevant genomic alterations. Cancer 122:702-711, 2016
39. Loriot Y, Necchi A, Park SH, et al: Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 381:338-348, 2019
40. Powles T, Csőszi T, Özgüroğlu M, et al: Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): A randomised, open-label, phase 3 trial. Lancet Oncol 22:931-945, 2021

41. Galsky MD, Arija JÁA, Bamias A, et al: Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): A multicentre, randomised, placebo-controlled phase 3 trial. Lancet 395:1547-1557, 2020
42. U S Food and Drug Administration: FDA Alerts Health Care Professionals and Oncology Clinical Investigators About an Efficacy Issue Identified in Clinical Trials for Some Patients Taking Keytruda (Pembrolizumab) or Tecentriq (Atezolizumab) as Monotherapy to Treat Urothelial Cancer With Low Expression of PD-L1. 2018. Drug Safety and Availability. https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-health-care-professionals-and-oncology-clinical-investigators-about-efficacy-issue
43. 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 23:406-410, 2012
44. Abe T, Shinohara N, Harabayashi T, et al: Impact of multimodal treatment on survival in patients with metastatic urothelial cancer. Eur Urol 52:1106-1113, 2007
45. De Santis M, Bellmunt J, Mead G, et al: Randomized phase II/III 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 30:191-199, 2012
46. Stadler WM, Kuzel T, Roth B, et al: Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. J Clin Oncol 15:3394-3398, 1997
47. Meluch AA, Greco FA, Burris HA III, et al: Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: A phase II trial of the Minnie pearl cancer research network. J Clin Oncol 19:3018-3024, 2001
48. Calabrò F, Lorusso V, Rosati G, et al: Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 115:2652-2659, 2009
49. Li J, Juliar B, Yiannoutsos C, et al: Weekly paclitaxel and gemcitabine in advanced transitional-cell carcinoma of the urothelium: A phase II Hoosier oncology group study. J Clin Oncol 23: 1185-1191, 2005
50. Powles T, Park SH, Voog E, et al: Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 383:1218-1230, 2020
51. Balar AV, Castellano D, O'Donnell PH, et al: First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): A multicentre, single-arm, phase 2 study. Lancet Oncol 18:1483-1492, 2017
52. Vuky J, Balar AV, Castellano D, et al: Long-term outcomes in KEYNOTE-052: Phase II study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. J Clin Oncol 38:2658-2666, 2020
53. 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, multicentre, phase 2 trial. Lancet 389:67-76, 2017
54. Goodman A: KEYNOTE-555 Supports 6-Week Pembrolizumab Dosing Schedule in Melanoma—The ASCO Post. 2020. https://ascopost.com/issues/june-10-2020/keynote-555-supports-6-week-pembrolizumab-dosing-schedule-in-melanoma/
55. Patel V, Collazo Lorduy A, Stern A, et al: Survival after metastasectomy for metastatic urothelial carcinoma: A systematic review and meta-analysis. Bladder Cancer 3:121-132, 2017
56. Siefker-Radtke AO, Walsh GL, Pisters LL, et al: Is there a role for surgery in the management of metastatic urothelial cancer? The M. D. Anderson experience. J Urol 171:145-148, 2004
57. Bellmunt J, de Wit R, Vaughn DJ, et al: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 376:1015-1026, 2017
58. Wong RL, Ferris LA, Do OA, et al: Efficacy of platinum rechallenge in metastatic urothelial carcinoma after previous platinum-based chemotherapy for metastatic disease. Oncologist 26:1026-1034, 2021
59. Fradet Y, Bellmunt J, Vaughn DJ, et al: Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: Results of >2 years of follow-up. Ann Oncol 30:970-976, 2019
60. Parikh M, Powles T: Immune checkpoint inhibition in advanced bladder and kidney cancer: Responses and further management. Am Soc Clin Oncol Ed Book 41:e182-e189, 2021
61. Sharma P, Retz M, Siefker-Radtke A, et al: Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. Lancet Oncol 18:312-322, 2017
62. Reference deleted
63. Apolo AB, Infante JR, Balmanoukian A, et al: Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: Results from a multicenter, phase Ib study. J Clin Oncol 35:2117-2124, 2017
64. Powles T, Durán I, van der Heijden MS, et al: Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicentre, open-label, phase 3 randomised controlled trial. Lancet 391:748-757, 2018
65. Massard C, Gordon MS, Sharma S, et al: Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 34:3119-3125, 2016
66. 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 3:e172411, 2017
67. Siefker-Radtke AO, Necchi A, Park SH, et al: Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: Long-term follow-up of a phase 2 study. Lancet Oncol 23:248-258, 2022
68. Fechner G, Siener R, Reimann M, et al: Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). Int J Clin Pract 60:27-31, 2006
69. Albers P, Siener R, Härtlein M, et al: Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. Onkologie 25:47-52, 2002
70. Yafi FA, North S, Kassouf W: First- and second-line therapy for metastatic urothelial carcinoma of the bladder. Curr Oncol 18:e25-e34, 2011
71. Yu EY, Petrylak DP, O'Donnell PH, et al: Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): A multicentre, single-arm, phase 2 trial. Lancet Oncol 22:872-882, 2021
72. Oing C, Rink M, Oechsle K, et al: Second line chemotherapy for advanced and metastatic urothelial carcinoma: Vinflunine and beyond-A comprehensive review of the current literature. J Urol 195: 254-263, 2016
73. Nassar AH, Umeton R, Kim J, et al: Mutational analysis of 472 urothelial carcinoma across grades and anatomic sites. Clin Cancer Res 25:2458-2470, 2019
74. Yang K, Yu W, Liu H, et al: Comparison of genomic characterization in upper tract urothelial carcinoma and urothelial carcinoma of the bladder. Oncologist 26:e1395-e1405, 2021
75. Tan KT, Yeh CN, Chang YC, et al: PRKDC: New biomarker and drug target for checkpoint blockade immunotherapy. J Immunother Cancer 8:e000485, 2020
76. Teo MY, Bambury RM, Zabor EC, et al: DNA damage response and repair gene alterations are associated with improved survival in patients with platinum-treated advanced urothelial carcinoma. Clin Cancer Res 23:3610-3618, 2017
77. Dariane C, Timsit M-O: DNA-Damage-Repair gene alterations in genitourinary malignancies. Eur Surg Res 63:155-164, 2022
78. Tripathi A, Gupta S: Androgen receptor in bladder cancer: A promising therapeutic target. Asian J Urol 7:284-290, 2020
79. Besançon M, Gris T, Joncas FH, et al: Combining antiandrogens with immunotherapy for bladder cancer treatment. Eur Urol Open Sci 43:35-44, 2022

