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REVIEW

WILEY

Systemic treatment of advanced and metastatic urothelial cancer: The landscape in Australia

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Abstract

The 5-year survival rate of metastatic urothelial carcinoma (mUC) is estimated to be as low as 5%. Currently, systemic platinum-based chemotherapy followed by avelumab maintenance therapy is the only first-line treatment for mUC that has an overall survival benefit. Cisplatin-based chemotherapy (usually in combination with gemcitabine) is the preferred treatment but carboplatin is substituted where contraindications to cisplatin exist. Treatment with immune checkpoint inhibitors, antibody-drug conjugates, and kinase inhibitors has not yet demonstrated superiority to chemotherapy as first-line therapy and remains investigational in this setting. A recent media release indicates that chemotherapy plus nivolumab gives an OS advantage as first-line treatment but results of this study have not yet been made public. Pembrolizumab remains an option in those having primary progression on first-line chemotherapy or within 12 months of neoadjuvant chemotherapy. The antibody-drug conjugate, enfortumab vedotin has TGA approval for patients whose cancer has progressed following chemotherapy and immunotherapy and has just received a positive Pharmaceutical Benefits Scheme recommendation. The use of molecular screens for somatic genetic mutations, gene amplifications, and protein expression is expanding as drugs that target such abnormalities show promise. However, despite these advances, a substantial proportion of patients with mUC have significant barriers to receiving any treatment, including advancing age, frailty, and comorbidities, and less toxic, effective therapies are needed.

1 | INTRODUCTION

Urothelial cancers are often attributed to chemical exposure, the most prevalent of which is tobacco use. Such tumors may arise in the bladder, the urethra, the ureters, or the renal pelvis. The most common primary tumor site in the bladder with the ureter or renal pelvis accounting for almost all others. Urethral cancers are rare. The incidence of bladder cancer is approximately three times greater in men than women, which may be attributed to a higher prevalence of smoking and exposure to occupational chemicals such as aromatic amines.[1] In Australia, bladder cancers account for 2% of cancers, with 3219 new diagnoses in 2022.[2] Globally, one-quarter of people with bladder cancer have muscle-invasive disease and a proportion of these will develop metastatic disease.[3] While the average 5-year survival rate for all

bladder cancers in Australia is 56%, the 5-year survival rate for patients with metastatic disease is estimated to be as low as 5%.[4]

Systemic chemotherapy is the mainstay first-line treatment for patients with metastatic urothelial carcinoma (mUC). Platinum-based chemotherapy is currently the standard first-line treatment, whereas single-agent systemic immunotherapy with immune checkpoint inhibitors (ICI) that inhibit the interaction between programmed death-ligand-1 (PD-L1) and its receptor programmed death receptor-1 (PD-1) has become the cornerstone maintenance and second-line treatment. Initial enthusiasm for immunotherapy as frontline monotherapy has waned with disappointing results in the initial phase III trials, although results of further combination trials are awaited. Conventional cisplatin-based chemotherapies have been the standard of care for fit patients since the 1980s; however, a large proportion (30–62%) of locally advanced or mUC patients are ineligible for first-line chemotherapy due to poor performance status, impaired renal function, and other comorbidities.[5] Despite the variety of therapeutic options available, the median survival for mUC with the best current practice is a sobering 17 months,[6] highlighting the difficulty in treating this disease and the unmet need for better therapeutics. To date, targeted therapies have not yielded a significant survival benefit in the first-line setting; however, several phase III trials are currently underway. A better understanding of the pathophysiology of this disease is needed to identify new therapeutic interventions.

Currently, there are no Australian treatment guidelines for mUC. When treating mUC, Australian physicians commonly follow international guidelines by the European Association of Urology (EAU) (Figure 1),[7] the United States National Comprehensive Cancer Network (NCCN),[8] and the European Society for Medical Oncology (ESMO).[9] On occasion agents recommended in such guidelines may be out of reach for Australian patients where they are not yet subsidized by the Pharmaceutical Benefits Scheme (PBS). The objective of this review is to provide an update on current Australian options in the treatment of mUC.

