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European Association of Urology

Review – Bladder Cancer

The 2021 Updated European Association of Urology Guidelines on Metastatic Urothelial Carcinoma

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Abstract

Context: Treatment of metastatic urothelial carcinoma is currently undergoing a rapid evolution.
Objective: This overview presents the updated European Association of Urology (EAU) guidelines for metastatic urothelial carcinoma.
Evidence acquisition: A comprehensive scoping exercise covering the topic of metastatic urothelial carcinoma is performed annually by the Guidelines Panel. Databases covered by the search included Medline, EMBASE, and the Cochrane Libraries, resulting in yearly guideline updates.
Evidence synthesis: Platinum-based chemotherapy is the recommended first-line standard therapy for all patients fit to receive either cisplatin or carboplatin. Patients positive for programmed death ligand 1 (PD-L1) and ineligible for cisplatin may receive immunotherapy (atezolizumab or pembrolizumab). In case of nonprogressive disease on platinum-based chemotherapy, subsequent maintenance immunotherapy (avelumab) is recommended. For patients without maintenance therapy, the recommended second-line regimen is immunotherapy (pembrolizumab). Later-line treatment has undergone recent advances: the antibody-drug conjugate enfortumab vedotin demonstrated improved overall survival and the fibroblast growth factor receptor (FGFR) inhibitor erdafitinib appears active in case of FGFR3 alterations.
Conclusions: This 2021 update of the EAU guideline provides detailed and contemporary information on the treatment of metastatic urothelial carcinoma for incorporation into clinical practice.

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Patient summary: In recent years, several new treatment options have been introduced for patients with metastatic urothelial cancer (including bladder cancer and cancer of the upper urinary tract and urethra). These include immunotherapy and targeted treatments. This updated guideline informs clinicians and patients about optimal tailoring of treatment of affected patients.

1. Introduction

Treatment of metastatic urothelial carcinoma (mUC) had remained largely unchanged since pivotal trials published over 20 yr ago set the standard of care for first-line treatment with cisplatin-based combinations demonstrating an overall survival (OS) benefit. In the past few years, this longstanding paradigm has been challenged by several large studies investigating the benefit of immunotherapy using checkpoint inhibitors. Moreover, novel compounds including both targeted therapy and antibody-drug conjugates (ADCs) have successfully been tested and approved in later treatment lines. With many advances in the treatment of urothelial cancer (UC), the European Association of Urology Muscle-invasive and Metastatic Guidelines Panel has decided to publish an updated version of their 2021 treatment recommendations for patients with metastatic disease.

2. First-line systemic therapy for metastatic disease

In general, patients with untreated mUC can be divided into three broad categories: fit for cisplatin-based chemotherapy, fit for carboplatin-based chemotherapy (but unfit for cisplatin), and unfit for any platinum-based chemotherapy.

2.1. Definitions: "fit for cisplatin, fit for carboplatin, and unfit for any platinum-based chemotherapy"

An international survey among bladder cancer (BC) experts [1] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria must be present: performance status (PS) >1, glomerular filtration rate (GFR) $\leq$60 ml/min, grade $\geq$2 audiometric hearing loss, grade $\geq$2 peripheral neuropathy, or New York Heart Association class III heart failure [2]. Around 50% of patients with BC are not eligible for cisplatin-based chemotherapy [2]. Renal function assessment is of utmost importance for treatment selection. Measuring GFR with radioisotopes (^{99}mTc DTPA or ^{51}Cr-EDTA) is recommended in equivocal cases.

Cisplatin has also been administered in patients with a lower GFR (40–60 ml/min) using different split-dose schedules. The respective studies were mostly small phase I and II trials in different settings (neoadjuvant and advanced disease) demonstrating that the use of split-dose cisplatin is feasible and appears to result in encouraging efficacy [3–5]. However, no prospective randomised trial has compared split-dose cisplatin with conventional dosing.

Most patients who are deemed unfit for cisplatin are able to receive carboplatin-based chemotherapy. However, some patients are deemed unfit for any platinum-based chemotherapy, that is, both cisplatin and carboplatin. Patients are unfit for any platinum-based chemotherapy in case of PS >2, GFR < 30 ml/min, or the combination of PS 2 and GFR < 60 ml/min, since the outcome in this patient population is poor regardless of whether the treatment is platinum based or not [6]. Patients with multiple comorbidities may also be poor candidates for platinum-based chemotherapy. Definitions of platinum eligibility for first-line treatment of mUC are summarised in Table 1.

