Cancer Treatment Reviews 89 (2020) 102072

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-tumour Treatment

Clinical evidence for the first-line treatment of advanced urothelial carcinoma: Current paradigms and emerging treatment options

Maria Koufopoulou[a], Paulo A.P. Miranda[b], Paulina Kazmierska[a], Sohan Deshpande[a], Priyanka Gaitonde[b,*]

[a] Evidence Synthesis, Modeling & Communication, Evidera, London, UK
[b] AstraZeneca, Gaithersburg, MD, USA

ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Platinum-based chemotherapy
Survival outcomes
Treatment guidelines
Urothelial carcinoma

ABSTRACT

Background: Patients with advanced urothelial carcinoma (UC) have poor outcomes, with 5-year survival rates of < 5% for those with metastatic, stage IV disease. We have reviewed current treatment paradigms and emerging treatment options for these patients.

Methods: The websites of seven national or international organizations were searched for metastatic UC treatment guidelines. Systematic literature reviews were conducted to identify evidence from randomized controlled trials (RCTs) of chemotherapy for patients with previously untreated, unresectable, stage IV UC. Searches included congress databases and articles published between 1990 and 2018. In order to align with the latest treatment paradigms in first-line advanced UC, a focused literature search was conducted to identify evidence supporting immuno-oncology (IO) agents.

Results: For advanced UC, guidelines universally recommend cisplatin-based chemotherapy as first-line treatment for eligible patients and carboplatin-based regimens for those unfit to receive cisplatin. Despite the evaluation of a number of different cytotoxic regimens over the years, including triplet combinations, survival outcomes have not improved markedly with chemotherapy. Median overall survival with standard of care chemotherapy is ~13 months. Based on the results of single-arm, phase II studies, recent treatment guidelines have included atezolizumab (anti-PD-L1) and pembrolizumab (anti-PD-1) as first-line options for cisplatin-ineligible patients whose tumors express high levels of PD-L1. However, emerging evidence from RCTs of IO agents, including both cisplatin-eligible and cisplatin-ineligible patients, suggest that survival times exceeding 20 months are possible.

Conclusions: After having reached a plateau with chemotherapy, the treatment landscape for advanced UC is evolving. Survival outcomes for patients with advanced UC are improving with treatment modalities involving IO agents.

Introduction

Bladder cancer ranks as the ninth most common malignancy worldwide, with more than 165,000 deaths reported in 2012 [1]. The highest incidence rates occur in Southern Europe, Western Europe, and North America, although mortality rates are highest in Western Asia and Northern Africa [1]. Urothelial carcinoma (UC; also known as transitional cell carcinoma) accounts for 90% of all bladder cancers in Western Europe and the United States; squamous cell bladder cancer due to schistosomiasis infections is more common in Africa [1].

An initial diagnosis of non–muscle-invasive bladder cancer occurs in approximately 70% of patients [2]. Treatment at the non–muscle-invasive stage includes transurethral resection of bladder tumor often followed by intravesical chemotherapy or intravesical bacillus Calmette-Guérin immunotherapy [2]. Approximately 25% of patients with bladder cancer will be diagnosed with muscle-invasive disease [3]. Treatment of muscle-invasive bladder cancer includes surgery (cystectomy) combined with adjuvant or neo-adjuvant cisplatin-based chemotherapy [2], or synchronous chemoradiotherapy as an alternative to cystectomy [4], whereas patients with unresectable, locally advanced disease receive chemotherapy [5]. Among patients newly diagnosed with bladder cancer, approximately 5% will have metastatic disease and, historically, outcomes for these patients have been very poor; the 5-year survival rate for those with stage IV disease and distant

* Corresponding author at: Health Economics and Payer Evidence, AstraZeneca, One MedImmune Way, Bldg. 200, Gaithersburg, MD 20878, USA.
E-mail address: priyanka.gaitonde@astrazeneca.com (P. Gaitonde).

https://doi.org/10.1016/j.ctrv.2020.102072
Received 24 March 2020; Received in revised form 2 July 2020; Accepted 6 July 2020

metastases is < 5% [6].

The current standard of care for the first-line treatment of advanced UC (locally advanced or metastatic, stage IV disease) is platinum-based combination chemotherapy [7]. Patients with good performance status, adequate renal function, and no comorbidities are candidates for cisplatin-based regimens. However, approximately 40% of patients are not fit enough to receive cisplatin-containing therapy; options for these patients include carboplatin-based regimens. Myelosuppression, nephrotoxicity, and ototoxicity are common adverse events associated with cisplatin-based regimens [7], which can have a negative impact on health-related quality of life (HRQoL).

Evidence suggests that patients who receive cisplatin-based regimens have better survival outcomes than patients who receive carboplatin-based regimens [8,9]. However, as cisplatin can have a negative impact on HRQoL, there is a need to investigate alternative treatments that have improved benefit-risk profiles for cisplatin-eligible patients. Based on the results of single-arm, phase II studies [10,11], atezolizumab (anti–programmed cell death ligand 1 [PD-L1]) and pembrolizumab (anti–programmed death 1 [PD-1) were approved by the US Food and Drug Administration (FDA) in 2017 for the first-line treatment of cisplatin-ineligible patients with stage IV UC and high tumor PD-L1 expression, or for patients not eligible for any platinum-based therapy regardless of PD-L1 status. In 2018, the European Medicines Agency (EMA) approved atezolizumab and pembrolizumab for the first-line treatment of cisplatin-ineligible patients with stage IV UC and high tumor PD-L1 expression. The anti–PD-L1 agents atezolizumab, avelumab, and durvalumab, as well as the anti–PD-1 agents nivolumab and pembrolizumab, are approved for the second-line treatment of locally advanced or metastatic UC, regardless of PD-L1 status [12]. These agents are currently being evaluated as first-line therapies for metastatic UC, alone and in combination with chemotherapy or other agents, including inhibitors of cytotoxic T-lymphocyte-associated antigen 4 (ipilimumab and tremelimumab).

Given the availability of new therapies, it is important to understand the profiles and clinical outcomes of different treatment options for patients with advanced UC. As there is currently no comprehensive review of first-line management strategies for advanced UC, we conducted a review of available treatment guidelines, a systematic literature review of clinical outcomes with chemotherapy, and a recent review of the literature for studies of immuno-oncology (IO) agents in order to fill this gap in evidence.

Methods

Review of treatment guidelines

To identify national and international treatment guidelines for UC, we reviewed the guidelines published by selected Health Technology Assessment bodies (the websites of 11 Health Technology Assessment agencies from seven countries were searched) and the websites of recognized professional/national associations. For national guidelines, those published in English that provided treatment recommendations by disease stage and line of therapy were selected. Documents detailing disease management guidelines for the first-line treatment of advanced UC were obtained from the websites of the American Society for Clinical Oncology (ASCO), American Urological Association (AUA), Canadian Health Service (CHS), European Association of Urology (EAU), European Society for Medical Oncology (ESMO), National Institute for Health and Care Excellence (NICE), and National Comprehensive Cancer Network (NCCN).

Systematic literature review

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, systematic literature reviews (SLRs) were conducted to identify research reporting evidence of the efficacy, safety, and HRQoL outcomes associated with first-line chemotherapy for advanced UC. The titles and abstracts of reports published in English between January 1990 and November 2018 were searched, using the terms detailed in Table A.1, in the following databases: Medline and Medline in-process (via PubMed.com), Embase and Embase in-process (via Embase.com), Cochrane Central Register of Controlled Trials (CENTRAL), Centre for Reviews and Dissemination (CDSR), and Database of Abstracts of Reviews of Effects (DARE). Meeting abstracts from ASCO, AUA, EAU, ESMO, and the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) conferences held between 2013 and 2018 were also searched for relevant presentations. ClinicalTrials.gov, the European Clinical Trials Database (EudraCT), the EMA, and the US FDA were also searched to identify relevant clinical trials.

Study selection criteria for the SLRs are reported in Table A.2. Titles and abstracts were assessed against the predefined selection criteria for inclusion in the review. The full-text publication of all included abstracts was then assessed by one reviewer, and all excluded full-text publications were confirmed by a second reviewer. Reference lists of systematic reviews and *meta*-analyses were reviewed to ensure that all relevant publications were identified in the search of databases. Information was extracted from full-text articles and independently validated. Logic checks and validation were performed on the extracted data for additional quality assurance.

Studies included in the SLRs were assessed for bias using NICE-recommended standardized scoring systems, which included a checklist to assess the quality of clinical efficacy and safety data specific to randomized controlled trials (RCTs), and Downs' and Black's checklist to assess the methodological quality of non-randomized studies [13]. Only studies with > 25 enrolled patients were included in the SLRs.

Review of evidence for IO agents

A literature search was conducted to identify evidence from completed and ongoing trials evaluating IO agents as first-line therapies for advanced UC. A search of PubMed, major oncology congresses, and ClinicalTrials.gov was undertaken, from June 2015 through June 2020. The search terms included bladder cancer, urothelial carcinoma, immune checkpoint inhibitor, anti–PD-1, anti–PD-L1, anti–CTLA-4, atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and tremelimumab.

Results

Treatment guidelines for advanced UC

Seven guideline documents pertaining to the treatment of UC were identified in Canada, Europe, the United Kingdom, and the United States (Table 1) [14–21] National Comprehensive Cancer Network (NCCN) guidelines were updated in March of 2020 [21], but recommendations remain unchanged for the first-line treatment of locally advanced or metastatic (stage IV) UC (Table 1). The European Society for Medical Oncology (ESMO) guidelines were published in 2014 [15] and were last updated in December of 2019 [20].

All guidelines recommended platinum-based chemotherapy as first-line treatment. Cisplatin-based chemotherapy is preferred for patients who have good performance status, adequate renal function, and absence of comorbidities (eg, impaired cardiac status, neuropathy, hearing loss). Specifically, gemcitabine plus cisplatin or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) are recommended for cisplatin-eligible patients. Carboplatin-based regimens (eg, gemcitabine plus carboplatin) are recommended in cases where cisplatin is contraindicated.

Along with gemcitabine plus carboplatin, preferred regimens for cisplatin-ineligible patients in the current NCCN guidelines include atezolizumab or pembrolizumab for patients with high tumor PD-L1

Table 1
Guidelines for the first-line treatment of advanced UC.