1.1 | First-line therapy

The specific chemotherapy regimen recommended for mUC is in part dependent on the medical fitness of the patient, particularly the presence of medical comorbidities.[8] The current first-line standard of care for treatment-naïve mUC is platinum-based chemotherapy, namely cisplatin (or carboplatin if the patient is cisplatin-ineligible). Nonplatinum combination chemotherapy is not recommended for first-line use in platinum-eligible mUC patients.[7]

1.1.1 | Cisplatin

The standard first-line treatment regimen is with gemcitabine plus cisplatin (GC). Not all patients are eligible to receive cisplatin, with up to 50% deemed unfit for cisplatin.[10] Poor performance status and renal function are the main limiting factors for the use of cisplatin in treating mUC. Guidelines exist for eligibility for the use of cisplatin in clinical trials.[11] The Galsky criteria[11] consider patients unfit for cisplatin if they have: a WHO or ECOG performance status ≥2; CTCAE version 4, grade 2 or above audiometric hearing loss; NYHA class III heart failure; CTCAE version 4, grade 2 or above peripheral neuropathy; and creatinine clearance (calculated or measured) less than 60 mL/min.[8,11,12]

Nephrotoxicity is a well-known side effect of cisplatin.[13] Patient and disease factors can lead to borderline kidney function prior to cisplatin treatment. As such, some patients receiving high-dose cisplatin experience renal dysfunction with treatment.[14] Advanced age patients are more likely to be cisplatin-ineligible since renal function typically declines by approximately 40% around the median age of advanced or mUC diagnosis (75 years old).[11,15]

Although cisplatin eligibility criteria can vary across the globe, major global bladder cancer guidelines (such as the NCCN 2020 guideline, the EAU 2023 guideline, and the 2021 ESMO Clinical Practice Guideline) strongly recommend the use of cisplatin-containing chemotherapy in patients with a metastatic bladder cancer who have a GFR of >50–60 mL/min (Figure 1).[7–9] Cisplatin is TGA approved for the treatment of malignancy in Australia and is subsidized on the PBS general schedule.

A number of alternate cisplatin-containing regimens are available; however, GC and a variation of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) are the most commonly used.[9] From comparisons between GC and MVAC, GC appears to be less toxic in patients with comorbidities; GC was associated with fewer treatment-related deaths than MVAC (1% vs. 3%); however, this was not statistically significant.[16] GC patients also fared better regarding weight, performance status, and fatigue, making GC more tolerable.[16] GC and MVAC exhibited similar efficacy; both yielding a median survival time of 12–15 months and a 5-year survival rate of approximately 13–15% in patients with locally advanced or mUC.[17] A randomized phase III trial comparing standard MVAC to dose-dense MVAC (ddMVAC) showed better survival and less overall toxicity with ddMVAC after a 7.3-year follow-up; 24.6% of patients were still alive on the ddMVAC arm versus 13.2% on the MVAC arm.[18,19] Overall, GC and ddMVAC can be given to cisplatin-eligible patients; however, GC is the recommended combination by major international guidelines.[7,8] Four to six cycles of GC or ddMVAC are currently recommended[7] and trials are underway investigating the efficacy of using only four or three cycles (ClinicalTrials.gov Identifier: NCT03296306). Retrospective analyses of large cohorts showed no difference in survival for four versus six or more cycles.[20,21]

To date, improvement in the efficacy of GC is yet to be achieved; the addition of paclitaxel to GC was investigated and, while paclitaxel plus GC gave a higher response rate and a 3.1-month survival benefit over GC, the survival benefit is small and the benefit is unlikely to outweigh the toxicity of adding another drug to the treatment regimen.[16,22] The incidence of febrile neutropenia was substantially higher in the presence of paclitaxel (13% vs. 4%, $P < 0.001$).[22] The combination of platinum-based chemotherapy with immunotherapy has not yielded significant benefits and is currently not advised.[9] Furthermore, immunotherapy alone is currently not recommended as first-line treatment for cisplatin-eligible patients.[9]