2.2. First-line chemotherapy in patients fit for cisplatin

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s, demonstrating OS of 12–14 mo in different series (for a review, see the study by Bellmunt and Petrylak [7]). Methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) and gemcitabine and cisplatin (GC) achieved survival of 14.8 and 13.8 mo, respectively [8]. Overall response rates (ORRs) were 46% for MVAC and 49% for GC. The lower toxicity of GC [9] compared with standard MVAC has resulted in GC becoming the standard regimen.

Dose-dense MVAC combined with granulocyte colony-stimulating factor is less toxic and more efficacious than standard MVAC in terms of complete response (CR) and 2-yr OS. However, there is no significant difference in median survival between the two regimens [10,11]. Further intensification of treatment using paclitaxel, cisplatin, and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the intention-to-treat (ITT) population of a phase III randomised controlled trial (RCT), comparing PCG with GC [12]. Similarly, addition of the angiogenesis inhibitor bevacizumab to GC did not result in OS improvement [13].

Table 1 – Definitions of platinum eligibility for first-line treatment of metastatic urothelial carcinoma

Platinum eligible		Platinum ineligible
Cisplatin eligible	Carboplatin eligible	
ECOG PS 0–1	ECOG PS 2 or GFR 30–60 ml/min	Any of the following:
GFR >50–60 ml/min	Or not fulfilling other cisplatin-eligibility criteria	GFR <30 ml/min
Audiometric hearing loss grade <2		ECOG PS >2
Peripheral neuropathy grade <2		ECOG PS 2 and GFR <60 ml/min
Cardiac insufficiency NYHA class <III		Comorbidities grade >2

GFR = growth factor receptor; ECOG = Eastern Cooperative Oncology Group; NYHA = New York Heart Association; PS = performance status.

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Disease sites have an impact on long-term survival. Among patients with lymph node–only disease, 20.9% were alive at 5 yr compared with only 6.8% of patients with visceral metastases [8]. In trials with long-term follow-up, approximately 10–15% of patients with mUC are alive at 5 yr and longer, suggesting a sustained benefit from cisplatin-based chemotherapy in a minority of patients [8,11].

Carboplatin-containing chemotherapy is not considered to be equivalent to cisplatin-based combinations, and should not be considered interchangeable or standard in patients fit for cisplatin. A comparative analysis of four randomised phase II trials of carboplatin versus cisplatin combination chemotherapy demonstrated lower CR rates and shorter OS for the carboplatin arms [14]. Recently, a retrospective study highlighted the importance of applying cisplatin in cisplatin-eligible patients in order to maintain benefit [15].

2.3. First-line chemotherapy in patients fit for carboplatin (but unfit for cisplatin)

Up to 50% of patients are not fit for cisplatin-containing chemotherapy, but most may be candidates for carboplatin [2]. The first randomised phase II/III trial in this setting was conducted by the European Organisation for Research and Treatment of Cancer (EORTC) and compared two carboplatin-containing regimens (methotrexate/carboplatin/vinblastine [M-CAVI] and gemcitabine/carboplatin [GemCarbo]) in patients unfit for cisplatin. The EORTC definitions for eligibility were GFR <60 ml/min and/or PS 2. Severe acute toxicity was 13.6% with GemCarbo versus 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI [6]. Based on these results, the combination of carboplatin and gemcitabine should be considered a standard of care in this patient group.

Combinations of gemcitabine and paclitaxel have been studied as first-line treatment and produced response rates between 38% and 60%, but have never been tested in randomised trials [16–18]. A randomised phase II trial assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine/gemcitabine vs vinflunine/carboplatin). Both regimens showed equal ORR and OS with less haematological toxicity for the combination of vinflunine/gemcitabine [19]. Nonplatinum combination chemotherapy is nevertheless not recommended for first-line use in platinum-eligible patients.

The use of single-agent chemotherapy has been associated with varying response rates. Responses with single agents are usually short, CRs are rare, and no long-term disease-free survival (DFS)/OS has been reported. It is not recommended for first-line treatment of mUC.

2.4. Integration of immunotherapy in the first-line chemotherapy treatment of patients fit for platinum-based treatment (cisplatin or carboplatin)

2.4.1. Immunotherapy combination approaches

In 2020, results of three phase III trials have been published, which investigated the use of immunotherapy in the first-line setting for platinum-eligible patients. The first trial to report was IMvigor130, investigating the combination of the programmed death ligand 1 (PD-L1) inhibitor atezolizumab plus platinum-gemcitabine chemotherapy versus chemotherapy plus placebo versus atezolizumab alone [20]. The primary endpoint of progression-free survival (PFS) benefit for the combination versus chemotherapy alone in the ITT group was reached (8.2 vs 6.3 mo [hazard ratio {HR}: 0.82, 95% confidence interval {CI}: 0.70–0.96; one-sided p = 0.007]), while OS was not significant at the interim analysis after a median follow-up of 11.8 mo. The small PFS benefit in the absence of an OS benefit has raised questions of its clinical significance. Owing to the sequential testing design, the comparison of chemotherapy versus atezolizumab alone has not yet been performed formally.

