EUROPEAN UROLOGY FOCUS 8 (2022) 1687–1695

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus

Review – Urothelial Cancer

Reassessment of the Efficacy of Carboplatin for Metastatic Urothelial Carcinoma in the Era of Immunotherapy: A Systematic Review and Meta-analysis

Keiichiro Mori [a,b], Victor M. Schuettfort [a,c], Takafumi Yanagisawa [a,b], Satoshi Katayama [a,d], Benjamin Pradere [a], Ekaterina Laukhtina [a,e], Pawel Rajwa [a,f], Hadi Mostafaei [a,g], Reza Sari Motlagh [a,h], Fahad Quhal [a,i], Marco Moschini [j], Francesco Soria [k], Jeremy Y.C. Teoh [l], David D'Andrea [a], Mohammad Abufaraj [a,m], Simone Albisinni [n], Wojciech Krajewski [o], Shin Egawa [b], Pierre I. Karakiewicz [p], Michael Rink [c], Shahrokh F. Shariat [a,e,q,r,s,t,u,], European Association of Urology–Young Academic Urologists Urothelial Carcinoma Working Group (EAU-YAU)*

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;* [b] *Department of Urology, The Jikei University School of Medicine, Tokyo, Japan;* [c] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [d] *Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan;* [e] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia;* [f] *Department of Urology, Medical University of Silesia, Zabrze, Poland;* [g] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran;* [h] *Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran;* [i] *Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia;* [j] *Klinik für Urologie, Luzerner Kantonsspital, Lucerne, Switzerland;* [k] *Division of Urology, Department of Surgical Sciences, University of Studies of Torino, Turin, Italy;* [l] *Department of Surgery, S.H. Ho Urology Centre, The Chinese University of Hong Kong, Hong Kong, China;* [m] *Research Division of Urology, Department of Special Surgery, The University of Jordan, Amman, Jordan;* [n] *Department of Urology, University Clinics of Brussels, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium;* [o] *Department of Department of Minimally Invasive and Robotic Urology, Wrocûçûçlaw Medical University, Wroclaw, Poland;* [p] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, Canada;* [q] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [r] *Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic;* [s] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [t] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria;* [u] *Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan*

Article info

Article history:
Accepted February 23, 2022
Available online 9 March 2022
Associate Editor: Christian Gratzke

Keywords:
Carboplatin
Cisplatin
Immune checkpoint inhibitors

Abstract

Context: Platinum-based combination chemotherapy is the standard treatment for advanced or metastatic urothelial carcinoma (AMUC). However, data comparing the efficacy of different platinum agents are limited.

Objective: This review aimed to assess the efficacy of carboplatin as a first-line treatment for AMUC using phase 3 randomized trial data.

Evidence acquisition: Multiple databases were searched for articles published until August 2021. Studies that compared overall survival (OS), complete response (CR), and objective response rates (ORRs) in chemotherapy-eligible patients with AMUC were deemed eligible.

Evidence synthesis: Four studies were included. Compared with immune checkpoint inhibitor (ICI) monotherapy, neither cisplatin- nor carboplatin-based chemotherapy was associated with significant OS (hazard ratio [HR]: 0.97, 95% confidence interval

* Corresponding author. Department of Urology, Medical University of Vienna, Währinger Gürtel 18-20, 1090, Vienna, Austria. Tel. +4314040026150; Fax: +4314040023320.
E-mail address: shahrokh.shariat@meduniwien.ac.at (S.F. Shariat).

https://doi.org/10.1016/j.euf.2022.02.007

Platinum-based chemotherapy
Urothelial carcinoma

[CI]: 0.85–1.11, $p = 0.64$ and HR: 0.90, 95% CI: 0.78–1.04, $p = 0.16$, respectively) and CR (odds ratio [OR]: 1.16, 95% CI: 0.70–1.92, $p = 0.57$ and OR: 0.89, 95% CI: 0.52–1.53, $p = 0.67$, respectively benefits, while both were associated with a favorable ORR (OR: 0.54, 95% CI: 0.40–0.74, $p < 0.001$ and OR: 0.58, 95% CI: 0.42–0.80, $p < 0.001$, respectively). A network meta-analysis (NMA)-based indirect comparison between carboplatin and cisplatin revealed that while cisplatin was slightly better than carboplatin in terms of OS, CR, and ORR, no significant difference was noted.

Conclusions: Cisplatin- and carboplatin-based chemotherapies offer similar OS/CR benefits to ICI monotherapy and elicit a greater ORR than ICI monotherapy. Moreover, our NMA demonstrated that both cisplatin- and carboplatin-based chemotherapy have a similar efficacy in terms of OS, CR, and ORR. Given that carboplatin-based chemotherapy is shown to be more effective in contemporary series than in historical controls, it is strongly recommended that carboplatin be re-examined for its value in the era of ICIs and beyond.

Patient summary: Cisplatin- as well as carboplatin-based chemotherapy is as effective as immune checkpoint inhibitors in terms of survival and eliciting a positive response. It is currently believed that cisplatin provides greater benefits than carboplatin; this requires re-evaluation.

1. Introduction

Survival outcomes for patients with advanced or metastatic urothelial carcinoma (AMUC) are extremely poor with the overall 5-yr survival rates of only approximately 5% [1,2]. Moreover, given that only approximately 50% of all AMUC patients receive any oncological treatment and only approximately 15–20% of all patients receive a second therapy line, the choice of an optimal first-line therapy is of utmost importance [3]. Platinum-based regimens are recommended as a first-line treatment for patients with previously untreated AMUC and deemed fit for chemotherapy [2]. Despite being the standard of care for decades, the available platinum agents remain insufficiently compared regarding their efficacy and safety.