APPENDIX.

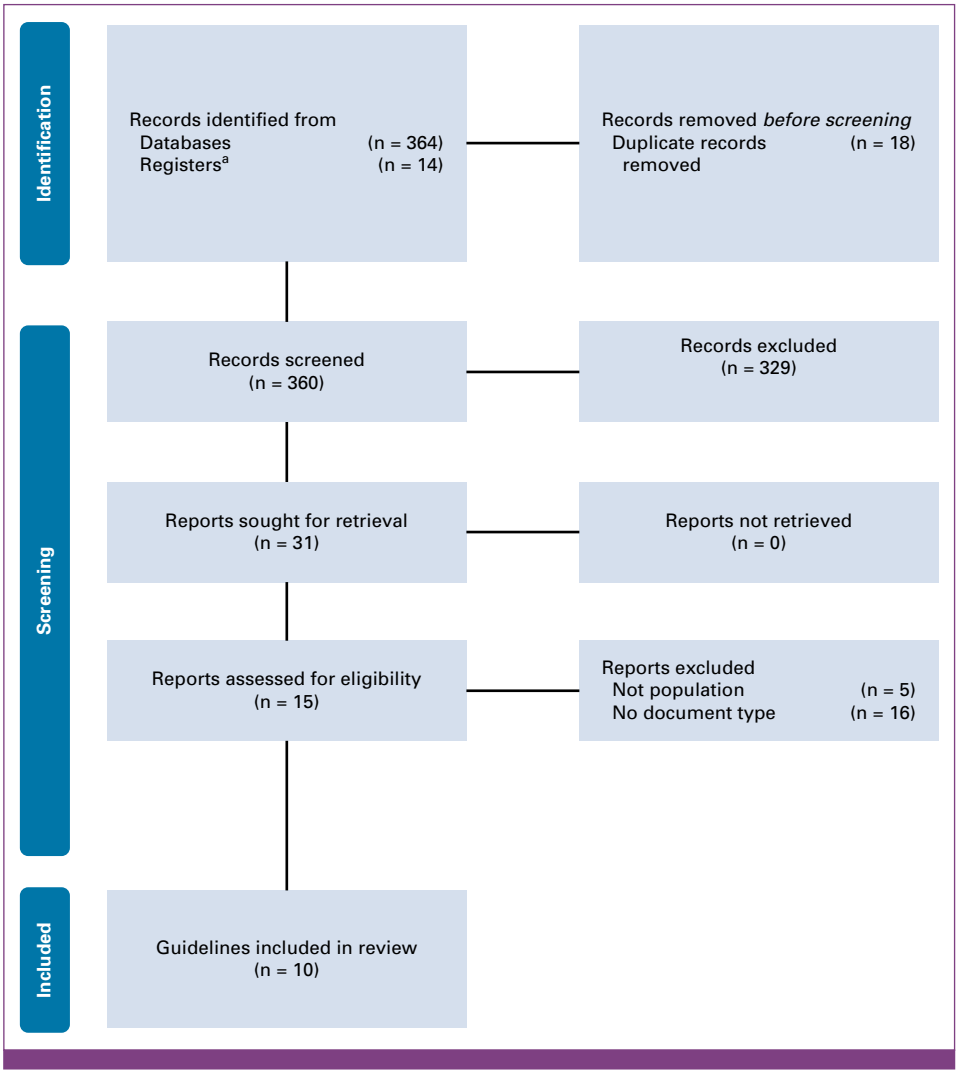

FIG A1. PRISMA 2020 flow diagram for systematic review. [a]Scientific societies, compilers, and developers of CPG. CPG, clinical practice guidelines; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.