The KEYNOTE 361 study had a very similar design using the PD-1 inhibitor pembrolizumab plus platinum-gemcitabine versus chemotherapy plus placebo versus pembrolizumab alone. The results of the primary endpoints of PFS and OS for the comparison of pembrolizumab plus chemotherapy versus chemotherapy plus placebo in the ITT population showed no benefit for the combination [21].

DANUBE compared the immunotherapy combination (immuno-oncology [IO]-IO) of CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab with chemotherapy alone or durvalumab alone [22]. The coprimary endpoint of improved OS for the IO-IO combination versus chemotherapy was not reached in the ITT group, nor was the OS improved for durvalumab monotherapy versus chemotherapy in the PD-L1–positive population.

In conclusion, these three trials do not support the use of the combination of PD-1/L1 checkpoint inhibitors plus chemotherapy or the IO-IO combination as first-line treatment.

2.4.2. Use of first-line single-agent immunotherapy in patients unfit for cisplatin-based chemotherapy

Based on the results of two single-arm phase II trials [23,24], the checkpoint inhibitors pembrolizumab and atezolizumab have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for first-line treatment in cisplatin-unfit patients in case of positive PD-L1 status. PD-L1 positivity for use of pembrolizumab is defined by immunohistochemistry as a combined positive score of $\geq$10 using the Dako 22C33 platform and for atezolizumab as positivity of $\geq$5% tumour-infiltrating immune cells using Ventana SP142.

Pembrolizumab was tested in 370 patients with advanced UC or mUC ineligible for cisplatin, showing an ORR of 29% and a CR in 7% of patients [23]. Atezolizumab was evaluated in the same patient population in a phase II trial (n = 119) showing an ORR of 23%, with 9% of patients achieving a CR [24].

The trials IMvigor 130, Keynote 361, and DANUBE all included an experimental arm with immunotherapy alone using atezolizumab, pembrolizumab, and durvalumab, respectively [20–22]. No benefit in terms of PFS or OS was found for the use of single-agent immunotherapy compared with platinum-based chemotherapy. The combination of carboplatin/gemcitabine therefore is considered the preferred first-line treatment choice for patients ineligible for cisplatin but eligible for carboplatin.

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2.4.3. Switch maintenance with immunotherapy after platinum-based chemotherapy

A randomised phase II trial evaluated switch maintenance treatment with pembrolizumab in patients achieving at least stable disease on platinum-based first-line chemotherapy. The primary endpoint of PFS was met (5.4 vs 3.0 mo, HR: 0.65, $p = 0.04$) but not the secondary endpoint of OS (22 vs 18.7 mo, HR: 0.91, 95% CI: 0.52–1.59) [25].

The JAVELIN Bladder 100 study investigated the impact of switch maintenance with the PD-L1 inhibitor avelumab after initial treatment with platinum-gemcitabine chemotherapy. Patients achieving at least stable disease or better after four to six cycles of platinum-gemcitabine were randomised to avelumab or best supportive care (BSC). OS was the primary endpoint, which improved to 21.4 mo with avelumab compared with 14.3 mo with BSC (HR: 0.69, 95% CI: 0.56–0.86; $p < 0.001$). Of patients who discontinued BSC and received subsequent treatment, 53% received immunotherapy. Immune-related adverse events (AEs) occurred in 29% of all patients, and 7% experienced grade 3 complications [26].

In conclusion, maintenance immunotherapy with avelumab is a standard of care for all patients with disease stabilisation on first-line platinum-based chemotherapy.

2.5. Treatment of patients unfit for any platinum-based chemotherapy

Very limited data exist regarding the optimal treatment for this patient population, which is characterised by severely impaired PS (PS >2) and/or severely impaired renal function (GFR <30 ml/min). Historically, the outcome in this patient group has been poor. BSC has often been chosen instead of systemic therapy. Most trials evaluating alternative treatment options to cisplatin-based chemotherapy did not focus specifically on this patient population, thereby making interpretation of data difficult. The FDA (but not EMA) has approved pembrolizumab and atezolizumab as first-line treatment for patients not fit to receive any platinum-based chemotherapy regardless of PD-L1 status, based on the results of two single-arm phase II trials [23,24]. These trials have not reported how many patients were unfit for any platinum-based chemotherapy.