Reference	Year	Population	Recommendation for First-line Treatment
NCCN [21]	2020	Locally advanced or metastatic (stage IV) UC	*Cisplatin eligible* ● Gemcitabine + cisplatin ● DDMVAC with growth factor support *Cisplatin ineligible* Preferred: ● Gemcitabine + carboplatin ● Atezolizumab (tumors expressing PD-L1 or ineligible for platinum-containing chemotherapy) ● Pembrolizumab (tumors expressing PD-L1 or ineligible for platinum-containing chemotherapy) Other recommended regimens: ● Gemcitabine or gemcitabine + paclitaxel Certain circumstances: ● Ifosfamide, doxorubicin, gemcitabine (for patients with good kidney function and PS)
ESMO [15,20]	2020	Advanced unresectable or metastatic UC	*Cisplatin eligible* ● Gemcitabine + cisplatin ● MVAC with G-CSF ● Dose-dense MVAC ● Paclitaxel + cisplatin + gemcitabine *Cisplatin ineligible (poor PS, impaired renal function, or comorbidities)* ● Gemcitabine + carboplatin ● Atezolizumab (PD-L1-positive tumors) ● Pembrolizumab (PD-L1-positive tumors) *Platinum ineligible (PS ≤ 2 + poor renal function)* ● Clinical trial ● Best supportive care
EAU [16]	2020	Advanced or metastatic UC	*Cisplatin eligible* ● Gemcitabine + cisplatin ● MVAC or high-dose MVAC ● Paclitaxel, cisplatin, and gemcitabine *Cisplatin ineligible* ● Gemcitabine + carboplatin ● Pembrolizumab (PD-L1-positive tumors) ● Atezolizumab (PD-L1-positive tumors) ● Alternative regimens *Platinum ineligible (PS ≥ 2)* ● Pembrolizumab (PD-L1-positive tumors) ● Atezolizumab (PD-L1-positive tumors) ● Best supportive care
ASCO/EAU [17]	2016	Metastatic muscle-invasive UC	*Cisplatin eligible* ● Gemcitabine + cisplatin ● MVAC or high-dose MVAC with G-CSF ● Carboplatin and non-platinum combination chemotherapy is not recommended *Cisplatin ineligible* ● Carboplatin-containing combination chemotherapy, preferably gemcitabine + carboplatin ● Single agents
CADTH [19]	2012	Advanced, unresectable metastatic UC	*Cisplatin eligible* ● Sequential gemcitabine + cisplatin, plus paclitaxel *Cisplatin ineligible* ● Gemcitabine + carboplatin
CHS [14]	2013	Metastatic UC	*Cisplatin eligible* ● Gemcitabine + cisplatin ● MVAC *Cisplatin ineligible* ● Gemcitabine + carboplatin ● Single-agent gemcitabine (if expected to poorly tolerate platinum agents)
NICE [18]	2015	Locally advanced or metastatic UC	*Cisplatin eligible* ● Gemcitabine + cisplatin ● Accelerated MVAC with G-CSF *Cisplatin ineligible* ● Gemcitabine + carboplatin

ASCO, American Society of Clinical Oncology; CADTH, Canadian Agency or Drugs and Technologies in Health; CHS, Canadian Health Service; DDMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EAU, European Association of Urology; ECOG, Eastern Cooperative Oncology Group; ESMO, European Society of Medical Oncology; G-CSF, granulocyte colony-stimulating factor; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; PS, performance status; UC, urothelial carcinoma.

expression or for those not eligible for any platinum-based chemotherapy, regardless of PD-L1 expression. In the recently updated ESMO guidelines, gemcitabine plus carboplatin remains the preferred regimen for cisplatin-ineligible patients; however, atezolizumab or pembrolizumab are recommended for cisplatin-ineligible patients with PD-L1-positive tumors. High PD-L1 expression for atezolizumab is defined as positive PD-L1 staining of tumor-infiltrating immune cells (ICs) of ≥ 5% as a proportion of the total tumor cell (TC) and IC area (VENTANA SP142 Assay), while for pembrolizumab, high PD-L1 expression is defined as positive PD-L1 staining of TCs plus ICs ≥ 10% as a proportion of the total TC area (combined positive score [CPS] ≥ 10) (PD-L1 IHC 223 pharmDx assay).

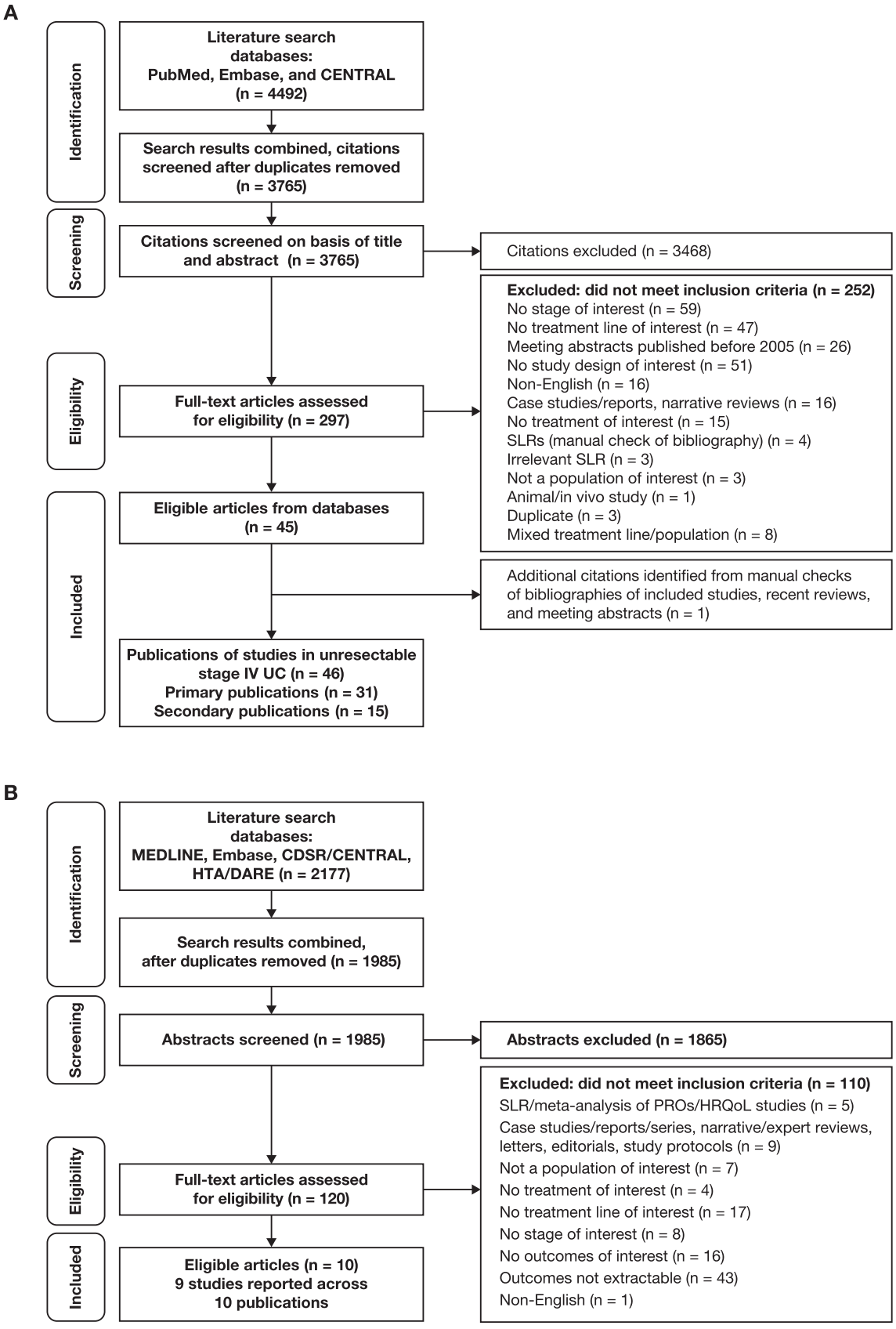

Fig. 1. PRISMA flow diagram of study selection. **(A)** Clinical and safety studies for the first-line treatment of urothelial carcinoma. **(B)** HRQoL analyses studies. CENTRAL, Cochrane Central Register of Controlled Trials; CDSR, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; PRO, patient-reported outcomes; SLR, systematic literature review.

Table 2
Clinical evidence from RCTs of first-line chemotherapy for advanced UC.

Reference	Intervention	Population	N	Follow-up Median (Range)	Objective Response Rate % (95% CI)	Progression-free Survival Median (95% CI)	Overall Survival Median (95% CI)	Grade 3+ AEs (most frequent hematologic)
Bamias et al. 2004 [31]	Docetaxel + cisplatin + G-CSF	Unresectable, metastatic, or recurrent UC ECOG PS 0–2	111	25.3 mo (3.2–51)	Overall: 37.4% (27.4–48.1)[a] ITT: 30.6%	NR	9.3 mo (7.9–10.7)	Neutropenia (19.2%), anemia (5.8%), neutropenic sepsis (3.8%), thrombocytopenia (0.9%)
	MVAC + G-CSF		109		Overall: 54.2% (42.9–65.2)[a] ITT: 41.3%		14.2 mo (12.5–15.9) $P = 0.026$	Neutropenia (35.9%), neutropenic sepsis (11.7%), anemia (7.8%), thrombocytopenia (5.8%)
Bamias et al. 2013 [22]	DD-MVAC (14 d) + G-CSF	Unresectable, metastatic, or recurrent urothelial TCC	63	52.1 mo (0.1– 82.5)	60.0%	8.5 mo	19.0 mo	Neutropenia (19.7%), anemia (11.5%), thrombocytopenia (8.2%)
	DD gemcitabine + cisplatin (14 d) + G-CSF	ECOG PS 0–1	63		65.3% $P = 0.67$	7.8 mo $P = 0.36$	18.0 mo $P = 0.98$	Neutropenia (13.6%), anemia (10.2%), thrombocytopenia (8.5%)
Bellmunt et al. 1997 [30]	MVAC	Urothelial TCC KPS ≥ 60	24	18 mo (6–60)	52% (30–73)	NR	16 mo (range, 3–24+)	Granulocytopenic fever (18%), anemia (3.7%), thrombocytopenia (3.7%)
	MCAVI		23		39% (20–62) $P = 0.3$		9 mo (range, 2–17) $P = 0.03$	Granulocytopenic fever (3.2%), anemia (3.2%), thrombocytopenia (3.2%)
Bellmunt et al. 2012 [33]	Paclitaxel + cisplatin + gemcitabine (21 d)	Stage IV locally advanced or metastatic urothelial TCC WHO PS 0–1	312	4.6 y (max. 6.8)	55.5% $P = 0.0031$	8.3 mo $P = 0.113$	15.8 mo (13.6–17.5) $P = 0.075$	Neutropenia (64.2%), WBC count (51.3%), thrombocytopenia (34.4%), hemoglobin (22.5%)
	Gemcitabine + cisplatin (28 d)		314		43.6%	7.6 mo	12.7 mo (11.0–14.4)	Thrombocytopenia (52.1%), neutropenia (50.5%), WBC count (38.7%), hemoglobin (25.6%)
Bellmunt et al 2017 [67]	Gemcitabine + cisplatin + apatorsen 600 mg	Metastatic or locally advanced UC KPS ≥ 70%	58	NR	57%	7.5 mo (6.0–9.9) $P = 0.20$	15.3 mo (10.7–23.2) $P = 0.25$	Neutropenia (48.3%), anemia (41.4%), hyperuricemia (31.0%), thrombocytopenia (29.3%), leukopenia (29.3%), lymphopenia (25.9%)
	Gemcitabine + cisplatin + apatorsen 1000 mg		60		50%	7.5 mo (4.9–8.9) $P = 0.37$	15.6 mo (11.5–19.2) $P = 0.32$	Neutropenia (56.7%), anemia (46.7%), leukopenia (41.7%), thrombocytopenia (36.7%), hyperuricemia (33.3%), lymphopenia (31.7%)
	Gemcitabine + cisplatin + placebo		61		61%	6.2 mo (4.9–8.0)	15.0 mo (11.7–19.4)	Hyperuricemia (44.3%), neutropenia (42.6%), anemia (37.7%), leukopenia (27.9%), lymphopenia (26.2%), thrombocytopenia (21.3%)
Culine et al. 2011 [51]	Gemcitabine + oxaliplatin	Advanced TCC of the urothelium (cisplatin ineligible)	22	21 mo	27% (11–50)	3.4 mo	8.1 mo (3.7–10.7)	Neutropenia (31.8%), anemia (13.5%), thrombopenia (22.7%)
	Gemcitabine		22		43% (22–66)	3.8 mo	5.4 mo (3.3–13.4)	Neutropenia (61.9%), anemia (42.9%), thrombopenia (19.0%)
Culine et al 2017 [25]	DD-MVAC + G-CSF	Locally advanced or metastatic bladder or upper urinary tract TCC	33	27 mo	70%	6.8 mo	20.2 mo	Hematologic (54.5%), infection/ febrile neutropenia (24.2%)
	DD-MVAC + panitumumab + G-CSF		63		48%	5.7 mo	12.5 mo	Hematologic (49.2%), infection/ febrile neutropenia (25.4%)
De Santis et al. 2012 [8]	Gemcitabine + carboplatin	Advanced urothelial cancer (cisplatin ineligible)	119	4.5 y (max. 7.8)	41.2%	5.8 mo	9.3 mo	Neutropenia (52.5%), leukopenia (44.9%), thrombocytopenia (48.3%)
	MCAVI		119		30.3% $P = 0.08$	4.2 mo $P = 0.78$	8.1 mo $P = 0.64$	Neutropenia (63.5%), leukopenia (46.6%), thrombocytopenia (19.4%)