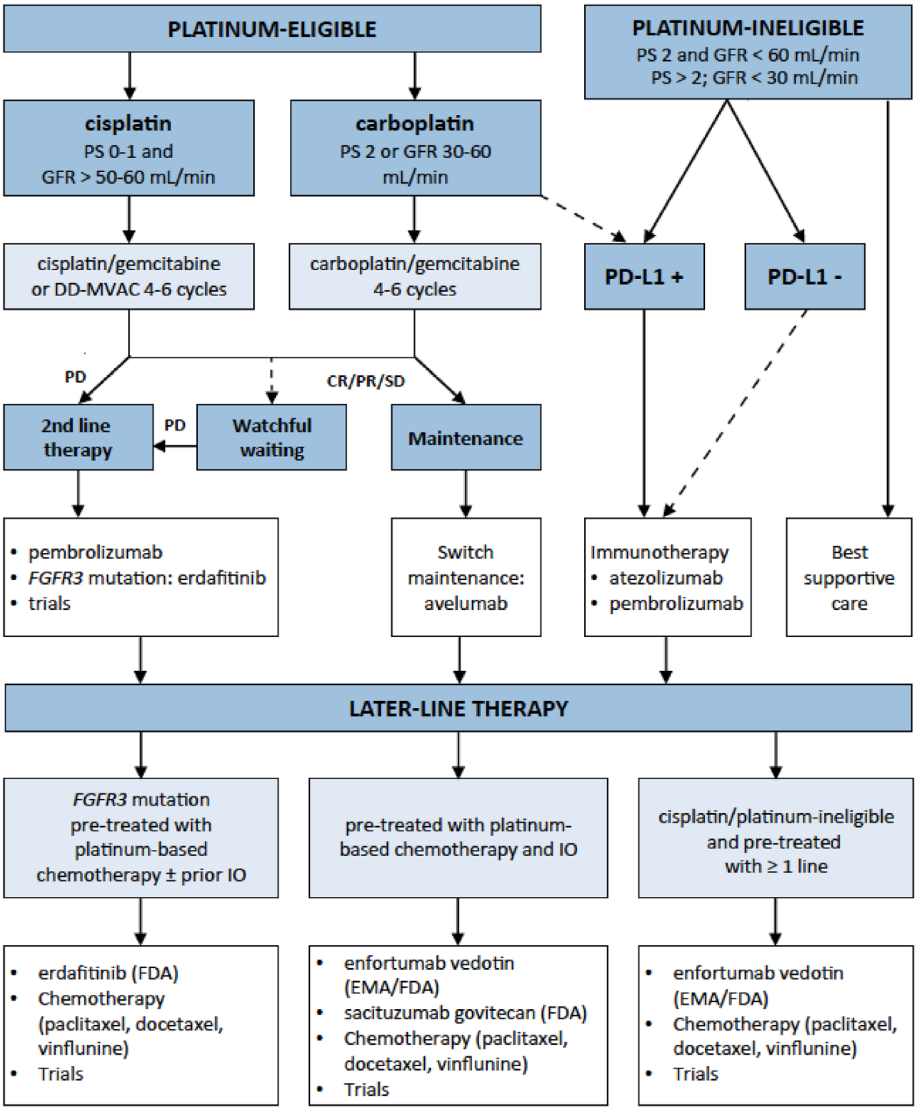

FIGURE 1 Flowchart for the management of metastatic urothelial carcinoma. Taken directly from the European Association of Urology 2023 guidelines on muscle-invasive and metastatic bladder cancer[7] with permission. BSC, best supportive care; CR, complete response; DD-MVAC, dose-dense methotrexate vinblastine doxorubicin cisplatin; EMA, European Medicines Agency; EV, enfortumab vedotin; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; GFR, glomerular filtration rate; IO, immunotherapy; PR, partial response; PS, performance status; SD, stable disease; PD, progressing disease. The dotted line represents a treatment option that is not approved worldwide.

Medically unfit/frail patients, defined as those with poor performance status, commonly show poor tolerance to cisplatin-based combination regimens. In this situation, options include substituting cisplatin with carboplatin or the use of split-dose cisplatin. Small studies have suggested that the administration of cisplatin in a split dose, where the total dose of cisplatin is divided and administered on separate days of the cycle (e.g., on days 1 and 2 or days 1 and 8), may increase its tolerability and allow for use in patients otherwise deemed unfit for cisplatin.[23,24] A pooled analysis of phase 2 trials using day 1 single dose or split dose cisplatin showed similar toxicity and efficacy results for mUC.[25] As such, GC split-dose may be an alternative to GCb for mUC patients who have borderline fitness for cisplatin.

1.1.2 | Carboplatin

Many cisplatin-ineligible patients with mUC patients remain fit for carboplatin-based chemotherapy.[26] A historical meta-analysis of clinical trials comparing cisplatin- to carboplatin-based chemotherapy demonstrated a higher likelihood of complete response or overall response with a cisplatin based approach.[27] The notion that carboplatin is less effective than cisplatin in mUC mostly comes from such retrospective analyses which are hindered by patient selection (poor-prognosis patients received carboplatin and good prognostic patients received cisplatin) or small randomized trials that used inadequate carboplatin dosing.[28] However, a recent post hoc review of patients receiving carboplatin or cisplatin combination therapy on standard of

care arm of the Danube study showed similar outcomes regardless of drug used (Powles et al. *Lancet Oncol* 2020; 21: 1574–88). Despite this, most guidelines state a preference for cisplatin over carboplatin for mUC. The carboplatin-based regimen GCb is usually preferred over other carboplatin-based regimens.[29] As such, up to six cycles of the GCb regimen should be considered a standard of care for cisplatin-ineligible patients who present with either a performance status of 2 or a GFR of 30–60 mL/min.[7–9,11,20] Carboplatin is TGA-approved for the treatment of malignancy in Australia and is subsidized on the PBS general schedule (Table 1).