3. Second-line systemic therapy for metastatic disease

3.1. Second-line chemotherapy

Second-line chemotherapy data are highly variable and derive mainly from small single-arm phase II trials apart from a single randomised phase III study. A reasonable strategy has been to rechallenge former platinum-sensitive patients if progression occurred at least 6–12 mo after first-line platinum-based combination chemotherapy. Second-line response rates of single-agent treatment with paclitaxel (weekly), docetaxel, gemcitabine, nab-paclitaxel, oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib, and bortezomib have ranged between 0% and 28% in small phase II trials [27,28].

The paclitaxel/gemcitabine combination has shown good response rates in small single-arm studies, but no adequate randomised phase III trial has been conducted [29,30].

Vinflunine was tested in a phase III RCT and compared against BSC in patients progressing after first-line treatment with platinum-based chemotherapy [31]. The results showed a very modest ORR (8.6%), a clinical benefit with a favourable safety profile, and a survival benefit, which was however statistically significant only in the eligible patient population (not in the ITT population).

A randomised phase III trial evaluated the addition of the angiogenesis inhibitor ramucirumab to docetaxel chemotherapy versus docetaxel alone, which resulted in improved PFS (4.1 vs 2.8 mo) and higher response rates (24.5% vs 14%), but no OS benefit was achieved [32,33].

3.2. Second-line immunotherapy for platinum pretreated patients

The immune checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy and safety in patients progressing during, or after, previous platinum-based chemotherapy in phase I, II, and III trials.

Pembrolizumab demonstrated a significant OS improvement as second-line treatment in a phase III RCT, leading to EMA and FDA approval. Patients ($n = 542$) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel, or vinflunine). The median OS with pembrolizumab was 10.3 mo (95% CI: 8.0–11.8) versus 7.4 mo (95% CI: 6.1–8.3) with chemotherapy (HR: 0.73, 95% CI: 0.59–0.91, $p = 0.002$) independent of PD-L1 expression levels [34].

Atezolizumab was the first checkpoint inhibitor approved by the FDA for mUC based on the results of phase I and II trials [35,36]. The phase III RCT IMvigor211, which included 931 patients comparing atezolizumab with second-line chemotherapy (paclitaxel, docetaxel, or vinflunine), did not meet its primary endpoint of improved OS for patients with high PD-L1 expression: 11.1 mo (atezolizumab) versus 10. 6 mo (chemotherapy; stratified HR: 0.87, 95% CI: 0.63–1.21, $p = 0.41$) [37].

The PD-1 inhibitor nivolumab was approved by the FDA based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pretreated patients. The primary endpoint of ORR was 19.6%, and OS was 8.74 mo for the entire group [38].

Based on level 1 evidence from a randomised trial, pembrolizumab has emerged in clinic as the preferred standard of care immunotherapy in the second-line setting.

3.3. Side-effect profile of immunotherapy

Checkpoint inhibitors including PD-1 or PD-L1 antibodies and CTLA-4 antibodies have a distinct side-effect profile associated with their mechanism of action, leading to enhanced immune system activity. These AEs can affect any organ in the body, leading to mild, moderate, or severe side effects. The most common organs affected are the skin, gastrointestinal tract, liver, lung, thyroid, and adrenal and pituitary glands. Other systems that may be affected include musculoskeletal, renal, nervous, haematological, ocular, and cardiovascular systems. Any change during immunotherapy treatment should raise a suspicion about a possible relation

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to the treatment. The nature of immune-related AEs has very well been characterised and published [39].

The timely and appropriate treatment of immune-related side effects is crucial to achieve optimal benefit from the treatment while maintaining safety. Clear guidelines for side-effect management have been published [40]. Immunotherapy treatment should be applied and supervised by trained clinicians only to ensure early side-effect recognition and treatment. In case of interruption of immunotherapy, rechallenge will require close monitoring for adverse events [41].

4. Integration of novel agents

4.1. Antibody-drug conjugates

The first ADC to report encouraging data was enfortumab vedotin, an ADC targeting Nectin-4, a cell adhesion molecule that is highly expressed in UC conjugated to monomethyl auristatin E (MMAE). A phase II single-arm study (EV-201) in 125 patients previously treated with platinum chemotherapy and checkpoint inhibition showed a confirmed objective response rate of 44%, including 12% CRs [42]. This data led to the accelerated FDA approval for enfortumab vedotin in locally advanced UC or mUC patients who have previously received a PD-1 or PD-L1 inhibitor, and platinum-containing chemotherapy [43]. Another cohort of the same EV-201 trial demonstrated similar promising results in a cohort of 91 patients who were cisplatin ineligible and had received prior immunotherapy [44]. A phase III RCT (n = 608) comparing enfortumab vedotin with single-agent chemotherapy after prior platinum chemotherapy and checkpoint inhibitor immunotherapy demonstrated significant survival benefit of almost 4 mo (12.88 vs 8.97 mo; HR: 0.7, 95% CI: 0.56–0.89) [45]. The most common treatment-related AEs included alopecia (45%), peripheral neuropathy (34%), fatigue (31%, 7.4% grade $\geq$3), decreased appetite (31%), diarrhoea (24%), nausea (23%), and skin rash (16%, 7.4% grade $\geq$3).