(*continued on next page*)

Table 2 (*continued*)

Reference	Intervention	Population	N	Follow-up Median (Range)	Objective Response Rate % (95% CI)	Progression-free Survival Median (95% CI)	Overall Survival Median (95% CI)	Grade 3+ AEs (most frequent hematologic)
De Santis et al. 2016 [50]	Vinflunine + gemcitabine	Locally advanced or metastatic UC (TCC predominant); ECOG PS 0–1, cisplatin ineligible	34	25.9 mo	44.1%	5.9 mo (4.2-9.4)	14.0 mo (8.3-20.1)	Neutropenia (38.2%), anemia (26.5%), thrombocytopenia (5.9%)
	Vinflunine + carboplatin		35		28.6%	6.1 mo (4.6-10.4)	12.8 mo (9.5-17.7) $P = 0.86$	Neutropenia (65.7%), anemia (25.7%), thrombocytopenia (20.0%)
De Wit et al. 1991 [54]	Carboplatin	Metastatic or unresectable urothelial TCC; WHO PS 0–2	15	NR	0%	NR	NR	Thrombocytopenia (33.3%), leukocytopenia (20.0%)
	Iproplatin		32		17% (4–31)			Thrombocytopenia (34.4%), leukocytopenia (3.1%)
Dogliotti et al. 2007 [9]	Gemcitabine + cisplatin (21 d)	Locally advanced or metastatic urothelial TCC; Zubrod PS 0–2	55	7.2 mo	65.9% (49.4–79.9)	NR	12.8 mo	Neutropenia (34.6%), thrombocytopenia (30.9%), anemia (20.0%), leukopenia (16.4%)
	Gemcitabine + carboplatin		55	6.9 mo	56.4% (39.6–72.2)		9.8 mo	Neutropenia (45.4%), thrombocytopenia (38.2%), anemia (25.4%), leukopenia (29.1%)
Dreicer et al. 2004 [46]	MVAC	Advanced or metastatic urothelial TCC; ECOG PS 0–2	43	32.5 mo	35.9%(21.2–52.8) $P = 0.63$	8.7 mo $P = 0.24$	15.4 mo $P = 0.65$	Neutropenia (67.4%), anemia (37.2%), thrombocytopenia (20.9%)
	Carboplatin + paclitaxel		41		30.8% (15.0–44.9)	5.2 mo	13.8 mo	Neutropenia (29.3%), anemia (4.9%), thrombocytopenia (9.8%)
Haggag et al. 2014 [23]	Low-dose gemcitabine + cisplatin (21 d)	Unresectable, recurrent, and/or metastatic urinary bladder cancer on top of bilharzial cystitis; ECOG PS 0-2	60	9.5 mo	41.7%	NR	12 mo (3.8–20.2) 1-year OS: 49.9%	Anemia (15.0%), neutropenia (10.0%), thrombocytopenia (15.0%)
	Standard-dose gemcitabine + cisplatin (21 d)		60		33.3% $P = 0.37$		16 mo (6.5–25.5) 1-year OS: 54.7% $P = 0.8$	Anemia (23.3%), neutropenia (16.7%), thrombocytopenia (6.7%)
Hussain et al. 2014 [38]	Gemcitabine + cisplatin (28 d)	Metastatic or locally advanced/unresectable UC; ECOG PS 0-2	28	NR	57.1% (37–76)	8.5 mo (5.7–10.4)	17.4 mo (12.8–NYR)	Neutropenia (42.8%), thrombocytopenia (39.3%), leukopenia (21.5%), anemia (10.7%)
	Gemcitabine + cisplatin + cetuximab (28 d)		59		61.4% (48–74) $P = 0.81$	7.6 mo (6.1–8.7) $P = 0.47$	14.3 mo (11.6–22.2) $P = 0.43$	Neutropenia (40.7%), thrombocytopenia (25.5%), leukopenia (30.5%), anemia (8.5%)
Krege et al. 2014 [36]	Gemcitabine + cisplatin + sorafenib (21 d)	Locally advanced or metastatic TCC of the bladder or upper urinary tract; ECOG PS 0–1	40	18 mo	52.5% (36.1–68.5) $P = 0.67$	6.2 mo (3.2–9.5) $P = 0.69$	11.2 mo (6.3–18.4) $P = 0.66$	Leukopenia (12.2%), thrombocytopenia (12.2%), anemia (9.8%), pancytopenia (4.9%)
	Gemcitabine + cisplatin + placebo (21 d)		49		46.9% (32.5–61.7)	6.0 (4.0-7.0)	10.4 mo (8.4–14.9)	Leukopenia (12.2%), thrombocytopenia (12.2%), anemia (14.3%), pancytopenia (8.2%)
Kuroda et al. 1998 [55]	Standard MEC	T3b, T4, or metastatic UC; WHO PS 0–2	24	NR	54%	NR	NR	Leukopenia 38.9%, thrombocytopenia (12.5%), anemia (23.6%)
	Intensified MEC + G-CSF		24		75%			Leukopenia (25.0%), thrombocytopenia (46.9%), anemia (17.2%)
	MVAC		24		42%			Leukopenia (44.8%), thrombocytopenia (13.4%), anemia (16.4%)

(*continued on next page*)

Table 2 (*continued*)

Reference	Intervention	Population	N	Follow-up Median (Range)	Objective Response Rate % (95% CI)	Progression-free Survival Median (95% CI)	Overall Survival Median (95% CI)	Grade 3+ AEs (most frequent hematologic)
Logothetis et al. 1990 [28]	MVAC	Metastatic UC (pure TCC and mixed histologic types)	55	NR	65% (52–77) $P < 0.05$	NR	11.2 mo (range, 1.2–37.4+) $P < 0.001$	Leukopenic fever (14%) [*frequency of toxicity courses*]
	CISCA		55		46% (32–62)		8.3 mo (range, 1.6–33.9+)	Leukopenic fever (5%) [*frequency of toxicity courses*]
Logothetis et al. 1995 [56]	Escalated MVAC	Metastatic or locally advanced, unresectable UC; ECOG PS 0-3	23	NR	NR	NR	NR	After 3 courses: leukopenic fever (0%), infection (15%); median (nadir): platelets, 28; hemoglobin level, 8.1
	Escalated MVAC + GM-CSF		25					After 3 courses: leukopenic fever (9%), infection (41%); median (nadir): platelets, 10; hemoglobin level, 7.8
Lorusso et al. 2005 [34]	Paclitaxel + gemcitabine + cisplatin (21 d)	Metastatic or unresectable TCC of urinary tract; ECOG PS 0-2	42	NR	43% (23–63)	NR	14.1 mo (range 0.5–19.6)	Leukopenia (49%), thrombocytopenia (36%), anemia (20%)
	Gemcitabine + cisplatin (28 d)		43		44% (28–60)		11.3 mo (range 0.5–16.6)	Leukopenia (35%), thrombocytopenia (21%), anemia (24%)
McCaffrey et al. 1997 [57]	Gallium nitrate + fluorouracil	Urothelial TCC; KPS 60%–80%	17	35 mo (2–51)	12% (1.4–36.4)	NR	19 mo	Anemia (58.8%), neutropenia (0%), thrombocytopenia (0%)
	Dose-intensified MVAC + G-CSF		17		94% (71.3–99.8)		17 mo	Anemia (70.6%), neutropenia (82.4%), thrombocytopenia (23.5%)
Mead et al. 1998 [52]	Methotrexate + vinblastine	Unresectable, advanced or metastatic TCC	106	NR	19%	3 mo	4.5 mo 1-yr OS rate: 16%	Neutropemic fever (1.9%), leukopenia (0%), thrombocytopenia (0%)
	Cisplatin + methotrexate + vinblastine		108		46%	5.5 mo $P = 0.0001$	7 mo 1-yr OS rate: 29% $P = 0.0065$	Neutropemic fever (10.2%), leukopenia (4.6%), thrombocytopenia (4.6%)
Miller et al. 2016 [35]	Gemcitabine + cisplatin + gefitinib 250 mg QD, followed by gefitinib maintenance (21 d)	Advanced or metastatic urothelial TCC; WHO PS 0–1	35	NR	58.6%	NR	13.3 mo (10.5–19.2)	Leukopenia (60.0%), anemia (28.6%), neutropenia (37.1%), pancytopenia (22.9%)
	Gemcitabine + cisplatin followed by gefitinib 250 mg QD (21 d)		37		53.3%		8.5 mo (7.0–14.5)	Leukopenia (54.1%), anemia (48.6%), neutropenia (18.9%), pancytopenia (18.9%)
	Gemcitabine + cisplatin followed by observation (21 d)		33		42.8%		15.9 mo (10.9–31.3)	Leukopenia (78.8%), anemia (30.3%), neutropenia (24.2%), pancytopenia (6.1%)
Oudard et al. 2015 [37]	Gemcitabine + cisplatin/carboplatin (21 d)	Advanced or metastatic UC overexpressing Her2; ECOG PS 0-2	29	NR	65.5%	10.2 mo (4.3–13.4)	15.7 mo (12.2–23.6)	Neutropenia (75.9%), thrombocytopenia (48.3%), anemia (41.4%)
	Gemcitabine + cisplatin/carboplatin + trastuzumab (21 d)		32		53.2% $P = 0.39$	8.2 mo (4.6–10.6) $P = 0.69$	14.1 mo (9.3–28.0) $P = 0.68$	Neutropenia (67.7%), thrombocytopenia (38.7%), anemia (38.3%)
	MVEC		29		71.4%	NR		