The only phase 3 trial comparing cisplatin and carboplatin in the literature was unable to detect any significant difference in survival benefits; however, the study was underpowered, failing to reach its accrual goal [4]. To date, small, single-center, phase 2 studies have demonstrated the superiority of cisplatin over carboplatin [5–8]. Contrarily, a phase 2 trial by Dogliotti et al [9] comparing the efficacy of gemcitabine/cisplatin with that of gemcitabine/carboplatin in AMUC reported no clinically significant difference in objective response rates (ORRs; 65.9% and 56.4%, respectively), median survival (12.8 and 9.8 mo, respectively), and/or time to disease progression (8.3 and 7.7 months, respectively), despite not being designed with sufficient power to detect significant differences between the study arms in terms of efficacy. Therefore, a thorough assessment of carboplatin versus cisplatin with respect to efficacy appears to be necessary, particularly given that approximately one-third of all patients deemed eligible for cisplatin actually receive carboplatin [10].

Recently, the DANUBE, IMvigor 130, and KEYNOTE 361 trials investigated the efficacy of immune checkpoint inhibitors (ICIs) and/or chemotherapy in the first-line setting for AMUC [10–12]. Interestingly, data from all three studies suggest that carboplatin might not be inferior to cisplatin and that carboplatin-based chemotherapy is more effective in contemporary series than in historic series [10–14]. In fact, based on the results from the Keynote-361 trial, the Food and Drug Administration has revised the indication for pembrolizumab, which was previously indicated as a treatment for all patients ineligible for cisplatin-containing chemotherapy [12]. Pembrolizumab is now only approved as a treatment of patients who are not eligible for any platinum-containing chemotherapy, thus emphasizing the importance of carboplatin in this treatment setting. Therefore, the aim of the current study was to re-evaluate the efficacy of carboplatin as a first-line treatment for AMUC using the recently reported data.

2. Evidence acquisition

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42021272996).

2.1. Search strategy

A systematic review, a meta-analysis (MA), and a network meta-analysis (NMA) were conducted on phase 3 randomized controlled trials (RCTs) in AMUC patients treated with first-line ICIs or chemotherapy according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [15]. A completed PRISMA 2009 checklist was used to describe the methodology of our study (c). PubMed, Web of Science, and Scopus were searched to identify reports published up to August 2021 that investigated first-line systemic therapy for AMUC. The following keywords were used in our search strategy: (urothelial carcinoma OR bladder cancer OR bladder carcinoma OR urothelial cancer) AND (metastatic OR advanced) AND (randomized). Furthermore, we reviewed relevant abstracts presented at major conferences, such as the American Society of Clinical Oncology and the European Society for Medical Oncology. The primary outcome of interest was overall survival (OS) and complete response (CR), and the secondary outcome was ORR. Initial screening was per-

formed independently by two investigators based on the titles and abstracts of the articles to identify ineligible reports. The reasons for exclusions were noted. Potentially relevant reports were subjected to full-text reviews, and the relevance of the reports was confirmed after the data extraction process. Disagreements were resolved via consensus with a separate committee of investigators.

2.2. Inclusion and exclusion criteria

Studies were included if they investigated AMUC patients (Patients) who had undergone carboplatin- or cisplatin-based chemotherapy (Intervention) compared with those treated with immunotherapy (Comparison) as a first-line treatment to assess their differential effects on OS, CR, and ORR (Outcome) in phase 3 randomized studies only. We also included RCTs comparing carboplatin- and cisplatin-based chemotherapies. We excluded observational studies, reviews, letters, editorials, replies from authors, case reports, and articles not published in English. Moreover, we excluded phase 2 trials. The references of all papers were scanned for additional studies of interest.

2.3. Data extraction

Two investigators independently extracted the following information from the included articles: study name, publication year, number of patients, treatment compound, age, sex, performance status (PS), primary tumor site, disease status, programmed death ligand-1 (PD-L1) status, cisplatin eligibility, subsequent therapy, oncological outcomes, and follow-up. Subsequently, the hazard ratios (HRs) and 95% confidence intervals (CIs) associated with OS were retrieved. All discrepancies regarding data extraction were resolved by consensus with the committee of investigators.

2.4. Risk of bias assessment

The "risk of bias" (RoB) evaluation of each study was performed using the Cochrane Collaboration's tool for assessing RoB [16]. This tool assesses selection (random sequence generation and allocation concealment), performance, detection, attrition, reporting, and other sources of bias (Supplementary Fig. 1). The RoB of each study was assessed independently by two authors. Disagreements were resolved by consultation with the coauthors.

2.5. Statistical analyses

2.5.1. Meta-analysis

ORR was defined as the proportion of enrolled and randomly assigned patients who achieved the best response of CR or partial response based on investigator assessment. First, forest plots were used to assess the HRs and to describe the relationships between treatment and survival outcomes (ICI therapy vs carboplatin-based chemotherapy and ICI therapy vs cisplatin-based chemotherapy). Second, forest plots were used to summarize the variables for dichotomous outcomes and to describe the relationships between treatment and CR/ORR (ICI therapy vs carboplatin-based chemotherapy and ICI therapy vs cisplatin-based chemotherapy). Dichotomous variables were presented as proportions and compared using odds ratios (ORs) and 95% CIs. The outcomes of the studies included in this MA were evaluated for heterogeneity using Cochrane's Q test and I^2 statistics. Significant heterogeneity was indicated by $p \leq 0.05$ in Cochrane's Q tests and a ratio of $\geq$50% in I^2 statistics. We used fixed-effect models to calculate nonheterogeneous results. Random-effect models were used in cases of heterogeneity [17–19].