Cisplatin eligibility guidelines were largely developed for deciding entry into clinical trials and are not strictly relevant to all patients seen in the clinic. They are not absolute rules that should be followed in every case but act as simple markers for consideration when choosing therapy. Many "real-world" patients with mUC are excluded from clinical trials so clinicians must interpret the results of clinical trials with this in mind. Whether cisplatin, split-dose cisplatin, carboplatin or no systemic therapy at all is chosen is a balance between a multitude of physical factors (other than just performance, renal, and neurological status) with the wishes of the patient. For example, some patients may be willing to accept the chance of worsening renal or neurological function or hearing loss for a perceived benefit from full-dose cisplatin. Others may wish to reduce toxicity and accept a possible reduction in efficacy.

1.1.3 | Options for platinum-ineligible patients

Immune checkpoint inhibitors are emerging as new targeted agents for the treatment of mUC. Bladder cancer is the third-highest mutating cancer, making checkpoint inhibitors a potential therapeutic option.[30] The immune checkpoint inhibitors pembrolizumab and atezolizumab have both received conditional approval in many countries after durable clinical responses were seen in nonrandomized phase II trials[31,32] Pembrolizumab is approved by the FDA as first-line option for mUC patients not eligible for any platinum-based chemotherapy, or in cisplatin-ineligible mUC patients whose tumors express programmed death-ligand 1 (PD-L1),[8] defined as stained tumor-infiltrating immune cells covering ≥5% of the tumor area[8,33] (Figure 1). Atezolizumab had a similar approval by the FDA but this was withdrawn in November 2022 after results from the phase III IMvigor130 trial (NCT02807636) failed to meet the postmarketing requirement necessary to convert the accelerated approval for atezolizumab into regular approval. The final results of this trial showed that atezolizumab monotherapy did not have a survival advantage over chemotherapy although had lower toxicity.[34] Exploratory analysis suggested a benefit for atezolizumab in patients whose tumors showed PD-L1 staining of ≥5% on infiltrating immune cells (PD-L1 2/3+) as determined by the SP142 assay.[10]

Given that phase III trials have failed to demonstrate a benefit of pembrolizumab or atezolizumab monotherapy over standard chemotherapy,[34,35] the evidence for the use of these immune checkpoint inhibitors as first-line treatment are ranked as weak by major guidelines.[7–9] In Australia, pembrolizumab is TGA-approved as monotherapy for the treatment of patients with locally advanced or mUC who are not eligible for any platinum-containing chemotherapy. Atezolizumab is also TGA-approved for cisplatin-ineligible patients with PD-L1 expressing tumor-infiltrating immune cells confirmed by a validated test (Table 1). However, pembrolizumab and atezolizumab are currently not PBS subsidized; the lack of PBS subsidy limits the uptake of these agents in Australia despite the presence of TGA registration.

It is attractive to consider immune checkpoint inhibitors rather than chemotherapy in patients with poor performance status (Eastern Cooperative Oncology Group (ECOG) score ≥2). However, the use of these agents in this setting is especially unclear. Retrospective cohort analysis showed that overall survival (OS) was lower in patients with performance status ≥2 versus 0–1 when treated in first-line with immune checkpoint inhibitors (7 months vs. 15 months, $P = 0.01$).[36] Furthermore, immune checkpoint inhibitor initiation in last 30 days of life was associated with increased odds of death in hospital (OR 2.89, $P = 0.04$).[36] The SAUL study enrolled a broad population of patients with mUC and treated them with atezolizumab monotherapy as a phase II study.[37] Subgroup analyses in patients with older age, renal impairment, or upper tract urothelial carcinoma showed safety and efficacy similar to those in patients without these characteristics. However, patients with ECOG PS 2 had a poor outcome with a median OS of only 2.3 months compared with 10.0 months for patients with ECOG PS 0/1.

1.2 | Nonchemotherapy combination therapies

DANUBE, an open-label, randomized, controlled, phase III trial in 1032 patients with untreated locally advanced or metastatic urothelial carcinoma, found that the PD-L1 inhibitor durvalumab ± the CTLA-4 inhibitor tremelimumab did not significantly improve OS compared with chemotherapy (gemcitabine + cisplatin or carboplatin).[38]

Enfortumab vedotin (EV) is an antibody-drug conjugate that delivers the microtubule-disrupting agent MMAE to cells expressing nectin-4, which is highly expressed in urothelial cancer.[39] In an ongoing multicohort study of 45 patients (EV-103; NCT03288545), EV plus pembrolizumab has been trialed as first-line therapy on cisplatin-ineligible mUC and has shown promising activity and durability, with a manageable safety profile.[40] A large phase III trial (EV302) is underway comparing EV plus pembrolizumab to platinum (cisplatin or carboplatin) and gemcitabine with a primary endpoint of OS. Of note, maintenance immunotherapy was not included in the control arm of this study until a study amendment, and the proportion of patients receiving this therapy will affect the interpretation of results. The trial is closed to accrual and results are awaited. EV is not currently TGA-approved for first-line use in Australia.