Preliminary results of the combination of enfortumab vedotin and pembrolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced UC/mUC have been reported, resulting in an ORR of 73.3%, with 15.6% CRs [46]. Treatment-related AEs of interest included any rash (48% all grade, 11% grade $\geq$3) and any peripheral neuropathy (50% all grade, 3% grade $\geq$3). This combination is currently under investigation in a phase III trial in the first-line setting for platinum-eligible patients (EV-302).

Based on these results, enfortumab vedotin has been approved by the FDA for patients who have received prior platinum-containing chemotherapy and prior immunotherapy with a PD-1 or PD-L1 inhibitor as well as for cisplatin-ineligible patients who have received one or more prior lines of therapy.

Another new and also promising ADC is sacituzumab govitecan, consisting of a humanised monoclonal antibody targeting trophoblast cell surface antigen 2 (Trop-2) conjugated to SN-38, the active metabolite of irinotecan. Sacituzumab govitecan was tested in 113 platinum and immunotherapy pretreated mUC patients and achieved an ORR of 27%, and a total of 77% had a decrease in measurable disease; the median PFS was 5.4 mo and the median OS was 10.9 mo [47]. Side effects consisted of haematological toxicities (neutropenia 34% grade $\geq$3, febrile neutropenia 10% grade $\geq$3), fatigue (52%), alopecia (47%), nausea (60%), diarrhoea (65%, 10% $\geq$grade 3), and decreased appetite (36%) [47]. Sacituzumab govitecan has received accelerated FDA approval for mUC with prior platinum and immunotherapy pretreatment. Several trials using sacituzumab govitecan as monotherapy or in combinations are on-going.

4.2. FGFR inhibition

Genomic profiling of UC has revealed common potentially actionable genomic alterations, including alterations in fibroblast growth factor receptor (*FGFR*) [48]. Erdafitinib is a pan-*FGFR* tyrosine kinase inhibitor and the first FDA-approved targeted therapy for mUC with susceptible *FGFR2/3* alterations following platinum-containing chemotherapy. The phase II trial of erdafitinib included 99 patients whose tumour harboured an *FGFR3* mutation or *FGFR2/3* fusion and who had disease progression following chemotherapy [49]. The confirmed ORR was 40%, and an additional 39% of patients had stable disease. A total of 22 patients had previously received immunotherapy, with only one patient achieving a response; yet the response rate for erdafitinib for this subgroup was 59%. At a median follow-up of 24 mo, the median PFS was 5.5 mo (95% CI: 4.0–6.0) and the median OS was 11.3 mo (95% CI: 9.7–15.2) [49]. Treatment-related AEs of grade $\geq$3 occurred in 46% of patients. Common AEs of grade $\geq$3 were hyponatraemia (11%), stomatitis (10%), and asthenia (7%), and 13 patients discontinued erdafitinib due to AEs, including retinal pigment epithelial detachment, hand-foot syndrome, dry mouth, and skin/nail events. In addition to erdafitinib, several other *FGFR* inhibitors are being evaluated, including infigratinib, which has demonstrated promising activity [50]. The increased identification of *FGFR3* mutations/fusion has led to several on-going trials with different agents and combination in different disease settings.

5. Current status of predictive biomarkers

The most important advance in recent years has been the recognition of alterations in *FGFR3* including mutations and gene fusions as a predictive marker for response to *FGFR* inhibitors [49]. It is recommended to screen mUC patients ideally at diagnosis of metastatic disease for *FGFR3* alterations to plan optimal treatment including trials.

Many efforts have focused on markers for predicting response to immune checkpoint inhibition.

PD-L1 expression by immunohistochemistry has been evaluated in many studies with mixed and so far inconclusive results. This may, in part, be related to the use of different antibodies and various scoring systems evaluating different compartments, that is, tumour cells, immune cells, or both. A major limitation of PD-L1 staining relates to the significant proportion of PD-L1–negative patients who respond to immune checkpoint blockade. The predictive value of PD-L1 was not confirmed in large phase III trials

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evaluating the integration of immunotherapy in the first-line setting for mUC [20–22]. At present, the only indication for PD-L1 testing in mUC is dictated by the current FDA and EMA approvals, and relates to the potential use of immune checkpoint inhibitors as first-line monotherapy in patients unfit for cisplatin-containing chemotherapy.