2.5.2. Network meta-analysis

An NMA was conducted with random- and fixed-effect models using a frequentist approach for the direct and indirect comparisons of the treatments evaluated, with immunotherapy as the common comparator arm (carboplatin- vs cisplatin-based chemotherapy) [20,21]. In OS assessment, contrast-based analyses were applied with estimated differences in the log HR and the standard error calculated from the published HR and CI [22]. The relative treatment effects were presented as HR and 95% credible interval (CrI) [20]. In the assessment of CR/ORRs, arm-based analyses were performed to estimate ORs and 95% CrIs from raw data presented in the selected manuscripts [20]. Network plots were utilized to illustrate the connectivity of the treatment networks in terms of OS/CR/ORR. All statistical analyses were performed using R 3.6.3 and Review manager 5.3; statistical significance was set at $p < 0.05$.

3. Evidence synthesis

3.1. Study selection and characteristics

Our initial search identified 2582 publications, and after the elimination of duplicates, a total of 1872 publications remained. A further 1840 articles were excluded after screening the titles and abstracts, and full-text reviews were performed for the remaining 32 articles (Supplementary Fig. 2). In accordance with the selection criteria, four articles comprising 3340 patients were identified for inclusion. Three studies, published between 2020 and 2021, comprised an assessment of first-line therapy and compared ICI therapy with chemotherapy (including carboplatin and cisplatin) [10–14]. The data extracted from these three studies are outlined in Table 1. In these three RCTs, a total of 2111 patients were treated with either ICI monotherapy (n = 1015; 48%) or chemotherapy alone (n = 1096; 52%); 56–57% of the patients in the DANUBE study, 30–37% in the IMvigor130 study, and 44–45% in the KEYNOTE361 study were cisplatin eligible. All patients were examined immunohistochemically for PD-L1 expression on tumor cells, tumor-infiltrating immune cells, or both. Of the patients with quantifiable PD-L1 expression, 60% in the DANUBE study, 24% in the IMvigor130 study, and 47% in the KEYNOTE361 study exhibited high PD-L1 expression. One last RCT chosen for inclusion was a direct comparison between CDDP- and CBDCA-based chemotherapies, where 85 patients were randomized to one or the other treatment regimen (41 to CBDCA-based chemotherapy and 44 to CDDP-based chemotherapy) [4].

3.2. Meta-analysis

3.2.1. ICI therapy versus cisplatin-based chemotherapy

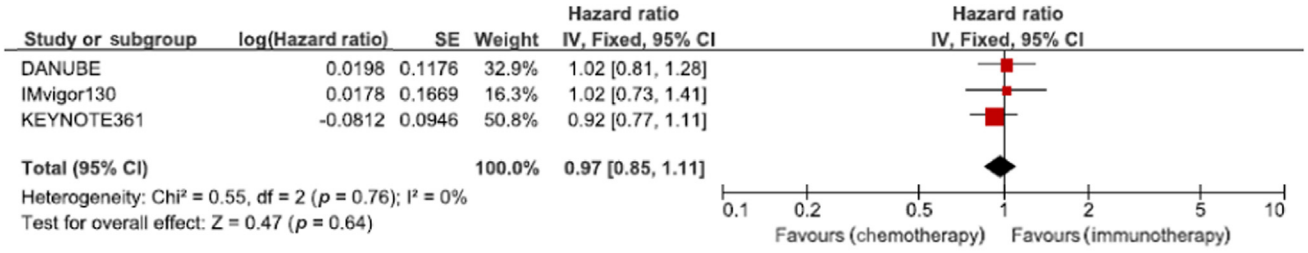
The forest plot in Figure 1A showed that cisplatin-based chemotherapy was not significantly different from ICI

Table 1 – Study demographics

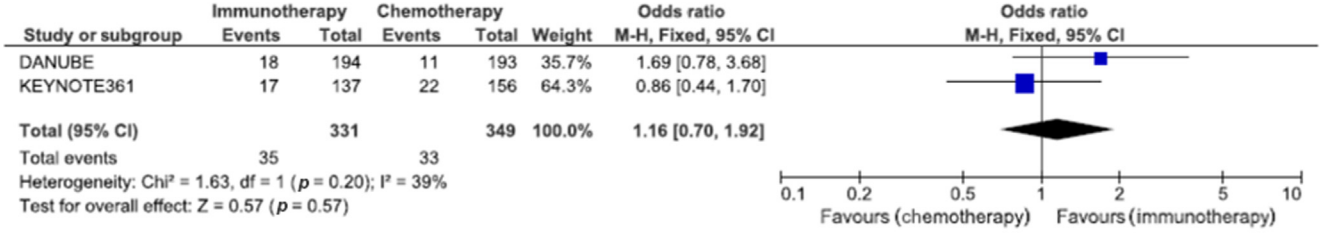
Study	IMvigor130			DANUBE			KEYNOTE361		
Year	2019			2020			2021		
Compound	Atezo Chemo	Atezo	Chemo	Durva Treme	Durva	Chemo	Pembro Chemo	Pembro	Chemo
Number	451	362	400	342	346	344	351	307	352
Age	69 (62–75)	67 (62–74)	67 (61–73)	68 (60–73)	67 (60–73)	68 (60–73)	69 (41–91)	68 (29–89)	69 (36–90)
Female (%)	25	23	26	25	28	20	23	26	26
ECOG PS 2 (%)	13	9	10	0	0	0	7	8	6
Primary tumor (lower tract), %	71	75	75	78	82	75	82	79	77
Disease status (metastatic), %	89	88	92	96	97	94	NR	NR	NR
Lymph node only (%)	18	19	17	21	18	22	23	21	27
Visceral meta (%)	57	56	60	78	82	77	74	78	72
High PD-L1 (%)	24	24	23	60	60	60	45	52	45
Cisplatin eligible	42	47	44	57	57	56	NR	NR	NR
Chemotherapy (cisplatin), %	30	37	34	NR	NR	52	46	45	46
Subsequent therapy (%)	26	40	41	45	47	54	35	41	61
Subsequent ICI therapy (%)	5	2	20	3	5	32	7	5	48
Follow-up (mo)	11.8			41.2			31.7		

Atezo = atezolizumab; Chemo = chemotherapy; Durva = durvalumab; ECOG = Eastern Cooperative Oncology Group; ICI = immune checkpoint inhibitor; NR = not reported; PD-L1 = programmed death ligand 1; Pembro = pembrolizumab; PS = performance status; Treme = tremelimumab.