CheckMate-901 is a Phase III, randomized, open-label trial evaluating nivolumab in combination with ipilimumab (primary study) or nivolumab in combination with chemotherapy (substudy) compared with standard-of-care chemotherapy alone, in patients with untreated

TABLE 1 Current agents approved for the treatment of metastatic urothelial carcinoma in Australia by the Therapeutic Goods Administration (TGA) and their subsidy status by the Pharmaceutical Benefits Scheme (PBS).

Agent	TGA Indication and registration date	PBS Indication and clinical criteria	Key clinical evidence supporting use
First-line			
Cisplatin	Cisplatin is indicated for the treatment of advanced or metastasized bladder carcinoma. March 7, 2019	Cisplatin may be used as a monotherapy or in combination with other chemotherapeutic agents in the treatment of advanced-stage, refractory bladder carcinoma.	Maase, Hansen[16] von der Maase, Sengelov[17]
ddMVAC	All drugs are indicated for the treatment of bladder cancer	All drugs are broadly indicated	EORTC study 30924 Sternberg, de Mulder[18]
Carboplatin	Carboplatin should be indicated as an alternative to cisplatin-based regimens for the treatment of advanced urothelial cancer, particularly in patients with poor performance status.	Broadly indicated for the treatment of bladder cancer	EORTC study 30986 De Santis, Bellmunt[29]
Maintenance			
Avelumab	BAVENCIO is indicated for the first-line maintenance treatment of patients with locally advanced or mUC whose disease has not progressed with first-line platinum-based induction chemotherapy. February 24, 2021	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer. Treatment Phase: Maintenance therapy—Initial treatment. Clinical criteria: • Patient must have received first-line platinum-based chemotherapy, AND • Patient must not have progressive disease following first-line platinum-based chemotherapy, AND • Patient must have a WHO performance status of 0 or 1, AND • The treatment must be the sole PBS-subsidised therapy for this condition.	JAVELIN Bladder 100 (NCT02603432)
Second-line			
Pembrolizumab	KEYTRUDA is indicated as monotherapy for the treatment of patients with locally advanced or mUC who are not eligible for cisplatin-containing therapy, or who have received platinum-containing chemotherapy. January 11, 2018	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer. Treatment Phase: Initial treatment. Clinical criteria: • The treatment must be the sole PBS-subsidised therapy for this condition, AND • The condition must have progressed on or after prior platinum-based chemotherapy; OR • The condition must have progressed on or within 12 months of completion of adjuvant platinum-containing chemotherapy following cystectomy for localized muscle-invasive urothelial cancer; OR • The condition must have progressed on or within 12 months of completion of neoadjuvant platinum-containing chemotherapy prior to cystectomy for localized muscle-invasive urothelial cancer, AND • Patient must have a WHO performance status of 2 or less, AND • Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition.	KEYNOTE-045 (NCT02256436) Bellmunt, Necchi[53] Fradet, Bellmunt[55]

(Continues)

TABLE 1 (Continued)

Agent	TGA Indication and registration date	PBS Indication and clinical criteria	Key clinical evidence supporting use
Atezolizumab	TECENTRIQ is indicated for the treatment of patients with locally advanced or mUC who are considered cisplatin ineligible and whose tumors express PD-L1 (as determined by a validated test) or are considered ineligible for any other platinum-containing chemotherapy regardless of the level of tumor PD-L1 expression. April 24, 2019	Not subsidised	Balar, Galsky[31]
Nivolumab	OPDIVO is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. February 9, 2018	Not subsidised	CheckMate 032 Sharma, Callahan[76] CheckMate 275 Sharma, Retz[54]
Third-line			
Enfortumab vedotin	PADCEV is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand-1 inhibitor. July 7, 2022	Not subsidised	EV-301 (NCT03474107) Powles, Rosenberg[56] EV-201 (NCT03219333) Rosenberg, O'Donnell[77]

unresectable or metastatic urothelial cancer in patients who are eligible for cisplatin-based chemotherapy. The primary endpoints of the primary study are OS in patients who are ineligible for cisplatin-based chemotherapy and OS in patients with tumor cell PD-L1 expression ≥1%. A media release for the primary study in May 2022 stated that the combination of nivolumab and ipilimumab did not meet the primary endpoint of OS in patients with PD-L1 ≥1% staining tumors at the final analysis.[41] Results of the sub-study are discussed below.