(*continued on next page*)

Table 2 (*continued*)

Reference	Intervention	Population	N	Follow-up Median (Range)	Objective Response Rate % (95% CI)	Progression-free Survival Median (95% CI)	Overall Survival Median (95% CI)	Grade 3+ AEs (most frequent hematologic)
Petrioli et al. 1996 [58]		Recurrent or metastatic bladder cancer; ECOG PS 0-3		21 (12–31)			13 mo (range, 4–31+)	During cycle 6 (grade 2–4): leukopenia (37%), thrombocytopenia (21%), anemia (25%)
	MVECa		28		40.7%		9.5 mo (range, 3–27+)	During cycle 6 (grade 2–4): leukopenia (58%), thrombocytopenia (26%), anemia (10%)
Pizzocaro et al. 1991 [59]	MVAC	Metastatic TCC of the urinary tract	14	NR	71.4%	NR	NR	Leukopenia (14.3%), thrombocytopenia (14.3%), anemia (7.1%)
	Methotrexate + cisplatin		14		50.0%			Leukopenia (7.1%), thrombocytopenia (7.1%), anemia (7.1%)
Saxman et al. 1997 [29]	Cisplatin	Metastatic UC KPS ≥ 60%	122	6 yr (minimum)	12% (7–19)	4.3 mo	8.2 mo	Decreased platelets (1.6%) and leukocytes (0.8%)
	MVAC		133		39% (30–48)	10.0 mo	12.5 mo $P = 0.00015$	Decreased platelets (4.8%) and leukocytes (19%)
Siefker-Radtke et al. 2002 [47]	MVAC	Unresectable, locally advanced or metastatic UC	86	60	59%	NR	12.5 mo	Anemia (23.3%), febrile neutropenia (19.8%), thrombocytopenia (7.0%)
	FAP		83	61	42%		12.5 mo	Anemia (10.8%), febrile neutropenia (4.8%), thrombocytopenia (2.4%)
Sternberg et al. 2006 [32]	MVAC	Locally advanced or metastatic TCC of the urinary tract; WHO PS 0–2	129	7.3 y	58% (48–67) $P = 0.06$	8.1 mo (7.0–9.9) $P = 0.017$	14.9 mo 5-yr OS rate: 13.5%	Whole blood cell (62.0%), platelets (17.1%), neutropenic fever (25.6%)
	HD-MVAC + G-CSF		134		72% $P = 0.016$	9.5 mo (7.6–12.2) $P = 0.017$	15.1 mo 5-yr OS rate: 21.8% $P = 0.042$	Whole blood cell (20.1%), platelets (20.9%), neutropenic fever (9.7%)
Sternberg et al. 2013 [53]	Larotaxel + cisplatin	Locally advanced or metastatic urothelial or bladder TCC; ECOG PS 0–2	166	NR	31% (22–41)	5.6 mo (4.1–6.2)	13.7 mo (11.2–17.1) $P = 0.33$	Neutropenia (34.0%), leukopenia (16.0%), anemia (7.4%), thrombocytopenia (1.9%)
	Gemcitabine + cisplatin (28 d)		171		43% (33–52)	7.6 mo (6.6–9.1)	14.3 mo (10.5–NYR)	Neutropenia (60.2%), leukopenia (42.2%), anemia (21.7%), thrombocytopenia (45.2%)
Trump et al. 1990 [24]	Carboplatin	Metastatic urothelial TCC; ECOG PS 0–3	32	NR	14% (3–35)	NR	5.0 mo $P = 0.76$	Severe or life-threatening myelosuppression-primarily thrombocytopenia (31%)
	Iproplatin (CHIP)		32		16% (5–36)		4.3 mo	Severe or life-threatening myelosuppression-primarily thrombocytopenia (34%)

(*continued on next page*)

Table 2 (*continued*)

Reference	Intervention	Population	N	Follow-up Median (Range)	Objective Response Rate % (95% CI)	Progression-free Survival Median (95% CI)	Overall Survival Median (95% CI)	Grade 3+ AEs (most frequent hematologic)
von der Maase et al. 2005 [27]	MVAC	Locally advanced or metastatic urothelial TCC; KPS ≥ 70	202	5 y	45.7% *P* = 0.51	8.3 mo (7.3–9.7) *P* = 0.63	15.2 mo (13.2–17.3) *P* = 0.66 5-yr OS rate: 13.0%	Neutropenia (82%), thrombocytopenia (57%), anemia (27%)
	Gemcitabine + cisplatin (28 d)		203		49.4%	7.7 mo (6.8–8.8)	14 mo (12.3–15.5) 5-yr OS rate: 15.3%	Neutropenia (71%), thrombocytopenia (21%), anemia (18%)

Where reported, *P* values indicate between-group differences.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHIP, *cis*-dichloro-*trans*-dihyroxy-bis-isopropylamine platinum IV; CI, confidence interval; d, days; DD, dose dense; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; FAP, fluorouracil, interferon-alpha-2b, and cisplatin; G-CSF, granulocyte–colony stimulating factor; HD, high dose; ITT, intent-to-treat (population); KPS, Karnofsky performance status; max, maximum; MCAVI, methotrexate, carboplatin, and vinblastine; MEC, methotrexate, epirubicin, and cisplatin; mo, months; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; MVEC, methotrexate, vinblastine, epirubicin, and cisplatin; MVECa, methotrexate, vinblastine, epirubicin, and carboplatin; NR, not reported; NYR, not yet reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QD, once daily; TCC, transitional cell carcinoma; UC, urothelial carcinoma; WHO, World Health Organization; wk, weeks; y, years.

[a] *P* = 0.017 for MVAC versus docetaxel + cisplatin; however, *P* = 0.100 when all randomized patients were analyzed and non-assessable patients were considered non-responders.

Efficacy of first-line chemotherapy for advanced UC

Of the 4492 publications identified in the searches for efficacy and safety studies on first-line chemotherapy for unresectable stage IV UC, 31 RCTs (with evidence reported in 46 publications) met the inclusion criteria and were included in the results (Fig. 1A).

Most RCTs compared various treatment schedules of platinum-based chemotherapies according to cycle length and dose density (Table 2). For example, studies that evaluated gemcitabine plus cisplatin evaluated different gemcitabine doses (cisplatin 70 mg/m^2 + gemcitabine 250–2500 mg/m^2 every 14, 21, or 28 days) [22,23]. MVAC chemotherapy was most often administered at the standard doses of 30 mg/m^2 methotrexate, 3 mg/m^2 vinblastine, 70 mg/m^2 cisplatin, and 30 mg/m^2 doxorubicin, but some trials reported dose ranges of methotrexate 34–60 mg/m^2, vinblastine 3.4–4 mg/m^2, doxorubicin 34–60 mg/m^2, and cisplatin 25–100 mg/m^2 every 14, 23, or 28 days. Carboplatin was administrated at area under the curve 4.5, 5, or 6–250, 300, and 400 mg/m^2 doses.

Efficacy data from studies of approved and experimental first-line treatments for UC are summarized in Table 2. In brief, median overall survival (OS) ranged from 4.3 months with iproplatin [24] to 20.2 months with dose-dense MVAC [25]. For standard of care regimens, gemcitabine plus cisplatin has shown improved OS versus gemcitabine plus carboplatin, although this difference did not reach statistical significance (median OS of 12.8 vs 9.8 months, respectively) [9]. When MVAC was compared with gemcitabine plus cisplatin in a randomized phase III trial, no significant differences in any efficacy endpoint were observed [26,27]. ORR was 49.4% with gemcitabine plus cisplatin and 45.7% with MVAC [26]. Follow-up analyses from this study showed a median OS of 14.0 months with gemcitabine plus cisplatin and 15.2 months with MVAC, and 5-year OS rates of 13.0% and 15.3%, respectively [27]. Median PFS was 7.7 months with gemcitabine plus cisplatin and 8.3 months with MVAC.

In most trials of MVAC chemotherapy, patients had longer OS (range, 12.1–20.2 months) [25,28] than those who received other chemotherapies, such as methotrexate, carboplatin, and vinblastine (MCAVI) or docetaxel plus cisplatin (8.2–19 months) [22,29,30,31]. In a phase III study that compared MVAC with supportive granulocyte-colony stimulating factor (G-CSF) to docetaxel plus cisplatin with G-CSF, median OS was 14.2 months for patients in the MVAC arm and 9.3 months for those in the docetaxel plus cisplatin arm (*P* = 0.026) [31]. Similar trends were seen for PFS – MVAC chemotherapy was associated with longer PFS (range, 8.1–10 months) compared with other chemotherapies (4.3–7.8 months). However, a phase III study by the EORTC showed improved survival outcomes with high-dose MVAC plus G-CSF versus standard MVAC [32]; PFS was 9.5 months with high-dose MVAC plus G-CSF versus 8.1 months for standard MVAC (*P* = 0.017), with a 5-year OS rate of 21.8% versus 13.5% (*P* = 0.042), respectively [32].

Two randomized studies investigated the addition of paclitaxel to gemcitabine plus cisplatin compared with gemcitabine plus cisplatin [33,34]. Both trials administered the paclitaxel regimen every 21 days and gemcitabine plus cisplatin every 28 days. In the phase III EORTC Intergroup Study 30987 [33], median OS was 15.8 months with paclitaxel and gemcitabine plus cisplatin versus 12.7 months with gemcitabine plus cisplatin (*P* = 0.075). In the eligible patient population, a significant improvement in OS by 3.2 months was observed with the addition of paclitaxel (*P* = 0.03). Median PFS was 8.3 months with paclitaxel and gemcitabine plus cisplatin versus 7.6 months with gemcitabine plus cisplatin, although this did not reach statistical significance. However, ORR was significantly higher with paclitaxel and gemcitabine plus cisplatin compared with gemcitabine plus cisplatin (55.5% vs 43.6%; *P* = 0.031).

Several studies have evaluated combinations of targeted agents with chemotherapy. One trial assessed gemcitabine plus cisplatin concomitant with or followed by gefitinib (sequential treatment), an

Table 3
Clinical trial results of first-line IO therapy for advanced UC.