A) Overall survival



B) Complete response



C) Objective response rate

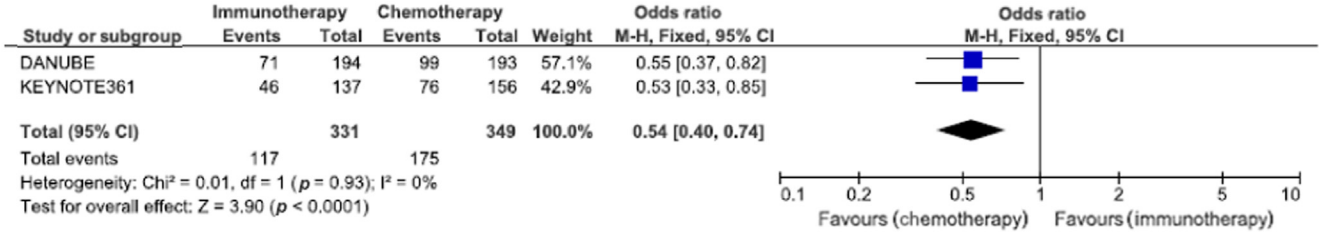


Fig. 1 – Forest plots showing the association between treatment and oncological outcomes in advanced or metastatic urothelial carcinoma (immune checkpoint inhibitor therapy vs cisplatin-based chemotherapy): (A) overall survival, (B) complete response rate, and (C) objective response rate. CI = confidence interval; df = degree of freedom; IV = inverse variance; M-H = Mantel-Haenszel; SE = standard error.

monotherapy in terms of OS benefits (pooled HR, 0.97; 95% CI, 0.85–1.11; $p = 0.64$). The Cochrane's Q test ($p = 0.76$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity. The forest plot in Figure 1B showed that cisplatin-based chemotherapy was not significantly different from ICI monotherapy in terms of CR benefits (pooled HR, 1.16; 95% CI, 0.70–1.92; $p = 0.57$). The Cochrane's Q test ($p = 0.20$) and I^2 test ($I^2 = 39\%$) revealed no significant heterogeneity. The forest plot in Figure 1C indicated that cisplatin-based chemotherapy was associated with a significantly better ORR than ICI monotherapy (pooled OR, 0.54; 95% CI, 0.40–0.74; $p < 0.001$). The Cochrane's Q test ($p = 0.93$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity.

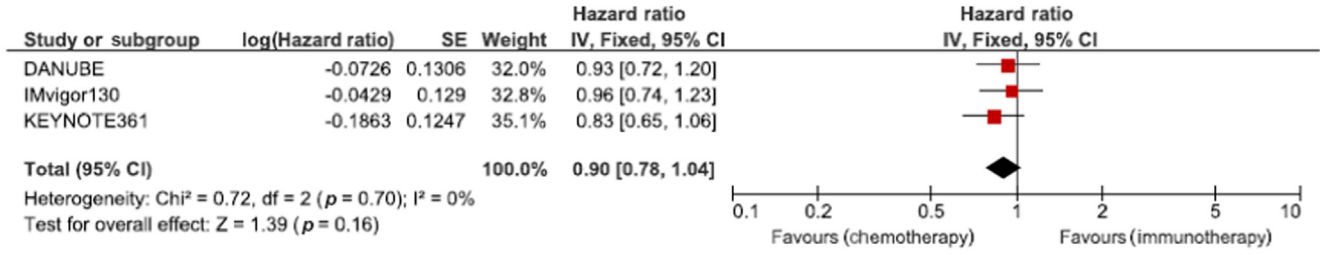
3.2.2. *ICI therapy versus carboplatin-based chemotherapy*

The forest plot in Figure 2A showed that carboplatin-based chemotherapy was not significantly different from ICI monotherapy in terms of OS benefits (pooled HR, 0.90; 95% CI, 0.78–1.04; $p = 0.16$). The Cochrane's Q test ($p = 0.70$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity. The forest plot in Figure 2B showed that cisplatin-based chemotherapy was not significantly different from ICI monotherapy in terms of CR benefits (pooled HR, 0.89; 95% CI, 0.52–1.53; $p = 0.67$). The Cochrane's Q test ($p = 0.84$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity. The forest plot in Figure 2C indicated that carboplatin-based chemotherapy was associated with a significantly better ORR than ICI monotherapy (pooled OR, 0.58; 95% CI, 0.42–0.80; $p < 0.001$). The Cochrane's Q test ($p = 0.55$) and I^2 test ($I^2 = 0\%$) revealed no significant heterogeneity.