Another biomarker that has been evaluated for predicting response to immunotherapy is high tumour mutational burden (TMB) [51]. Neoantigen burden and TMB have been associated with a response to immune checkpoint blockade in several malignancies. High TMB has been associated with a response to immune checkpoint inhibitors in mUC in small

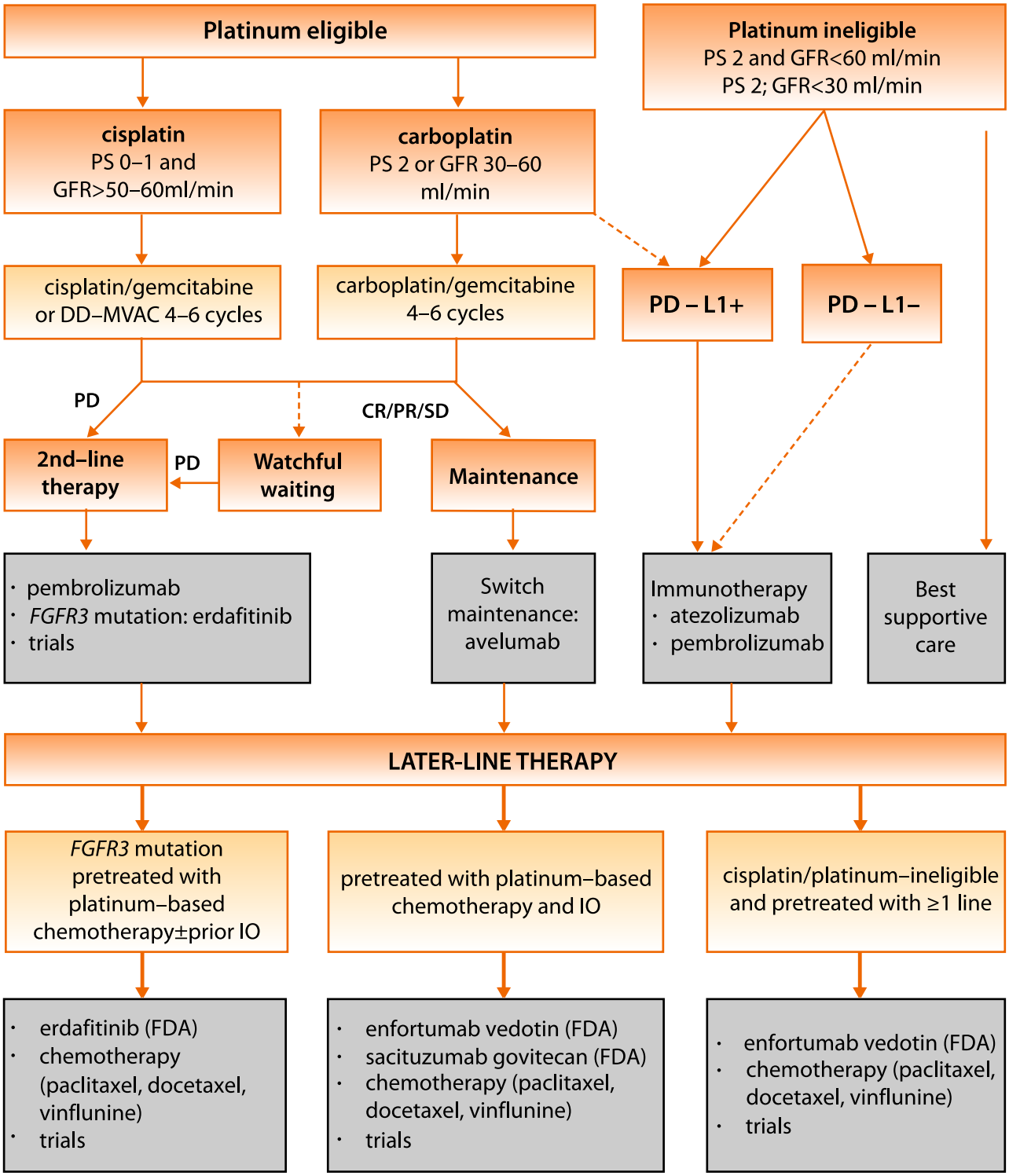

Fig. 1 – Flowchart for the management of metastatic urothelial carcinoma. Treatment within clinical trials is highly encouraged. CR = complete response; DD-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PD = progressive disease; PD-L1 = programmed death ligand 1; PR = partial response; PS = performance status; SD = stable disease.