Study [Ref]	Intervention	Population	N (All/PD-L1 high)	Follow-up (median)	Response		PFS (median)	OS (median)	OS rate
					All patients	PD-L1 high			
Phase II (IMvigor210)[a] [10]	Atezolizumab monotherapy	Cisplatin-ineligible	119/32	17.2 mo	23%	28%	2.7 mo	15.9 mo	1-yr: 57%
Phase II (IMvigor210) [39]	Atezolizumab monotherapy	Cisplatin-ineligible	119/32	29 mo	24%	–	–	16.3 mo	1-yr: 58% 2-yr: 41%
Phase II (KEYNOTE-052)[b] [11]	Pembrolizumab monotherapy	Cisplatin-ineligible	370/110	5 mo	24%	38%	2 mo	–	–
Phase II (KEYNOTE-052)[b] [40]	Pembrolizumab monotherapy	Cisplatin-ineligible	370/110	11.5 mo	29%	47%	2.3 mo	11.5 mo	1-yr: 48%
Phase II [41]	GC followed by GC + ipilimumab	Cisplatin-eligible	36	–	39%	–	7.9 mo	13.9 mo	1-yr: 61% 2-yr: 31%
Phase III (IMvigor130)[a] [42]	Atezolizumab + CT	Cisplatin-eligible, cisplatin-ineligible	451/108	11.8 mo	47%	–	8.2 mo	16.0 mo	–
	Atezolizumab		360/88		23%	39%	–	15.7 mo	–
	Placebo + CT		400/91		44%	44%	6.3 mo	13.4 mo	–
Phase III (JAVELIN Bladder 100)[c] [45]	Avelumab + BSC	Cisplatin-eligible, cisplatin-ineligible	350	–	9.7%	13.8%	3.7 mo	21.4 mo[d]	1-yr: 71%
	BSC alone		350		1.4%	1.2%	2.0 mo	14.3 mo[d]	1-yr: 58%

BSC, best supportive care; GC, gemcitabine plus cisplatin; CT, platinum-based chemotherapy; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[a] PD-L1 assessed using the VENTANA SP142 assay: IC PD-L1 staining ≥ 5% as a proportion of the total TC and IC area.

[b] PD-L1 assessed using the pharmDx 22C assay: CPS ≥ 10.

[c] PD-L1 assessed using the VENTANA SP263 assay: TC PD-L1 staining ≥ 25%, or ≥ 25% or 100% of ICs if the percentage of ICs was > 1% or ≤ 1%, respectively.

[d] From randomization (after chemotherapy).

inhibitor of epidermal growth factor receptor (EGFR), 250 mg once daily [35]. Treatment without gefitinib led to an OS of 15.9 months, whereas gefitinib resulted in a median OS of 13.3 months for concomitant treatment and 8.5 months for sequential treatment. OS, PFS, and ORR were similar for gemcitabine plus cisplatin in combination with sorafenib (a multi-kinase inhibitor) [36], trastuzumab (anti–HER2 antibody) [37], and cetuximab (anti-EGFR antibody) [38], compared with gemcitabine plus cisplatin alone or plus placebo.

First-line therapy with IO agents

Evidence to support the initial regulatory approvals of IO agents as first-line treatments for advanced UC were based on the results of multicenter, single-arm, phase II studies with objective response or ORR as the primary endpoints (Table 3). In the IMvigor210 study of cisplatin-ineligible patients, atezolizumab treatment resulted in an ORR of 23%, with median PFS of 2.7 months and median OS of 15.9 months [10]. An ORR of 28% was reported for IC membrane positivity of PD-L1 ≥ 5% and 21% for IC membrane positivity of PD-L1 < 1%. In an updated analysis at a median follow-up of > 2 years, ORR was 24% and median OS was 16.3 months with 1- and 2-year OS rates of 58% and 41%, respectively [39]. In the KEYNOTE-052 study of cisplatin-ineligible patients treated pembrolizumab, an ORR of 24% was reported [11]. A follow-up analysis showed a confirmed ORR of 29% and median OS of 11.5 months [40]. However, in patients with a CPS ≥ 10 for PD-L1 expression, the ORR was 47% and median OS was 18.5 months.

As platinum-based chemotherapy has been the standard of care for the first-line treatment of advanced UC for almost two decades, the efficacy of IO agents in combination with chemotherapy is of interest. One of the earliest studies to evaluate such a combination was a multicenter, single-arm, phase II study in 36 chemotherapy-naive patients [41]. In this study, gemcitabine plus cisplatin followed by ipilimumab in combination with gemcitabine plus cisplatin yielded an ORR of 69% and a 1-year OS rate of 61%. Median PFS was 7.9 months. More recently, the results of the phase III IMvigor130 study were reported, which evaluated atezolizumab with or without platinum-based chemotherapy in untreated, cisplatin-eligible and cisplatin-ineligible patients with advanced UC [42]. This study demonstrated a significant improvement in PFS with atezolizumab plus platinum-based chemotherapy versus chemotherapy alone (median PFS of 8.2 vs 6.3 months). Subgroup analyses showed that longer PFS was observed among both cisplatin-eligible and cisplatin-ineligible patients. Median OS was 16.0 months with atezolizumab plus platinum-based chemotherapy versus 13.4 months with chemotherapy alone, but this difference did not reach statistical significance. In contrast, it was reported on June 9, 2020 that the KEYNOTE-361 study did not meet either of its co-primary endpoints, as pembrolizumab plus platinum-based chemotherapy did not yield a statistically significant improvement in PFS or OS versus chemotherapy in patients with untreated advanced UC [43].

Data are emerging from ongoing phase III studies evaluating different regimens for untreated advanced UC, such as IO plus IO combinations as potential non-chemotherapy treatment options or IO agents as maintenance therapy. Although results have yet to be published, it was revealed that the DANUBE trial did not meet the primary endpoints of improved OS with durvalumab versus standard of care chemotherapy in patients with high tumor PD-L1 expression (≥ 25% of tumor or tumor-associated immune cells staining positive for PD-L1) nor with durvalumab plus tremelimumab versus standard of care chemotherapy in all randomized patients [44]. In the JAVELIN Bladder 100 trial, patients with untreated advanced UC who achieved an objective response or stable disease with platinum-based chemotherapy were randomized to maintenance avelumab plus best supportive care or best supportive care [45]. From the date of randomization (after chemotherapy), median OS was 21.4 months for avelumab versus 14.3 for best supportive care. Longer OS with avelumab was observed in both

patients who had received gemcitabine plus cisplatin and in those who had received gemcitabine plus carboplatin.

Safety of first-line treatments for advanced UC

While the survival outcomes with gemcitabine plus cisplatin are similar to those of MVAC in advanced UC [27], the former has an overall better safety profile and thus higher benefit-risk ratio compared with MVAC (Table 2) [26]. Common adverse events (AEs) with gemcitabine plus cisplatin include anemia, diarrhea, thrombocytopenia, and neutropenia. When compared with MVAC, patients treated with gemcitabine plus cisplatin have higher rates of grade 3–4 anemia (27% vs 18%) and grade 3–4 thrombocytopenia (57% vs 21%) [26]. However, higher rates of grade 3–4 AEs reported for MVAC compared with gemcitabine plus cisplatin include neutropenia (82% vs 71%), alopecia (55% vs 11%), mucositis (22% vs 1%), infection (15% vs 3%), diarrhea (8% vs 3%), and pulmonary (6% vs 3%) [26]. The frequency of severe toxicities is also higher in patients treated with MVAC compared with gemcitabine plus carboplatin, with grade 4 AEs in 33% and 15% of patients, respectively [46]. As expected, the addition of G-CSF to MVAC results in considerably lower frequencies of toxicities than reported for MVAC without G-CSF [32].

In the phase III study of advanced UC in which dose-dense gemcitabine plus cisplatin (over 14 days) was compared with dose-dense MVAC, the former was shown to have better tolerability [22]. Grade 3–4 AEs were reported in 50% of patients in the dose-dense MVAC group and in 44% of patients in the dose-dense gemcitabine plus cisplatin group, with discontinuations due to toxicity of 13% and 3%, respectively. Neutropenic infections, in particular, occurred less frequently in the gemcitabine plus cisplatin group than in the MVAC group (0% vs 8%). Conversely, studies that have compared MVAC with other experimental regimens have shown a more favorable safety profile with MVAC. In one such study, non-hematologic AEs of at least grade 3 were reported in 48% of patients who received MVAC compared with 71% of patients who received fluorouracil plus interferon–alpha-2b and cisplatin [47].

For IO agents, the safety profile observed across studies of advanced UC was generally consistent with that reported in other tumor types. In the IMvigor210 study, treatment-related AEs of any grade and of grade 3–4 occurred in 66% and 16% of patients treated with atezolizumab, respectively, the most common being fatigue, diarrhea, and pruritus [10]. Among 119 treated patients, one death was due to study drug toxicity. In the CheckMate-052 study, treatment-related AEs of any grade and of grade 3–4 occurred in 68% and 20% of patients treated with pembrolizumab, respectively, the most common being fatigue and pruritus [40]. One death among 370 treated patients was related to study drug toxicity. As expected, the rate of AEs was higher in the IMvigor130 trial. AEs (any causality) were reported in $>$ 99% of patients in the atezolizumab plus platinum-based chemotherapy group and in 99% of patients in the chemotherapy group, with grade 3–4 AEs in 85% and 86% of patients, respectively [42]. Treatment-related AEs of any grade and of grade 3–4 were reported in 96% and 81% of patients, respectively, in both groups. AEs leading to treatment discontinuation occurred in 34% of patients in both groups. Deaths related to study drug toxicity were reported in 6% of patients in the atezolizumab plus platinum-based chemotherapy group and in 5% of patients in the chemotherapy group. In the JAVELIN Bladder 100 trial, the rate of treatment-emergent AEs (any causality) of any grade and of grade 3–4 were similar to that reported for atezolizumab monotherapy in IMvigor130 (98% vs 93% and 47% vs 42%) [42,45], suggesting that prior chemotherapy does not meaningfully impact the safety profile of an IO agent used as first-line maintenance therapy.

HRQoL assessments

Among nine clinical trials that reported HRQoL results in ten publications (Fig. 1B), three were RCTs of first-line chemotherapy. In the phase III that compared gemcitabine plus cisplatin and MVAC, HRQoL was assessed (using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire –Core 30 [EORTC QLQ-C30]) in 165 of 203 (81%) patients in the gemcitabine plus cisplatin arm and in 161 of 202 patients (80%) in the MVAC arm, with on-study compliance in 87.2% and 84.4% of patients, respectively [26]. HRQoL was similar in both groups, with improvements from baseline in median scores for emotional functioning and pain. However, fewer patients in the gemcitabine plus cisplatin arm reported a $\geq$ 10-point worsening of fatigue from baseline compared with the MVAC arm (44% and 49%, respectively). The authors noted that the better safety and tolerability of gemcitabine plus cisplatin compared with MVAC was not reflected in the HRQoL results; this might be partially due to the use of generic HRQoL questionnaires as opposed to disease- or treatment-specific instruments and, therefore, may not have addressed the presence of any toxicities (such as mucositis and neutropenic sepsis) that are of a particular concern in the treatment of UC with MVAC. Another explanation could be that patients who discontinued therapy because of toxicity may not have completed a questionnaire at that cycle. In a separate analysis of data from this trial, certain HRQoL parameters (such as high physical functioning, low role functioning, and no anorexia), were found to be predictive of longer survival in univariate models [48].

Assessment of study bias and gaps in evidence

We used the criteria of the Centre for Reviews and Dissemination, University of York, [49] to assess the quality of the included RCTs. The assessment included selection bias, performance bias, attrition bias, crossover effects, and detection bias (ie, whether a precise definition of outcome assessment was provided and use of valid and reliable methods to assess outcomes). Overall risk of bias was determined to be low in five studies [8,27,33,34,50], moderate in two studies [11,22], high in seven studies [9,31,35,36,51–53], and very high in sixteen studies [23,24,28,29,30,32,37,38,46,47,54–59]. The results of one study were published as a meeting abstract and therefore its quality was not assessed based on a lack of reported information [25].