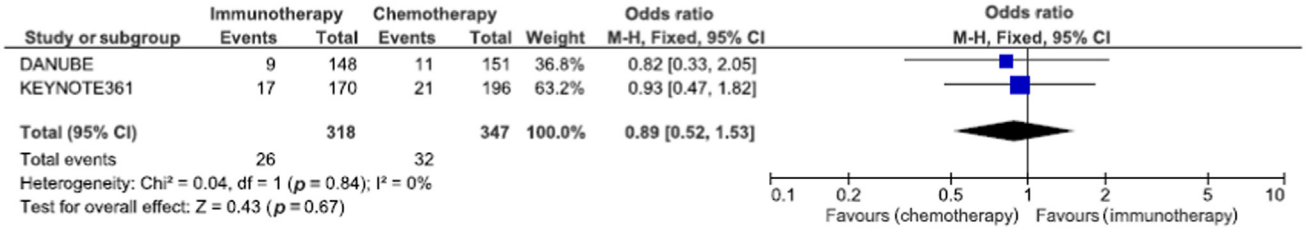
3.3. *Network meta-analysis*

An NMA of the three treatments was performed with regard to OS, CR, and ORR. The networks of eligible comparisons were graphically represented in network plots in terms of OS (Supplementary Fig. 3A) and CR/ORR (Supplementary Fig. 3B). We compared cisplatin- and carboplatin-based chemotherapies with ICI therapy as a common comparator arm. The analysis revealed that cisplatin-based chemotherapy did not differ significantly from carboplatin-based chemotherapy in terms of OS, CR, and ORR (pooled HR, 1.07; 95% CrI, 0.89–1.29; pooled OR, 0.99; 95%CrI, 0.41–

A) Overall survival



B) Complete response



C) Objective response rate

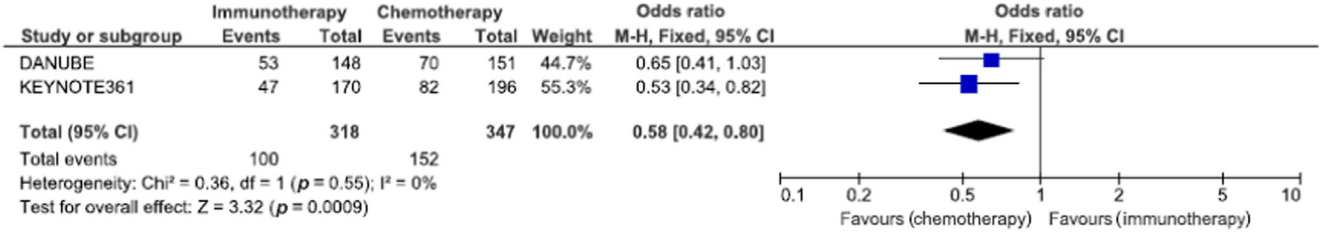


Fig. 2 – Forest plots showing the association between treatment and oncological outcomes in advanced or metastatic urothelial carcinoma (immune checkpoint inhibitor therapy versus carboplatin-based chemotherapy): (A) overall survival, (B) complete response rate, and (C) objective response rate. CI = confidence interval; df = degree of freedom; IV = inverse variance; M-H = Mantel-Haenszel; SE = standard error.

Table 2 – Pooled hazard ratio (HR) derived from network meta-analysis (the association of treatment with overall survival in metastatic urothelial carcinoma)

Carboplatin-based chemotherapy		
1.07 (0.89–1.29)	Cisplatin-based chemotherapy	
1.12 (0.98–1.27)	1.04 (0.91–1.18)	Immunotherapy

Pooled HR (95% credible interval) was derived from network meta-analysis.
Bold indicates statistically significant comparison.

Table 3 – Pooled odds ratio (OR) derived from network meta-analysis (the association of treatment with complete response rate in metastatic urothelial carcinoma)

Carboplatin-based chemotherapy		
0.99 (0.41–2.40)	Cisplatin-based chemotherapy	
0.97 (0.50–1.89)	0.98 (0.52–1.85)	Immunotherapy

Pooled OR (95% credible interval) was derived from network meta-analysis.
Bold indicates statistically significant comparison.

Table 4 – Pooled odds ratio (OR) derived from network meta-analysis (the association of treatment with objective response rate in metastatic urothelial carcinoma)

Carboplatin-based chemotherapy		
0.92 (0.61–1.37)	Cisplatin-based chemotherapy	
1.70 (1.26–2.31)	1.86 (1.39–2.50)	Immunotherapy

Pooled OR (95% credible interval) was derived from network meta-analysis.
Bold indicates statistically significant comparison.

2.40; and pooled OR, 0.92; 95%CrI, 0.61–1.37, respectively; Tables 2–4).

3.4. Discussion

We conducted a systematic review and MA to assess the efficacy of carboplatin and cisplatin as first-line therapies in patients with AMUC. We also performed an NMA to indirectly compare carboplatin and cisplatin; this approach revealed several findings of interest. First, both cisplatin- and carboplatin-based chemotherapy were similar to ICI monotherapy in terms of OS/CR benefits but superior to ICI monotherapy in terms of ORRs. Second, a comparison of ICI monotherapy versus cisplatin- and carboplatin-based chemotherapies showed that cisplatin was not significantly different from carboplatin, despite the latter being slightly inferior to cisplatin in terms of both OS (HR [0.97 vs 0.90]) and ORR (OR [0.54 vs 0.58]). Moreover, carboplatin-based chemotherapy was slightly superior to cisplatin in terms of CR. Furthermore, an NMA-based indirect comparison showed no significant difference between cisplatin and carboplatin.