The use of the tyrosine kinase inhibitor lenvatinib with pembrolizumab has been examined in a randomized, double-blind, multicenter, global, phase III study of first-line pembrolizumab + lenvatinib versus pembrolizumab + placebo in platinum-ineligible patients (LEAP-011). The addition of lenvatinib to pembrolizumab did not improve progression-free survival (4.2 vs. 4.0 months) or OS (11.2 vs. 13.8 months).[42] Furthermore, treatment-emergent adverse events were higher in patients taking lenvatinib compared with placebo (86.9% vs. 67.1%).[42]

1.2.1 | First-line chemotherapy plus immunotherapy combinations

None of the published studies using immunotherapy in combination with chemotherapy have shown an improvement in OS in mUC patients. There are at least three randomized trials in this setting that have failed to show an OS benefit for chemotherapy plus immunotherapy in the first-line metastatic setting—the DANUBE, IMvigor130, and the Keynote 361 studies. The Nile study remains unreported.

As mentioned above, the primary study of the CheckMate-901 study using nivolumab plus ipilimumab (primary study) compared with chemotherapy was negative. The substudy examined nivolumab in combination with chemotherapy compared with chemotherapy alone. A media release by the sponsor in July 2023 has said that the substudy has met the dual primary endpoints of OS and progression-free survival as assessed by Blinded Independent Central Review at the final analysis.[43] These results have been yet made available for public peer review.

The KEYNOTE-361 study was a randomized, open-label phase III trial of 1010 patients. The addition of pembrolizumab to first-line platinum-based chemotherapy (cisplatin or carboplatin) did not significantly improve progression-free survival or OS over platinum-based chemotherapy alone. The authors concluded that this combination should not be adopted for treatment of advanced urothelial carcinoma.[35]

The IMvigor130 study was a multicenter, randomized, placebo-controlled phase III trial of 1213 patients with locally advanced or metastatic urothelial carcinoma. Atezolizumab as monotherapy or in combination with platinum-based chemotherapy was compared with platinum-based chemotherapy alone. The three-drug combination was found to significantly improve progression-free survival over chemotherapy alone (8.2 vs. 6.3 months, respectively; $P = 0.007$).[10] The final survival analysis was presented at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium in 2023 and showed the median OS was 16.1 months for atezolizumab plus platinum-based chemotherapy compared with 13.4 months for chemotherapy alone (Hazard ratio of 0.85 (95% CI, 0.73–1.00). The one-sided *p*-value was 0.023 which did not meet the prespecified

interim efficacy boundary required to declare statistical significance ($P = 0.007$).[10,44]

An unanswered question is why the combination of ICIs with chemotherapy has so far proved ineffective in mUC, whereas similar combinations convey an OS advantage relative to chemotherapy alone in lung cancer, head and neck cancer, and other cancers. It has been suggested that chemotherapy may reduce the effectiveness of immunotherapy when used in combination but why this would happen for mUC and not in other cancers (such as NSCLC or head and neck cancer) has not been elucidated.

Another possible explanation is that trials in mUC remain diluted with cancers with driver oncogene mutations or amplifications (for example as FGFR or HER-2), and which may be less responsive to immunotherapy. It is known, for example, that lung adenocarcinoma is a heterogeneous disease with therapeutic decisions driven by the presence or absence of targetable oncogenic mutations (e.g., epidermal Growth Factor Receptor [EFGR] mutations) and fusions (e.g., Anaplastic Lymphoma Kinase [ALK] fusion). First-line immunotherapy studies in NSCLC have enriched their populations by rationally excluding patients with EGFR mutations and ALK fusions who rarely benefit from ICIs and directing them to oncogene-targeted therapy. mUC studies to date have not identified markers that allow for positive or negative selection of patients based on their likelihood to benefit from ICIs. It is possible that this lack of biomarkers has obscured a population that may benefit from frontline ICIs. It has been suggested that patients with FGFR mutation in mUC have an inferior response to immunotherapy however this mutation is not routinely tested for at diagnosis of mUC.[45] Furthermore, while PD-L1 IHC can be a very useful biomarker for the selection of patients for ICI monotherapy in NSCLC no such finding has been made in mUC.[46–48]

1.3 | Maintenance therapy

Currently, the checkpoint inhibitor avelumab is the recommended maintenance treatment for patients who show response to first-line platinum-based chemotherapy.[8] In the JAVELIN 100 study, a randomized phase III trial, a greater proportion of mUC patients whose disease did not progress after platinum-based chemotherapy survived at 1 year with avelumab (71.3%) compared with best supportive care alone (58.4%); OS was also significantly prolonged (median OS of 21.4 vs. 14.3 months, $P = 0.001$).[49] Grade ≥3 adverse events were reported in 47.4% of patients treated with avelumab compared with 25.2% of those with best supportive care alone.[49] Testing of the safety and efficacy of avelumab in combination with other antitumor agents as mUC maintenance therapy is ongoing in Australia in phase II randomized, open-label study (JAVELIN Bladder Medley; NCT05327530); this study is currently recruiting patients and results are awaited. Avelumab is currently TGA-approved and PBS-subsidized as maintenance therapy in mUC management in Australia (Table 1).