Among the RCTs that investigated the efficacy and safety of chemotherapy in advanced UC, 16 reported an appropriate method of randomization and five reported adequate allocation concealment. In 21 studies, patient baseline characteristics across treatment arms were comparable [8,9,22,23,27–34,38,46,47,50–52,55,56,58]. One study did not report baseline characteristics of the patients [59]. Seven studies used open-label designs [9,22,27,33,34,37,50], and six had a crossover design [24,29,38,54,57,59], which may have impacted survival outcomes in four cases [24,29,38,57]. All trials used Response Evaluation Criteria In Solid Tumors or World Health Organization (WHO) criteria to assess ORRs and National Cancer Institute or WHO criteria to grade AEs, and most included precise definitions of survival outcomes.

Discussion

Platinum-based combination chemotherapy has remained the standard of care for the first-line treatment of advanced UC for two decades. Most treatment guidelines recommend gemcitabine plus cisplatin or MVAC for cisplatin-eligible patients. However, given that the efficacy of these two regimens is similar, gemcitabine plus cisplatin is most commonly used due to a better overall safety profile compared with MVAC. Some guidelines (EAU) also recommend paclitaxel in combination with gemcitabine plus cisplatin for eligible patients, whereas other guidelines (NCCN) do not recommend this regimen based on the risk–benefit profile. Patients unfit to receive cisplatin, often due to impaired renal function, can be treated with carboplatin-based regimens which are less nephrotoxic [60]. Although survival outcomes with gemcitabine plus

carboplatin are worse than with gemcitabine plus cisplatin, patients unfit for cisplatin typically have prognostic factors that are associated with poor survival outcomes.

In accordance with treatment guidelines, most RCTs used cisplatin-based therapies as comparators (MVAC and gemcitabine plus cisplatin). Among the studies that assessed guideline-recommended treatments, dose-dense MVAC was associated with the longest OS and highest ORR [25,37,57]. In contrast, gemcitabine monotherapy was associated with a median OS of only 5.4 months and median PFS of 3.8 months, and carboplatin plus paclitaxel with an ORR of only 31% [46,51]. Notably, these studies evaluated small numbers of patients, and thus the results should be interpreted with caution. Collectively, a number of different chemotherapeutic regimens have been evaluated over the past three decades, including variations of dose and schedule for platinum-containing regimens, platinum-free doublets, novel combinations with three or more agents, and sequential regimens. However, no chemotherapeutic regimen has been shown to improve upon standard of care chemotherapy as toxicities outweighed the benefits, and thus treatment options for patients with advanced UC, particularly for cisplatin-eligible patients, had reached a plateau.

The treatment landscape for advanced UC changed in 2017 and 2018 when the US FDA and EMA, respectively, approved atezolizumab and pembrolizumab for cisplatin-ineligible patients. These approvals ushered in a new era for the treatment of advanced UC as they offered the first non-chemotherapeutic options for patients. Based on survival outcomes of patients with low tumor PD-L1 expression who received atezolizumab or pembrolizumab monotherapy compared with platinum-based chemotherapy, the use of these IO agents was subsequently restricted to cisplatin-ineligible patients with high tumor PD-L1 expression. In a *meta*-analysis of studies of IO agents in advanced UC, PD-L1 expression was found to be predictive of response [12]. In the phase II study of atezolizumab, patients with IC PD-L1 expression ≥ 5% had an ORR of 28%, compared with an ORR of 21% for those with IC PD-L1 expression < 1% [10]. Pembrolizumab yielded an ORR of 47% for patients with PD-L1 CPS ≥ 10, compared with an ORR of 29% ORR for the full population [40]. It remains unclear if long-term survival outcomes with these agents are associated with PD-L1 expression.

The phase II study of ipilimumab and gemcitabine plus cisplatin provided evidence for the feasibility of combining an IO agent with standard of care chemotherapy [41]. Results from IMvigor130 were the first to be reported for a phase III study that evaluated the combination of an IO agent and platinum-based chemotherapy as a first-line treatment for advanced UC, and the first RCT to evaluate an IO agent in both cisplatin-eligible and cisplatin-ineligible patients [42]. This study demonstrated a significant improvement in PFS of 1.9 months with atezolizumab plus platinum-based chemotherapy versus chemotherapy alone. Subgroup analyses suggested longer PFS in both cisplatin-eligible and cisplatin-ineligible patients. At the interim analysis, median OS was 15.7 months for atezolizumab monotherapy, consistent with that initially reported from the IMvigor210 study in cisplatin-ineligible patients (median OS of 15.9 months) [10]. Data also suggest that, with atezolizumab monotherapy, patients with high tumor PD-L1 expression may have higher ORR as well as longer OS compared with the overall population and those with low PD-L1 expression. In contrast to the IMvigor130 trial [42], the KEYNOTE-361 study of pembrolizumab plus platinum-based chemotherapy did not significantly improve PFS or OS versus chemotherapy alone [43].

The recently reported results from the JAVELIN Bladder 100 study [45] showed a median OS of 21.4 months with avelumab, which was assessed from the time chemotherapy was stopped and maintenance therapy was initiated. Thus, considering the 3.5 months when patients received induction platinum-based chemotherapy, the actual median OS may be closer to 25 months. Importantly, a significant improvement in OS was observed in a biomarker unselected population. However, median OS had not been reached in patients with high tumor PD-L1 expression, suggesting that PD-L1-positive patients may derive an even greater survival benefit. Although this is the first study to demonstrate a significant improvement in OS with an IO agent as a first-line therapy for advanced UC, a remaining unmet need is a non-chemotherapy option for cisplatin-eligible patients. The anti–PD-L1 agent, durvalumab, was approved for the second-line treatment of UC based on the results of a phase I/II study that showed increased antitumor activity in patients with tumors expressing high PD-L1 levels [61]. In an exploratory analysis of response and PD-L1 expression, a scoring algorithm was identified with a combined assessment of PD-L1 staining in TCs and ICs (PD-L1 defined as “high” for ≥ 25% staining in either TCs or ICs). The DANUBE trial, evaluating durvalumab with or without tremelimumab as a first-line treatment for advanced UC (ClinicalTrials.gov, NCT02516241) [62], did not meet either of its primary endpoints. Secondary and exploratory analyses of data from DANUBE and KEYNOTE-361 may provide insight into the efficacy of durvalumab, with and without tremelimumab, and pembrolizumab in untreated, metastatic UC.

Most of the trials included in this report did not specifically address the impact of treatment tolerability on HRQoL, an important outcome measure for both patients and physicians. Similar to the evidence for clinical efficacy and safety of chemotherapeutic regimens, the HRQoL studies support an unmet need for additional treatment options among patients with metastatic UC. Future studies are needed to provide additional HRQoL-related data on first-line treatments, particularly for IO agents. In designing future studies, we recommend that investigators select the instruments that will best elucidate the effects of tolerability, such as Functional Assessment of Cancer Therapy — Bladder Cancer, which was designed to evaluate patient-reported outcomes associated with bladder cancer therapy [63].

Some countries, such as Scotland, have indicated that additional cost and evidence of clinical efficacy are required to justify the cost of IO agents relative to their benefits [64]. The request for cost-benefit evidence, and the recent inclusion of these agents in ESMO and EAU treatment guidelines, highlight the need for additional evidence to support their use in patients with high PD-L1 tumor expression, particularly those who are ineligible for platinum-based therapy. IO agents have the potential to improve outcomes and HRQoL for patients with metastatic UC, particularly those with tumors that express PD-L1, but longer-term outcomes must support and validate the evidence reported thus far. In addition, there is a lack of consistency among IO clinical trials with regard to the assessment of PD-L1 expression, as there are different cutoffs, scoring algorithms, and companion assays used [65,66]. Therefore, explanation of benefits of one IO therapy compared to another using indirect comparisons becomes challenging as the PD-L1 algorithm acts as an effect modifier.

Limitations

One limitation of the SLRs is the availability of data specifically related to the first-line treatment of advanced UC. Many publications addressed subsequent treatment lines, did not specify treatment line, or grouped the results of first-line treatment with those of subsequent therapies. Among the trials identified in the SLRs, many were assessed to have moderate (n = 2), high (n = 7), or very high (n = 16) risk of bias. Only five RCTs were categorized as low risk. Lack of detail in the publications (eg, unclear randomization or statistical methods) was primarily responsible for these classifications, although open-label and crossover study designs also contributed.

As with any literature review, it is possible that some studies may not have been captured by the search terms, or that relevant studies may have been excluded if their abstracts did not clearly describe the patient population, methodology, and/or results. To minimize these possibilities, efforts were made to manually review bibliographies and use thorough search strings in multiple databases, and where necessary, the abstract lists of conferences were manually searched. Results were independently reviewed in duplicate or triplicate to avoid the omission

of any potentially relevant publications. For IO agents, different study designs, patient populations, and inconsistent outcomes across trials, along with variations in the assays, scoring algorithms, and cutoffs used to measure PD-L1, has rendered the interpretation of data a challenge at present [66].

Conclusions

Global guidelines for the first-line treatment of advanced UC continue to evolve with emerging data on IO agents. Clinical evidence indicates poor long-term outcomes and tolerability profiles with current standard of care options, emphasizing the need for new treatments that yield prolonged survival, with improved benefit-risk profiles. Our SLRs demonstrate a paucity of information related to HRQoL assessments of first-line treatments for advanced UC. Future studies are needed to fill these gaps, particularly given the recent approvals of IO agents for cisplatin-ineligible populations and the potential for newly approved therapies in cisplatin-eligible patients. In addition, cost-effectiveness analyses and assessments of HRQoL data will support the treatment decisions of physicians and patients and influence treatment guideline recommendations.

Funding

Funding for this work was provided by AstraZeneca.

CRediT authorship contribution statement

Maria Koufopoulou: Conceptualization, Data curation, Formal analysis, Methodology. **Paulo A.P. Miranda:** Writing - review & editing, Validation. **Paulina Kazmierska:** Formal analysis, Methodology. **Sohan Deshpande:** Data curation, Methodology, Formal analysis, Validation. **Priyanka Gaitonde:** Conceptualization, Supervision, Validation, Funding acquisition, Writing - review & editing. **:** .

Declaration of Competing Interest

PM and PG are employees of AstraZeneca, which funded this work. MK, PK, and SD are employees of Evidera.

Acknowledgements

Medical writing support, which was in accordance with Good Publication Practice guidelines, was provided by Ward A. Pedersen of Parexel and was funded by AstraZeneca. Editorial assistance was provided by Patricia Goodfriend of Parexel and was funded by AstraZeneca.