Currently, platinum-based combination chemotherapy is the established standard of care for a first-line treatment for AMUC [2]. In patients with AMUC, guideline recommendations are tailored according to eligibility for cisplatin-based treatment [2]. Cisplatin-based chemotherapy is preferred for patients who have adequate renal function, good PS, and absence of comorbidities [2,23]. However, approximately 50% of patients are unfit to receive cisplatin-containing regimens, and treatment options for these patients include carboplatin-based regimens [2,24]. Of the standard regimens available, gemcitabine plus cisplatin have attained improved OS compared with gemcitabine plus carboplatin, although significant statistical differences were not recorded [9]. Moreover, patients unfit for cisplatin typically have prognostic factors such as poor PS that are associated with poor survival outcomes [2]. Thus, while several phase 2 trials of carboplatin versus cisplatin combination chemotherapy have shown a lower CR rate and shorter OS for the carboplatin arms, it remains unclear whether carboplatin-based chemotherapy may offer a prognosis comparable with that of cisplatin-based chemotherapy [25].

Carboplatin shares a common mechanism of action with cisplatin but exhibits different pharmacokinetics [26]. One mechanism of action common to all platinum agents is that following cellular uptake, these agents bind covalently to DNA nucleobases to form a variety of DNA adducts, and induce apoptosis through the inhibition of tumor cell apoptosis and other mechanisms [27]. However, cisplatin and carboplatin differ in terms of the extent of DNA adduct formation, which has been hypothesized to account for differences in their efficacy [27]. Further, cisplatin exhibits greater mutagenicity than carboplatin and is more likely to damage the DNA [28]. Carboplatin is less likely to cause renal damage due to its structural configuration; the structure is unlikely to form a substrate for organic cation transporter 2, the transporter involved in cisplatin uptake, thus making its uptake by proximal tubular cells unlikely [29]. ICIs have antitumor activity in urothelial carcinoma (UC) and a more favorable safety profile than chemotherapy; however, trials of first-line ICI monotherapy have not yet shown improved OS when compared with chemotherapy alone [30]. In our current MA, it was shown that cisplatin- and carboplatin-based chemotherapies elicit a greater ORR than and offer similar OS/CR benefits to ICI monotherapy. Switch-maintenance therapy could potentially serve as a novel treatment strategy intended to enhance antitumor activity in UC through the use of agents with different mechanisms of action [31]. Maintenance treatment can target tumor cell populations surviving after first-line chemotherapy, thus increasing the depth of responses and/or prolonging treatment effects, while avoiding cumulative toxicity, potential cross-resistance, and increased treatment cost [32]. It is well known that chemotherapy exerts not only direct cytotoxic effects on tumor cells, but also induces antitumor immune responses by promoting the release and presentation of tumor antigens, and by reducing immunoinhibitory cells [33]. Several chemotherapeutic agents and platinum-based combinations induce immunogenic cell death, stimulating immune responses against tumors through the release of signals from dying cells [34,35]. Additionally, chemotherapy may also upregulate the expression of PD-L1, a key immune checkpoint molecule [36–38]. The expression of damage-associated molecular patterns, including ATP and HMGB1, using non–

small cell lung cancer (NSCLC) cells, has been recorded with cisplatin and carboplatin to a certain extent [39,40]. Furthermore, it has been suggested that both cisplatin and carboplatin have a role in promoting antitumor immune responses by reducing the number of myeloid-derived suppressor cells [41,42]. Of particular note, it is also suggested that cisplatin not only enhances T-cell activity, but also induces tumor cell PD-L1 upregulation, thus possibly accounting in part for the additive antitumor activity between cisplatin-based chemotherapy and PD-L1/programmed death protein-1 (PD-1) inhibition [37,43–45]. Indeed, the expression of PD-L1 in NSCLC cells is shown to be upregulated following preoperative cisplatin-based chemotherapy in NSCLC patients (before vs after chemotherapy, 11% vs 26%; $p = 0.017$) [36]. Overall, there is a clear rationale for exploring ICIs as a first-line maintenance therapy for AMUC, given the immunogenic nature of UC, antitumor activity and favorable safety profile of ICIs, and cytotoxic and immunogenic effects of chemotherapy [31]. In the JAVELIN Bladder 100 phase 3 trial, avelumab as first-line maintenance therapy led to significant prolongation of OS, compared with the best supportive care (BSC), in patients with AMUC not experiencing disease progression on first-line platinum-containing chemotherapy [46]. While the trial design permitted the inclusion of patients who had received first-line combination chemotherapy with cisplatin plus gemcitabine or carboplatin plus gemcitabine [46], carboplatin-treated patients tended to be less fit than cisplatin-treated patients, as reflected by a higher proportion of Eastern Cooperative Oncology Group PS 1 (49% vs 32%), median age (71 vs 66 yr), and rate of renal impairment (63% vs 36%) [47]. The improvement in OS with avelumab versus BSC was similar irrespective of the first-line chemotherapy, with the HRs being 0.69 (95% CI, 0.51–0.94) and 0.66 (95% CI, 0.47–0.91) in the cisplatin plus gemcitabine and carboplatin plus gemcitabine subgroups, respectively, and the median postchemotherapy OS being 25.3 and 19.9 mo, respectively, with avelumab maintenance therapy [46,47]. Similarly, in our current MA/NMA, we found that while cisplatin was slightly more efficacious than carboplatin, the two agents were not significantly different in terms of efficacy. Further, the JAVELIN Bladder 100 phase 3 trial demonstrated that those achieving CR with first-line chemotherapy had an HR for OS of 0.81 (0.47–1.38) on avelumab and BSC, with their median OS remaining unreached and faring better than those achieving partial response with first-line chemotherapy [46]. Moreover, another study demonstrated that those achieving CR with preoperative chemotherapy had significantly prolonged cancer-specific and recurrence-free survival [48]. While these data point to the importance of achieving CR with chemotherapy, this study demonstrated no difference in CR rate with cisplatin-based versus carboplatin-based chemotherapy. However, it must be considered that while the DANUBE trial did not comprise patients with PS 2, the KEYNOTE361 and IMvigor130 trials included several patients with poor PS in their carboplatin arms [10–14]. Carboplatin was shown to be comparable with cisplatin with respect to efficacy in our study, and there is a possibility that the efficacy of carboplatin might have been underestimated owing to its use in patients with worse PS, which is known to be associated with worse survival; therefore, carboplatin needs to be reassessed for its efficacy in a similar patient cohort.