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single-arm trials [35,52], but was not confirmed so far in randomised trials. Other markers that have been evaluated in predicting a response to immune checkpoint inhibitors include molecular subtypes, CD8 expression by immunohistochemistry, and other immune gene cell signatures. Recent work has focused on the importance of stroma, including the role of transforming growth factors in predicting response to immune checkpoint blockade [53,54].

In conclusion, apart from *FGFR3* alterations, there are currently no further validated predictive molecular markers that are routinely used in clinical practice.

6. Special situations

6.1. Impact of prior neoadjuvant/adjuvant therapy on treatment sequence

Perioperative systemic treatment is increasingly used in UC, including cisplatin-based chemotherapy in the neoadjuvant setting for BC and adjuvant platinum-based chemotherapy for upper tract UC [55]. Many on-going phase III trials investigate the use of immunotherapy in this setting as well. So far, one trial has reported a significant DFS benefit for adjuvant treatment with nivolumab compared with placebo, whereas one trial reported no significant benefit using atezolizumab versus placebo in the same setting and another trial reported negative findings [56,57]. It is expected that an increased number of patients with mUC would have received pretreatment with platinum and/or immunotherapy agents. No prospective trials have investigated the treatment of such patients. The choice of treatment in these patients depends on the applied perioperative treatment and the time until relapse. If at least 12 mo have passed since the end of perioperative treatment, the same systemic treatment as in treatment-naïve patients is recommended.

6.2. Systemic treatment of metastatic disease with histology other than pure UC

Pure urothelial carcinoma (PUC) represents the predominant histology in over 90% of patients with mUC. Variant histologies (eg, micropapillary, nested, and sarcomatoid) and divergent differentiation (eg, squamous cell carcinoma and adenocarcinoma) can be found in addition to PUC in up to 33% of patients. Such patients were often excluded from large phase II and phase III trials, and therefore the knowledge about the best management of such patients is limited. The respective literature was reviewed recently [58], and an expert Delphi survey and consensus conference provided guidance [59]. In case of predominant PUC, it is recommended to treat patients with mixed histology the same way as patients with PUC histology. Patients with predominant nonurothelial differentiation such as small cell neuroendocrine carcinoma, urachal adenocarcinoma, squamous cell carcinoma, and adenocarcinoma should be treated individually.

7. Summary: treatment algorithm for mUC update 2021

Fig. 1 summarises the treatment algorithm for metastatic BC based on the evidence discussed in this article.

Patients with treatment-naïve mUC are grouped according to platinum eligibility based on clear definitions. In general, first-line treatment consists of platinum-based chemotherapy in which cisplatin is to be preferred to carboplatin. Patients who are cisplatin ineligible but carboplatin eligible should receive carboplatin-gemcitabine combination chemotherapy. In case of positive PD-L1 status, treatment with checkpoint inhibitors (atezolizumab or pembrolizumab) could be an alternative option.

Patients unfit for both cisplatin and carboplatin (platinum unfit) can be considered for immunotherapy (FDA approved irrespective of PD-L1 status, EMA approved only for PD-L1 positive) or receive BSC.

In cases of disease stabilisation on platinum-based chemotherapy switch, maintenance treatment with immunotherapy (avelumab) is recommended. Alternatively, patients can be followed closely and receive second-line immunotherapy at the time of progression (pembrolizumab).

It is recommended to determine FGFR mutation status before deciding about second-line treatment. Patients with *FGFR3* mutations are candidates for FGFR inhibitor treatment. Enfortumab vedotin therapy is the new standard in case of progression after platinum chemotherapy and immunotherapy but has not yet been approved in Europe. The optimal sequence of novel agents and potential combinations are the subject of many on-going trials. It is generally recommended to treat patients within on-going clinical trials.