Appendix A

See Tables A1 and A2

Table A1
Search terms for the systematic literature review.[a]

Search Criteria	Search Terms
Clinical Outcomes	
Patient population	
1	'urinary bladder neoplasms'/exp OR 'urethral neoplasm':ab,ti
2	'carcinoma, transitional cell'/exp/mj OR cancer*:ab,ti OR carcinoma*:ab,ti OR adenoma*:ab,ti OR adenocarcinoma*:ab,ti OR squamous:ab,ti OR neoplasm*:ab,ti OR tumor*:ab,ti OR malignan*:ab,ti
3	Bladder:ab,ti OR urethra*:ab,ti OR ureter*:ab,ti OR urotheli*:ab,ti OR calice*:ab,ti
4	#2 AND #3
5	#1 OR #4
Treatment line	
6	'first line':ab,ti OR first-line:ab,ti OR 'front line':ab,ti OR front-line:ab,ti OR '1st line':ab,ti OR 1st-line:ab,ti OR 'induction therapy':ab,ti OR 'primary therapy':ab,ti OR 'primary treatment':ab,ti OR ((primary:ab,ti OR initial:ab,ti OR induction:ab,ti OR naïve:ab,ti) AND (therapy:ab,ti OR treatment:ab,ti)) OR (front:ab,ti AND line:ab,ti) OR (induction:ab,ti AND therapy:ab,ti) OR (first:ab,ti AND line:ab,ti) OR untreated:ab,ti OR un-treated:ab,ti OR 'treatment naïve':ab,ti OR treatment-naïve:ab,ti
7	Unresectable:ab,ti OR 'stage four':ab,ti OR 'stage 4':ab,ti OR 'stage IV':ab,ti OR 'stage iv':ab,ti OR 'late stage':ab,ti OR 'late-stage':ab,ti OR advance*:ab,ti OR inoperable:ab,ti OR metastasi*:ab,ti OR metastatic:ab,ti
8	#6 OR #7
Study design	
9	'clinical trial'/exp OR 'clinical trial' OR random* OR placebo:ab,ti OR 'clinical article'/de OR 'clinical trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'major clinical study'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de AND [article]/lim
10	[controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [article in press]/lim
11	#9 OR #10
Publication types	
12	Letter:it OR editorial:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR 'case report'/de OR 'retrospective study'/de
13	Review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison'))
14	#12 OR #13
Studies of interest	
15	(#5 AND #8 AND #11) NOT #14
Other limits	
16	#15 AND [humans]/lim AND ([adult]/lim OR [aged]/lim OR [very elderly]/lim)
17	#16 NOT ('animal experiment'/de OR 'cancer cell culture'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de OR 'nonhuman'/de)
18	#17 AND [english]/lim AND [abstracts]/lim AND [1990–2018]/py
19	#18 NOT ('surgery'/lnk OR 'radiotherapy'/lnk)
HRQoL/PROs/Utilities Outcomes	
Patient population	
1	'urinary bladder neoplasms'/exp OR 'urethral neoplasm':ab,ti

(*continued on next page*)

Table A1 (*continued*)

Search Criteria	Search Terms
2	'carcinoma, transitional cell'/exp/mj OR cancer*:ab,ti OR carcinoma*:ab,ti OR adenoma*:ab,ti OR adenocarcinoma*:ab,ti OR squamous:ab,ti OR neoplasm*:ab,ti OR tumor*:ab,ti OR malignan*:ab,ti
3	Bladder:ab,ti OR urethra*:ab,ti OR ureter*:ab,ti OR urotheli*:ab,ti OR calice*:ab,ti
4	#2 AND #3
5	#1 OR #4
Outcomes	
6	'eq-5d':ab,ti OR eq5d:ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti
7	utility:ab,ti OR utilities:ab,ti
8	sf16:ab,ti OR 'sf 16′:ab,ti OR 'short form 16′:ab,ti OR 'shortform 16′:ab,ti OR 'sf sixteen':ab,ti OR sfsixteen:ab,ti OR 'shortform sixteen':ab,ti OR 'short form sixteen':ab,ti OR sf12:ab,ti OR 'sf 12′:ab,ti OR 'short form 12′:ab,ti OR 'shortform 12′:ab,ti OR 'sf twelve':ab,ti OR sftwelve:ab,ti OR 'shortform twelve':ab,ti OR 'short form twelve':ab,ti OR sf36:ab,ti OR 'sf 36′:ab,ti OR 'short form 36′:ab,ti OR 'shortform 36′:ab,ti OR 'sf thirtysix':ab,ti OR 'sf thirty six':ab,ti OR 'shortform thirtysix':ab,ti OR 'shortform thirty six':ab,ti OR 'short form thirtysix':ab,ti OR 'short form thirty six':ab,ti OR fact:ab,ti OR 'functional assessment of cancer therapy':ab,ti OR eortc:ab,ti OR qlq:ab,ti OR utility:ab,ti OR utilities:ab,ti OR BCI:ab,ti OR 'bladder cancer index':ab,ti OR 'EORTC QLQ-BLM30′:ab,ti OR FACT-BI:ab,ti OR FACT-VCI:ab,ti
9	'patient reported':ab,ti OR 'patient-reported':ab,ti OR 'patients reported':ab,ti
10	'self report*':ab,ti OR 'functional status':ab,ti OR 'health status':ab,ti OR 'physical function':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti
11	disab*:ab,ti OR satisfa*:ab,ti
12	questionnaire:ab,ti OR satisfaction:ab,ti OR sexual:ab,ti OR sleep:ab,ti OR 'sickness impact profile':ab,ti
13	burden:ab,ti AND (patient:ab,ti OR carer:ab,ti OR caregiver:ab,ti)
14	'quality of life' OR 'health related quality of life':ab,ti OR hrqol:ab,ti OR hqol:ab,ti OR 'hr qol':ab,ti OR qol:ab,ti
15	'medical leave':ab,ti OR (work:ab,ti AND disability:ab,ti) OR absenteeism:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti
16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
Publication types	
17	Letter:it OR editorial:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR 'case report'/de
18	Review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison'))
19	#17 OR #18
Studies of interest	
20	#5 AND #16 NOT #19
Other limits	
21	#20 AND [humans]/lim AND ([adult]/lim OR [aged]/lim OR [very elderly]/lim)
22	#21 NOT ('animal experiment'/de OR 'cancer cell culture'/de OR 'human cell'/de OR 'human tissue'/de OR 'in vitro study'/de OR 'nonhuman'/de)
23	#22 AND [english]/lim AND [abstracts]/lim AND [1990–2016]/py
24	#23 NOT ('surgery'/lnk OR 'radiotherapy'/lnk)

[a] Search strategy for Embase (via Embase.com).

Table A2
Inclusion criteria for systematic literature reviews.

Inclusion Criteria			Exclusion Criteria
Domain	**First-line Clinical Outcomes**	**HRQoL/PROs/Utilities**	**All Searches**
Population	Adults with unresectable stage IV UC who received first-line chemotherapy		• Any population other than unresectable stage IV UC treated with first-line chemotherapy, including grouped outcomes for both first- and subsequent-line systemic treatments • Studies in which line of therapy was unclear
Intervention/ Comparators[a]	Chemotherapeutic/systemic agents (approved or under investigation) for the treatment of stage IV and locally advanced and/or metastatic (stage IV) UC as monotherapy or combination therapy		• Studies related to surgery, radiotherapy, radioimmunotherapy, "watch and wait"/no treatment, prophylactic or palliative care alone, or BCG vaccine • Intravesical or oral administration
Outcomes	Efficacy • OS, PFS • TTP, TTF • Duration of response • Disease control rate • Overall response • Progression Safety: Overall, severe, and grade 3–4 AEs	• HRQoL/PROs evaluated with disease-specific or generic questionnaires Symptoms Functional impairment, activity limitations • Utilities/disutilities • Caregiver burden	• In vitro, animal, fetal • Molecular, genetic • Pathology • Pharmacokinetics/pharmacodynamics
Study Designs	Phase II and III RCTs	• Phase II and III RCTs • Prospective interventional studies • Real-world observational studies	• Narrative or non-systematic reviews • Case studies/reports • Editorials • Study protocols
Time Period	• Literature databases (1990–2018*) • SLRs/*meta*-analyses (2014–2018)		Publication outside of the specified time windows
Country	None		None
Language	English		Non-English
Sample Size	> 25 patients	None	N/A

AE, adverse event; BCG, bacillus Calmette-Guérin; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RCT, randomized control trial; SLR, systematic literature review; TTF, time to treatment failure; TTP, time to progression; UC, urothelial carcinoma.

References

[1] Wong MCS, Fung FDH, Leung C, Cheung WWL, Goggins WB, Ng CF. The global epidemiology of bladder cancer: a joinpoint regression analysis of its incidence and mortality trends and projection. Sci Rep 2018;8:1129. https://doi.org/10.1038/s41598-018-19199-z.

[2] Lavaud P, Hamilou Z, Loriot Y, Massard C. Durvalumab in urothelial cancers. Expert Rev Anticancer Ther 2018;18:311–8.

[3] Bukhari N, Al-Shamsi HO, Azam F. Update on the treatment of metastatic urothelial carcinoma. ScientificWorldJournal 2018;2018:5682078. https://doi.org/10.1155/2018/5682078.

[4] James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477–88.

[5] Bellmunt J, Petrylak DP. New therapeutic challenges in advanced bladder cancer. Semin Oncol 2012;39:598–607.

[6] National Institutes of Health/National Cancer Institute. Surveillance Epidemiology and End Results (SEER) program, Cancer Stat Facts: Bladder Cancer. 2018. https://seer.cancer.gov/statfacts/html/urinb.html [accessed November 11, 2019].

[7] Bellmunt J. Treatment of metastatic urothelial cancer of the bladder and urinary tract. 2019. https://www.uptodate.com/contents/treatment-of-metastatic-urothelial-cancer-of-the-bladder-and-urinary-tract. [accessed September 21, 2019].

[8] De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, 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 2012;30:191–9.

[9] Dogliotti L, Carteni G, Siena S, Bertetto O, Martoni A, Bono A, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol 2007;52:134–41.

[10] Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, 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.

[11] Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, 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.

[12] Ghate K, Amir E, Kuksis M, Hernandez-Barajas D, Rodriguez-Romo L, Booth CM, et al. PD-L1 expression and clinical outcomes in patients with advanced urothelial carcinoma treated with checkpoint inhibitors: a meta-analysis. Cancer Treat Rev 2019;76:51–6.

[13] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377–84.

[14] Alberta Health Services. Muscle invasive and locally advanced/metastatic bladder cancer clinical practice guideline GU-002 version 5. 2013. http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gu002-bladder.pdf. [accessed November 11, 2019].

[15] Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A, et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3). https://doi.org/10.1093/annonc/mdu223. iii40-8.

[16] European Association of Urology (EAU). Muscle-invasive and metastatic bladder cancer. Summary of changes. 2020. 2020. https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=summary-of-changes. [accessed June 15, 2020].

[17] Milowsky MI, Rumble RB, Booth CM, Gilligan T, Eapen LJ, Hauke RJ, et al. Guideline on muscle-invasive and metastatic bladder cancer (European Association of Urology guideline): American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 2016;34:1945–52.

[18] National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management, NICE guideline. 2015. https://www.nice.org.uk/guidance/ng2. [accessed November 11, 2019].