Despite being comprehensive in nature, this systematic review has some limitations. First, the patient characteristics differed at the time of study enrollment among the DANUBE, IMvigor130, and KEYNOTE361 trials, despite having similar study designs, treatment lines, and target diseases. Indeed, a much larger proportion (48%) of patients undergoing chemotherapy received subsequent ICI therapy in the KEYNOTE361 trial than in the other trials, likely contributing to the favorable OS outcomes in its chemotherapy arm as well as to the underestimation of the efficacy of pembrolizumab in patients receiving ICI therapy [12]. Moreover, it must be noted that, despite being uniformly categorized as immunotherapy, ICIs included both PD-1 and PD-L1 inhibitors, which differ in their mechanisms of action and possibly efficacy [49]. Second, while the NMA involved an indirect approach to compare outcomes from the RCTs, this approach falls short of a head-to-head comparison. Moreover, the only available phase 3 direct comparison between cisplatin and carboplatin was underpowered. Thus, the findings reported herein need to be validated in well-designed comparative trials. Third, given the lack of data for OS and ORR with cisplatin-based chemotherapy in the KEYNOTE361 trial, this MA evaluated the available data on all chemotherapeutic regimens from the RCTs, including carboplatin-based chemotherapy. Moreover, it must be noted that despite being categorized uniformly as cisplatin-based chemotherapy, this included both patients who were cisplatin eligible and those treated with cisplatin, which differed strictly. Fourth, while the method of Guyot et al [50] represents a better method for analysis of survival over time, it was not available for use in this study, given the paucity of survival curve data with cisplatin versus carboplatin from all the RCTs included. Finally, the OS data from the IMvigor130 trial remained immature at the time of this review, and the study outcomes might vary considerably in their final analyses. Furthermore, as the CheckMate 901 and NILE trials are still underway, the value of carboplatin-based chemotherapy in patients with AMUC could vary depending on the results of these trials.

4. Conclusions

Our analyses suggest that, in AMUC patients, there is no OS/CR difference between cisplatin- and carboplatin-based chemotherapy compared with ICI monotherapy; however, both chemotherapies offer a more favorable ORR than ICI monotherapy. Moreover, our MA/NMA reveals that there is no difference in OS, CR, and ORR between cisplatin- and carboplatin-based chemotherapy. This suggests a need for a reappraisal of the efficacy and role of carboplatin in the era of ICIs. Carboplatin-based chemotherapy seems to be more effective in contemporary series than in historical controls; moreover, it offers additive effects to ICI therapy, is associated with fewer adverse effects than cisplatin, and is preferentially used for patients with poor PS. These findings might be of value in determining personalized treatment strategies for AMUC patients.

***Author contributions*:** Keiichiro Mori had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mori, Schuettfort, Shariat.
Acquisition of data: Mori, Schuettfort, Yanagisawa, Katayama.
Analysis and interpretation of data: Mori, Schuettfort, Laukhtina, Mostafaei.
Drafting of the manuscript: Mori, Shariat.
Critical revision of the manuscript for important intellectual content: Schuettfort, Yanagisawa, Katayama, Pradere, Laukhtina, Rajwa, Mostafaei, Motlagh, Quhal, Moschini, Soria, Teoh, D'Andrea, Abufaraj, Albisinni, Krajewski, Egawa, Karakiewicz, Rink.
Statistical analysis: Mori, Schuettfort, Laukhtina, Mostafaei.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Rink, Shariat.
Other: None.

Financial disclosures: Keiichiro Mori certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** Victor M. Schuettfort, Ekaterina Laukhtina, and Pawel Rajwa are supported by the EUSP Scholarship of the European Association of Urology. Keiichiro Mori is supported by The Uehara Memorial Foundation.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.02.007.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.
[2] Witjes JA, Bruins HM, Cathomas R, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. Eur Urol 2021;79:82–104.
[3] Swami U, Grivas P, Pal SK, Agarwal N. Utilization of systemic therapy for treatment of advanced urothelial carcinoma: lessons from real world experience. Cancer Treat Res Commun 2021;27:100325.
[4] Dreicer R, Manola J, Roth BJ, 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.
[5] Robinson AG, Wei X, Vera-Badillo FE, Mackillop WJ, Booth CM. Palliative chemotherapy for bladder cancer: treatment delivery and outcomes in the general population. Clin Genitourin Cancer 2017;15:e535–41.
[6] Petrioli R, Frediani B, Manganelli 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.
[7] Bellmunt J, Ribas A, Eres N, et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer 1997;80:1966–72.
[8] Izumi K, Iwamoto H, Yaegashi H, et al. Gemcitabine plus cisplatin split versus gemcitabine plus carboplatin for advanced urothelial cancer with cisplatin-unfit renal function. In Vivo 2019;33:167–72.
[9] Dogliotti L, Cartenì G, Siena S, 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] Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1547–57.
[11] Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2020;21:1574–88.
[12] Powles T, Csőszi T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:931–45.
[13] Powles T. DANUBE post-hoc analysis: outcomes for durvalumab with or without tremelimumab by cisplatin eligibility and PD-L1 biomarker status in metastatic urothelial carcinoma. EAU Congress 2021.
[14] Powles T, Csőszi T, Ozguroglu M, et al. 1L pembrolizumab (pembro) versus chemotherapy (chemo) for choice-of-carboplatin patients with advanced urothelial carcinoma (UC) in KEYNOTE-361. J Clin Oncol 2021;39:450.
[15] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
[16] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[17] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemp Clin Trials 2007;28:105–14.
[18] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[19] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[20] van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth. Methods 2012;3:285–99.
[21] Dias S, Welton NJ, Sutton AJ, Ades AE. NICE decision support unit technical support documents. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. London, UK: National Institute for Health and Care Excellence (NICE); 2014. (Copyright © 2014 National Institute for Health and Clinical Excellence, unless otherwise stated. All rights reserved.)
[22] Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol 2010;10:54.
[23] De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30:191–9.
[24] Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432–8.
[25] Galsky MD, Chen GJ, Oh WK, et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. Ann Oncol 2012;23:406–10.
[26] Van Echo DA, Egorin MJ, Aisner J. The pharmacology of carboplatin. Semin Oncol 1989;16:1–6.
[27] Vermorken JB, ten Bokkel Huinink WW, Eisenhauer EA, et al. Carboplatin versus cisplatin. Ann Oncol 1993;4:S41–8.
[28] Szikriszt B, Póti Á, Németh E, Kanu N, Swanton C, Szüts D. Cisplatin is more mutagenic than carboplatin or oxaliplatin at equitoxic concentrations. bioRxiv 2020:2020.08.11.245969.
[29] Yonezawa A, Masuda S, Yokoo S, Katsura T, Inui K. Cisplatin and oxaliplatin, but not carboplatin and nedaplatin, are substrates for human organic cation transporters (SLC22A1-3 and multidrug and toxin extrusion family). J Pharmacol Exp Ther 2006;319:879–86.