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References

[1] 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 2011;12:211–4.
[2] 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.
[3] 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 2012;3:855–9.
[4] Hussain SA, Stocken DD, Riley P, et al. A phase I/II study of gemcitabine and fractionated cisplatin in an outpatient setting using a 21-day schedule in patients with advanced and metastatic bladder cancer. Br J Cancer 2004;91:844–9.
[5] Morales-Barrera R, Bellmunt J, Suárez C, et al. Cisplatin and gemcitabine administered every two weeks in patients with locally advanced or metastatic urothelial carcinoma and impaired renal function. Eur J Cancer 2012;48:1816–21.
[6] 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 "unfit" for cisplatin-based chemotherapy: phase II–results of EORTC study 30986. J Clin Oncol 2009;27:5634–9.
[7] Bellmunt J, Petrylak DP. New therapeutic challenges in advanced bladder cancer. Semin Oncol 2012;39:598–607.
[8] 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.
[9] 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 III study. J Clin Oncol 2000;18:3068–77.
[10] Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. J Clin Oncol 2001;19:2638–46.
[11] Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006;42:50–4.
[12] Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012;30:1107–13.
[13] Rosenberg JE, Ballman KA, Halabi S, et al. Randomized phase III trial of gemcitabine and cisplatin with bevacizumab or placebo in patients with advanced urothelial carcinoma: results of CALGB 90601 (Alliance). J Clin Oncol 2021;39:2486–96.
[14] 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.
[15] Bamias A, Tzannis K, Harshman LC, et al. Impact of contemporary patterns of chemotherapy utilization on survival in patients with advanced cancer of the urinary tract: a Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Ann Oncol 2018;29:361–9.
[16] Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer 2001;92:2993–8.
[17] Meluch AA, Greco FA, Burris 3rd HA, 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 2001;19:3018–24.
[18] Calabrò F, Lorusso V, Rosati G, et al. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. Cancer 2009;115:2652–9.
[19] De Santis M, Wiechno PJ, Bellmunt J, et al. Vinflunine-gemcitabine versus vinflunine-carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: results of an international randomized phase II trial (JASINT1). Ann Oncol 2016;27:449–54.
[20] 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 2020;395:1547–57.
[21] 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 2021;22:931–45.
[22] Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2020;21:1574–88.
[23] 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 2017;18:1483–92.
[24] 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 2017;389:67–76.
[25] Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. J Clin Oncol 2020;38:1797–806.
[26] 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.
[27] Oing C, Rink M, Oechsle K, Seidel C, von Amsberg G, Bokemeyer C. Second line chemotherapy for advanced and metastatic urothelial carcinoma: vinflunine and beyond—a comprehensive review of the current literature. J Urol 2016;195:254–63.
[28] 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.
[29] Albers P, Park S-I, Niegisch G, et al. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. Ann Oncol 2011;22:288–94.
[30] Fechner G, Siener R, Reimann M, Kobalz L, Albers P. 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 2006;60:27–31.
[31] Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454–61.
[32] Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. Lancet 2017;390:2266–77.
[33] Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): overall survival and updated results of a randomised, double-blind, phase 3 trial. Lancet Oncol 2020;21:105–20.
[34] 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.
[35] 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, multicentre, phase 2 trial. Lancet 2016;387:1909–20.
[36] Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515:558–62.
[37] 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 2018;391:748–57.
[38] 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 2017;18:312–22.
[39] Longo DL, Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68.
[40] Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714–68.
[41] Maher VE, Fernandes LL, Weinstock C, et al. Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. J Clin Oncol 2019;37:2730–7.
[42] Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol 2019;37:2592–600.
[43] Chang E, Weinstock C, Zhang L, et al. FDA approval summary: enfortumab vedotin for locally advanced or metastatic urothelial carcinoma. Clin Cancer Res 2021;27:922–7.
[44] 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 2021;22:872–82.
[45] Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384:1125–35.
[46] Rosenberg JE, Flaig TW, Friedlander TW, et al. Study EV-103: Preliminary durability results of enfortumab vedotin plus pembrolizumab for locally advanced or metastatic urothelial carcinoma. J Clin Oncol 2020;38:441.
[47] Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A phase II 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.
[48] Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 2018;174:1033.
[49] Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 2019;381:338–48.
[50] Pal SK, Rosenberg JE, Hoffman-Censits JH, et al. Efficacy of BGJ398, a fibroblast growth factor receptor 1–3 inhibitor, in patients with previously treated advanced urothelial carcinoma with FGFR3 alterations. Cancer Discov 2018;8:812–21.
[51] Kandoth C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. Nature 2013;502:333–9.
[52] Sharma P, Callahan MK, Bono P, et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016;17:1590–8.
[53] Mariathasan S, Turley SJ, Nickles D, et al. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature 2018;554:544–8.
[54] Wang L, Saci A, Szabo PM, et al. EMT- and stroma-related gene expression and resistance to PD-1 blockade in urothelial cancer. Nat Commun 2018;9:3503.
[55] Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet 2020;395:1268–77.
[56] Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 2021;384:2102–14.
[57] Bellmunt J, Hussain M, Gschwend JE, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:525–37.
[58] Veskimäe E, Espinos EL, Bruins HM, et al. What is the prognostic and clinical importance of urothelial and nonurothelial histological variants of bladder cancer in predicting oncological outcomes in patients with muscle-invasive and metastatic bladder cancer? A European Association of Urology Muscle Invasive and Metastatic Bladder Cancer Guidelines Panel systematic review. Eur Urol Oncol 2019;2:625–42.
[59] Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO consensus statements on the management of advanced and variant bladder cancer—an international collaborative multistakeholder effort: under the auspices of the EAU-ESMO Guidelines Committees. Eur Urol 2020;77:223–50.

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