[19] Princess Margaret Cancer Centre. Princess Margaret Cancer Centre clinical practice guidelines. 2012. http://www.uhn.ca/PrincessMargaret/Health_Professionals/Programs_Departments/Genitourinary_GU/Documents/CPG_GU_Urothelial.pdf. [accessed November 11, 2019].

[20] European Society for Medical Oncology (ESMO). eUpdate - bladder cancer treatment recommendations 2019. https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer/eupdate-bladder-cancer-treatment-recommendations3. [accessed June 15, 2020].

[21] Flaig TW, Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, et al. Bladder Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020;18:329–54.

[22] Bamias A, Dafni U, Karadimou A, Timotheadou E, Aravantinos G, Psyrri A, et al. Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03). Ann Oncol 2013;24:1011–7.

[23] Haggag R, Farag K, Abu-Taleb F, Shamaa S, Zekri AR, Elbolkainy T, et al. Low-dose versus standard-dose gemcitabine infusion and cisplatin for patients with advanced bladder cancer: a randomized phase II trial-an update. Med Oncol 2014;31:811.

[24] Trump DL, Elson P, Madajewicz S, Dickman SH, Hahn RG, Harris JE, et al. Randomized phase II evaluation of carboplatin and CHIP in advanced transitional cell carcinoma of the urothelium. The Eastern Cooperative Oncology Group. J Urol 1990;144:1119–22.

[25] Culine S, Flechon A, Gravis G, Roubaud G, Loriot Y, Joly F, et al. Results of the GETUG-AFU 19 trial: a randomized phase II study of dose dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) with or without anti-epidermal growth factor receptor (EGF-R) monoclonal antibody panitumumab (PANI) in advanced transitional cell carcinoma (ATCC). J Clin Oncol 2017;35:307.

[26] von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, 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.

[27] von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, 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.

[28] Logothetis CJ, Dexeus FH, Finn L, Sella A, Amato RJ, Ayala AG, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990;8:1050–5.

[29] Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 1997;15:2564–9.

[30] Bellmunt J, Ribas A, Eres N, Albanell J, Almanza C, Bermejo B, et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer 1997;80:1966–72.

[31] Bamias A, Aravantinos G, Deliveliotis C, Bafaloukos D, Kalofonos C, Xiros N, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. J Clin Oncol 2004;22:220–8.

[32] Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, 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.

[33] Bellmunt J, von der Maase H, Mead GM, Skoneczna I, De Santis M, Daugaard G, 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.

[34] Lorusso V, Crucitta E, Silvestris N, Rosati G, Manzione L, De Lena M, et al. Randomised, open-label, phase II trial of paclitaxel, gemcitabine and cisplatin versus gemcitabine and cisplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium. Oncol Rep 2005;13:283–7.

[35] Miller K, Morant R, Stenzl A, Zuna I, Wirth M. A phase II study of the Central European Society of anticancer-drug research (CESAR) group: results of an open-label study of gemcitabine plus cisplatin with or without concomitant or sequential gefitinib in patients with advanced or metastatic transitional cell carcinoma of the urothelium. Urol Int 2016;96:5–13.

[36] Krege S, Rexer H, vom Dorp F, de Geeter P, Klotz T, Retz M, et al. Prospective randomized double-blind multicentre phase II study comparing gemcitabine and cisplatin plus sorafenib chemotherapy with gemcitabine and cisplatin plus placebo in locally advanced and/or metastasized urothelial cancer: SUSE (AUO-AB 31/05). BJU Int 2014;113:429–36.

[37] Oudard S, Culine S, Vano Y, Goldwasser F, Theodore C, Nguyen T, et al. Multicentre randomised phase II trial of gemcitabine + platinum, with or without trastuzumab, in advanced or metastatic urothelial carcinoma overexpressing Her2. Eur J Cancer 2015;51:45–54.

[38] Hussain M, Daignault S, Agarwal N, Grivas PD, Siefker-Radtke AO, Puzanov I, et al. A randomized phase 2 trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial carcinoma. Cancer 2014;120:2684–93.

[39] Balar AV, Dreicer R, Loriot Y, Perez-Gracia JL, Hoffman-Censits JH, Petrylak D, et al. Atezolizumab (atezo) in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial cancer (mUC): long-term efficacy from phase 2 study IMvigor210. J Clin Oncol 2018;36(suppl 15). abstract 4523.

[40] Vuky J, Balar AV, Castellano D, O'Donnell PH, Grivas P, Bellmunt J, et al. Updated efficacy and safety of KEYNOTE-052: a single-arm phase 2 study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol 2018;36(suppl 15). abstract 4524.

[41] Galsky MD, Wang H, Hahn NM, Twardowski P, Pal SK, Albany C, et al. Phase 2 trial of gemcitabine, cisplatin, plus ipilimumab in patients with metastatic urothelial cancer and impact of DNA damage response gene mutations on outcomes. Eur Urol 2018;73:751–9.

[42] Galsky MD, Arija JAA, Bamias A, Davis ID, De Santis M, Kikuchi E, 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.

[43] Merck/MSD. Merck provides update on phase 3 KEYNOTE-361 trial evaluating KEYTRUDA® (pembrolizumab) as monotherapy and in combination with chemotherapy in patients with advanced or metastatic urothelial carcinoma [press release]. 2020. https://investors.merck.com/news/press-release-details/2020/Merck-Provides-Update-on-Phase-3-KEYNOTE-361-Trial-Evaluating-KEYTRUDA-pembrolizumab-as-Monotherapy-and-in-Combination-with-Chemotherapy-in-Patients-with-Advanced-or-Metastatic-Urothelial-Carcinoma/default.aspx. accessed June 10, 2020.

[44] AstraZeneca. Update on phase III DANUBE trial for imfinzi and tremelimumab in unresectable, stage IV bladder cancer [press release] March 6, 2020. 2020. https://

www.astrazeneca.com/media-centre/press-releases/2020/update-on-phase-iii-danube-trial-for-imfinzi-and-tremelimumab-in-unresectable-stage-iv-bladder-cancer-06032020.html. accessed June 15, 2020.
[45] Powles T, Park SH, Voog E, Caserta C, B.P. V, Gurney H. Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis. J Clin Oncol 2020;38:Abst LBA1. DOI: 10.1200/JCO.2020.38.18_suppl.LBA1.
[46] Dreicer R, Manola J, Roth BJ, See WA, Kuross S, Edelman MJ, et al. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. Cancer 2004;100:1639–45.
[47] Siefker-Radtke AO, Millikan RE, Tu SM, Moore Jr. DF, Smith TL, Williams D, et al. Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. J Clin Oncol 2002;20:1361–7.
[48] Roychowdhury DF, Hayden A, Liepa AM. Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol 2003;21:673–8.
[49] Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. 3rd ed. York, UK: York Publishing Services, Ltd; 2008.
[50] De Santis M, Wiechno PJ, Bellmunt J, Lucas C, Su WC, Albiges L, 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.
[51] Culine S, Flechon A, Guillot A, Le Moulec S, Pouessel D, Rolland F, et al. Gemcitabine or gemcitabine plus oxaliplatin in the first-line treatment of patients with advanced transitional cell carcinoma of the urothelium unfit for cisplatin-based chemotherapy: a randomized phase 2 study of the French Genitourinary Tumor Group (GETUG V01). Eur Urol 2011;60:1251–7.
[52] Mead GM, Russell M, Clark P, Harland SJ, Harper PG, Cowan R, et al. A randomized trial comparing methotrexate and vinblastine (MV) with cisplatin, methotrexate and vinblastine (CMV) in advanced transitional cell carcinoma: results and a report on prognostic factors in a Medical Research Council study. MRC Advanced Bladder Cancer Working Party. Br J Cancer 1998;78:1067–75.
[53] Sternberg CN, Skoneczna IA, Castellano D, Theodore C, Blais N, Voog E, et al. Larotaxel with cisplatin in the first-line treatment of locally advanced/metastatic urothelial tract or bladder cancer: a randomized, active-controlled, phase III trial (CILAB). Oncology 2013;85:208–15.
[54] de Wit R, Tesselaar M, Kok TC, Seynaeve C, Rodenburg CJ, Verweij J, et al. Randomised phase II trial of carboplatin and iproplatin in advanced urothelial cancer. Eur J Cancer 1991;27:1383–5.
[55] Kuroda M, Kotake T, Akaza H, Hinotsu S, Kakizoe T. Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese Urothelial Cancer Research Group. Jpn J Clin Oncol 1998;28:497–501.
[56] Logothetis CJ, Finn LD, Smith T, Kilbourn RG, Ellerhorst JA, Zukiwski AA, et al. Escalated MVAC with or without recombinant human granulocyte-macrophage colony-stimulating factor for the initial treatment of advanced malignant urothelial tumors: results of a randomized trial. J Clin Oncol 1995;13:2272–7.
[57] McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Heineman M, Hirsch J, et al. Phase II randomized trial of gallium nitrate plus fluorouracil versus methotrexate, vinblastine, doxorubicin, and cisplatin in patients with advanced transitional-cell carcinoma. J Clin Oncol 1997;15:2449–55.
[58] Petrioli R, Frediani B, Manganelli A, Barbanti G, De Capua B, De Lauretis A, et al. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. Cancer 1996;77:344–51.
[59] Pizzocaro G, Milani A, Piva L, Faustini M, Spino E. Methotrexate, vinblastine, adriamycin and cisplatin versus methotrexate and cisplatin in advanced urothelial cancer. A randomized study. Eur Urol 1991;20:89–92.
[60] Yafi FA, North S, Kassouf W. First- and second-line therapy for metastatic urothelial carcinoma of the bladder. Curr Oncol 2011;18:e25–34.
[61] Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 2017;3:e172411.
[62] US National Library of Medicine, ClinicalTrials.gov. Study of MEDI4736 (durvalumab) with or without tremelimumab versus standard of care chemotherapy in urothelial cancer. 2015. https://clinicaltrials.gov/ct2/show/NCT02516241. [accessed January 8, 2020].
[63] Degboe A, Ivanescu C, Rohay JM, Turner RR, Cella D. Validity and performance of the Functional Assessment of Cancer Therapy-Bladder (FACT-Bl) among advanced urothelial cancer patients. Support Care Cancer 2019;27:4189–98.
[64] Scottish Medicines Consortium. Advising on new medicines for Scotland. 2019. http://www.scottishmedicines.org.uk/. [accessed November 11, 2019].
[65] Zajac M, Scott M, Ratcliffe M, Scorer P, Barker C, Al-Masri H, et al. Concordance among four commercially available, validated programmed cell death ligand-1 assays in urothelial carcinoma. Diagn Pathol 2019;14:99.
[66] Powles T, Walker J, Williams JA, Bellmunt J. The evolving role of PD-L1 testing in patients with metastatic urothelial carcinoma. Cancer Treat Rev 2020;82:101925https://doi.org/10.1016/j.ctrv.2019.101925.
[67] Bellmunt J, Eigl BJ, Senkus E, Loriot Y, Twardowski P, Castellano D, et al. Borealis-1: a randomized, first-line, placebo-controlled, phase II study evaluating apatorsen and chemotherapy for patients with advanced urothelial cancer. Ann Oncol 2017;28:2481–8.