[30] Mori K, Pradere B, Moschini M, et al. First-line immune-checkpoint inhibitor combination therapy for chemotherapy-eligible patients with metastatic urothelial carcinoma: a systematic review and meta-analysis. Eur J Cancer 2021;151:35–48.
[31] Grivas P, Agarwal N, Pal S, et al. Avelumab first-line maintenance in locally advanced or metastatic urothelial carcinoma: applying clinical trial findings to clinical practice. Cancer Treat Rev 2021;97:102187.
[32] Grivas P, Monk BJ, Petrylak D, et al. Immune checkpoint inhibitors as switch or continuation maintenance therapy in solid tumors: rationale and current state. Target Oncol 2019;14:505–25.
[33] Ménard C, Martin F, Apetoh L, Bouyer F, Ghiringhelli F. Cancer chemotherapy: not only a direct cytotoxic effect, but also an adjuvant for antitumor immunity. Cancer Immunol Immunother 2008;57:1579–87.
[34] Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell 2015;28:690–714.
[35] de Biasi AR, Villena-Vargas J, Adusumilli PS. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. Clin Cancer Res 2014;20:5384–91.
[36] Fournel L, Wu Z, Stadler N, et al. Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer. Cancer Lett 2019;464:5–14.
[37] Tsai T-F, Lin J-F, Lin Y-C, et al. Cisplatin contributes to programmed death-ligand 1 expression in bladder cancer through ERK1/2-AP-1 signaling pathway. Biosci Rep 2019, 39:BSR20190362.
[38] Mori K, Abufaraj M, Mostafaei H, et al. The predictive value of programmed death ligand 1 in patients with metastatic renal cell carcinoma treated with immune-checkpoint inhibitors: a systematic review and meta-analysis. Eur Urol 2021;79:783–92.
[39] Fumet JD, Limagne E, Thibaudin M, Ghiringhelli F. Immunogenic cell death and elimination of immunosuppressive cells: a double-edged sword of chemotherapy. Cancers (Basel) 2020;12:2637.
[40] Flieswasser T, Van Loenhout J, Freire Boullosa L, et al. Clinically relevant chemotherapeutics have the ability to induce immunogenic cell death in non-small cell lung cancer. Cells 2020;9:1474.
[41] Wu K, Tan MY, Jiang JT, et al. Cisplatin inhibits the progression of bladder cancer by selectively depleting G-MDSCs: a novel chemoimmunomodulating strategy. Clin Immunol 2018;193:60–9.
[42] Yang G, Shen W, Zhang Y, et al. Accumulation of myeloid-derived suppressor cells (MDSCs) induced by low levels of IL-6 correlates with poor prognosis in bladder cancer. Oncotarget 2017;8:38378–88.
[43] Osa A, Uenami T, Koyama S, et al. Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients. JCI Insight 2018;3:e59125.
[44] Osa A, Uenami T, Naito Y, et al. Monitoring antibody binding to T cells in a pembrolizumab-treated patient with lung adenocarcinoma on hemodialysis. Thorac Cancer 2019;10:2183–7.
[45] Tran L, Allen CT, Xiao R, et al. Cisplatin alters antitumor immunity and synergizes with PD-1/PD-L1 inhibition in head and neck squamous cell carcinoma. Cancer Immunol Res 2017;5:1141–51.
[46] Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020;383:1218–30.
[47] Grivas P, Park SH, Voog E, et al. 704MO Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone with 1L chemotherapy (CTx) for advanced urothelial carcinoma (UC): subgroup analyses from JAVELIN Bladder 100. Ann Oncol 2020;31:S555–6.
[48] Ho PL, Willis DL, Patil J, et al. Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: the M.D. Anderson Cancer Center experience. Urol Oncol 2016;34(59):e1–8.
[49] Mori K, Pradere B, Quhal F, et al. Differences in oncological and toxicity outcomes between programmed cell death-1 and programmed cell death ligand-1 inhibitors in metastatic renal cell carcinoma: a systematic review and meta-analysis. Cancer Treat Rev 2021;99:102242.
[50] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.