Pembrolizumab was tested in a phase II setting as a maintenance therapeutic after initial chemotherapy (NCT02500121). Progression-free survival was significantly longer with maintenance pembrolizumab versus placebo (5.4 vs. 3.0 months, log-rank $P = 0.04$). No difference in OS was detected between groups; however, the study was not powered for this endpoint.[50] Pembrolizumab is not approved as maintenance therapy in Australia.

The role of other agents such as rucaparib and vinflunine have also been investigated in the maintenance setting; although these agents have shown a progression-free survival benefit in randomized phase II trials, they have not yet established an OS benefit.[51,52]

1.4 | Second-line therapy

Patients with metastatic disease who relapse after platinum-based chemotherapy have a grim median survival of five to seven months.[17,29] Prior to the availability of maintenance avelumab single-agent ICIs targeting PD-1 or PD-L1 were the standard treatment of care for mUC patients whose disease has progressed following platinum-based chemotherapy.

Pembrolizumab has been tested in a phase III setting of recurrent advanced urothelial carcinoma where it was shown to convey an OS benefit compared with chemotherapy (14.9% vs. 8.7% 5-year survival rate) in patients that progressed after platinum-based chemotherapy.[53] In Australia, pembrolizumab is TGA-approved and PBS-subsidized for patients with locally advanced or mUC who have received platinum-containing chemotherapy.

The PD-1 inhibitor nivolumab was trialed in a single-arm phase II study of 270 patients with mUC. The overall objective response rate (ORR) was 19.6%, and responses were seen at all levels of PD-L1 expression, with no differences between more or less than 5% PD-L1 positivity. The authors concluded that nivolumab provided meaningful clinical benefit, irrespective of PD-L1 expression, and displayed an acceptable safety profile.[54] In Australia, nivolumab is TGA-approved for patients with locally advanced or mUC who have received platinum-containing chemotherapy. Nivolumab is currently not subsidized by the PBS in Australia.

Taxanes and vinflunine are alternative, albeit less attractive, second-line chemotherapeutic options for platinum-refractory disease who receive maintenance avelumab. These agents are the second-line treatment option for patients progressing on maintenance avelumab therapy since pembrolizumab is restricted to patients who are immunotherapy naïve; there is also no clear association with a survival benefit using taxanes or vinflunine.[9,55] Retreatment with platinum-based chemotherapy instead of taxanes/vinflunine is recommended for tumors that relapse more than one year after initial chemotherapy.[9] Taxanes are TGA approved for use in Australia while vinflunine is not.

1.5 | Beyond second-line therapy

1.5.1 | Antibody-drug conjugates

At present, US and European guidelines recommend the use of EV for patients with a performance status of 0 or 1 who have progressed

on or after treatment with a platinum-containing chemotherapy regimen and either a PD-1 or PD-L1 inhibitor.[8,9] A phase III trial showed that EV treatment prolonged OS (13 vs. 9 months, $P = 0.001$) and progression-free survival (5.5 vs. 3.7 months, $P < 0.001$) compared with chemotherapy in patients who progressed after chemotherapy or immune checkpoint inhibitor therapy.[56] EV is currently TGA approved for use in Australia for adults with locally advanced or mUC who have previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor (Table 1), and the drug had recently received a positive recommendation by the PBAC.

The antibody-drug conjugate sacituzumab govitecan has also demonstrated effectiveness for the treatment of previously treated mUC. A phase II trial of 113 patients with advanced, unresectable, or metastatic urothelial carcinoma that had progressed following prior platinum-based and PD-1/PD-L1 checkpoint inhibitor therapy showed a median OS of 11 months and a manageable safety profile.[57] The phase 3 TROPIC study comparing sacituzumab govitecan to salvage chemotherapy recently closed to recruitment and results are awaited (ClinicalTrials.gov Identifier: NCT04527991). Sacituzumab govitecan is yet to be approved for urothelial carcinoma in Australia.

1.5.2 | Molecularly-targeted agents

Recent insights into the genetic and molecular drivers of bladder cancer have opened the door for targeted molecular therapy. Certain genetic characteristics may be used to predict an individual's likely response to therapeutics and help with decisions regarding treatment. Genomic profiling of 295 cases of advanced urothelial carcinoma found the most clinically relevant genomic alterations in CDKN2A (34%), FGFR3 (21%), PIK3CA (20%), and ERBB2 (17%).[58]

Around 20% of advanced and metastatic urothelial carcinoma patients carry oncogenic mutations to the fibroblast growth factor receptor 3 (FGFR3) gene.[59] A phase II trial found the pan-FGFR kinase inhibitor erdafitinib achieved a 40% response rate (consisting of 3% complete responses and 37% partial responses) and had a manageable safety profile, with a median OS of 11 months.[60] Based on this limited data, erdafitinib was approved as second-line treatment for patients with locally advanced or mUC whose disease progressed during or after platinum-based chemotherapy and whose tumors express susceptible FGFR3 or FGFR2 genetic mutations.[8] Erdafitinib is not currently approved for use or subsidized in Australia. The phase III trial (THOR; NCT03390504) was presented at ASCO ASM in June 2023 and showed an OS advantage for erdafinitinib compared with chemotherapy (docetaxel or vinflunine) in patients with refractory mUC harboring selected FGFR alterations.[61] The NORSE study using erdafitinib with or without cetrelimab (anti-PD-1 antibody) as first-line therapy in cisplatin-ineligible patients showed a response rate of around 50% and a duration of response of almost a year.[62] Other FGFR inhibitors are currently under investigation.[59] Mutations to other genes, including p53, ERCC1, ERCC2, and others, are also under investigation; however, none have been validated yet.

The human epidermal growth factor receptor 2 (HER2, also known as ERRB2) represents another rationale therapeutic target in mUC. The definition of what constitutes a HER2 enriched mUC is not standardized yet and as such the number of patients who may potentially benefit from such an approach is unclear.[63] At present the predominant agent for HER2 directed antibody drug conjugates is trastuzumab deruxtecan (T-DXd). This combines the anti-HER2 monoclonal antibody with a topoisomerase I inhibitor, deruxtecan, via a cleavable linker. Remarkable efficacy has been achieved in breast cancer and to a lesser extent gastric cancer with this agent.[64–66] T-DXd blocks signaling via HER2, which is upregulated during cancer growth.[67] T-DXd combined with nivolumab in a phase 1b study of patients with HER2-expressing advanced/metastatic urothelial carcinoma (NCT03523572) has shown antitumor activity.[68] RC48-ADC (disitamab vedotin) is a novel humanized anti-HER2 antibody-drug conjugate. It has been trialed in a single-arm phase II study in HER2-positive locally advanced or mUC patients who failed platinum-based chemotherapy. To date, RC48-ADC has shown promising efficacy with a manageable safety profile (overall response rate was 50.5% (95% CI, 40.6–60.3%).[69]

1.6 | Microsatellite instability-high tumors

In general, single-agent ICI treatment remains inferior to chemotherapy as first-line therapy in mUC. However, tumors in patients with Lynch syndrome are more likely to respond to immunotherapeutics. Lynch syndrome is an autosomal-dominant hereditary tumor syndrome. It is estimated that 80,000 people in Australia (1 in 280 people) have Lynch syndrome.[70] People with Lynch syndrome have an increased risk of developing urinary tract cancer, especially in the upper tract.[71] Lynch syndrome is caused by pathogenic variants in various genes (MLH1, MSH1, MSH6, or PMS2), leading to microsatellite instability (MSI) and increased risk of tumor development.[72] Risk of bladder cancer in Lynch syndrome is increased in MSH2 mutation carriers.[71] Most Lynch syndrome cancers show activation of the immune response system, making these patients ideal candidates for ICI-based therapies.[73] A small series of 10 patients with mismatch repair deficiency or microsatellite instability and advanced upper tract urothelial cancer showed a 90% response to immunotherapy, including a high complete remission rate.[74] Screening for Lynch syndrome upon diagnosis will inform treatment of this subpopulation. Current guidelines recommend testing for Lynch syndrome for those identified as high-risk following a thorough family history evaluation.[8] Consideration of screening for Lynch syndrome should be particularly made in the presence of upper tract urothelial carcinoma.[75]

2 | CONCLUSION

In Australia, across the globe, the current standard of care for mUC patients is first-line platinum-based chemotherapy followed by maintenance therapy with the immune checkpoint inhibitor avelumab.

Studies continue to demonstrate that immunotherapy alone or in combination with chemotherapy offers no advantage to chemotherapy as first-line therapy in mUC. The chemotherapy backbone (i.e., cisplatin or carboplatin) is ultimately decided based on the fitness of the patient although cisplatin is favored because of a perceived greater efficacy. First-line therapies combining ICIs with ADCs have the potential to change the treatment landscape and the results of the EV-302 phase III trial (comparing EV + pembrolizumab vs. chemotherapy) are eagerly awaited. As more therapeutics become available, molecular profiling looking for FGFR3 mutations or HER2 upregulation will become important. Single-agent pembrolizumab continues to have a role in those progressing on first-line chemotherapy. Advances that improve the survival and quality of life for patients with mUC are to be welcomed.

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