available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com



European Association of Urology

Effect of Sex on the Oncological Outcomes in Response to Immunotherapy and Antibody-drug Conjugates in Patients with Urothelial and Kidney Cancer: A Systematic Review and a Network Meta-analysis

Clara Cerrato [a], *Fabio Crocerossa* [b], *Michele Marchioni* [c], *Gianluca Giannarini* [d], *Shilpa Gupta* [e], *Laurence Albiges* [f], *Oscar Brouwer* [g], *Maarten Albersen* [h], *Christian Fankhauser* [i,j,k], *Marc Oliver Grimm* [l], *Giorgio Gandaglia* [m], *Morgan Roupret* [n], *Maria Carmen Mir* [o,*], *on behalf of the ESOU Board*

[a] *University Hospital Southampton NHS Trust, Southampton, UK;* [b] *Department of Urology, Magna Graecia University of Catanzaro, Catanzaro, Italy;* [c] *Department of Urology, Universita "G. D'annunzio", Chieti, Italy;* [d] *Urology Unit, "Santa Maria della Misericordia" University Hospital, Udine, Italy;* [e] *Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA;* [f] *Department of Cancer Medicine, Gustave Roussy, Université Paris-Saclay, Villejuif, France;* [g] *The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands;* [h] *Department of Urology, University Hospitals Leuven, Leuven, Belgium;* [i] *Department of Urology, Luzerner Kantonsspital, Luzern, Switzerland;* [j] *University of Lucerne, Lucerne, Switzerland;* [k] *University of Zurich, Zurich, Switzerland;* [l] *Jena University Hospital, Jena, Germany;* [m] *Department of Urology, Division of Experimental Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [n] *GRC 5 Predictive Onco-Uro, Department of Urology, AP-HP, Pitié Salpétrière Hospital, Sorbonne University, Paris, France;* [o] *Department of Urology, Hospital Universitario La Ribera, Valencia, Spain*

Article info

Article history:
Received 28 January 2024
Received in Revised form
3 March 2024
Accepted 26 March 2024
Available online 21 April 2024

Associate Editor: Morgan Rouprêt

Keywords:
Immune checkpoint inhibitors
Antibody-drug conjugates
Renal cell carcinoma
Transitional cell carcinoma
Sex

Abstract

Background and objective: Immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs) herald a transformative era in metastatic renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) treatment, amid acknowledged sex-based disparities in these cancers. We conducted a systematic review and network meta-analysis (NMA) to identify sex-specific differences in the efficacy of ICI/ADC monotherapy or combination therapies for RCC and TCC survival, in metastatic and adjuvant settings.

Methods: A systematic search was conducted up to October 2023 for English articles on ICIs and ADCs as systemic therapies (ICIs in first-line and adjuvant treatment for RCC, ICIs and ADCs in first- and second-line treatment for TCC). Randomised clinical trials were considered. The primary objective was overall survival (OS) of ICIs and ADCs between males and females. The secondary outcomes included progression-free survival, overall response rate, disease-free survival, and recurrence-free survival. Treatment efficacy was evaluated by sex via odds ratios (ORs) and confidence intervals compared with controls. Log ORs were used for creating a frequentist NMA. This meta-analysis was registered on PROSPERO (CRD42023468632).

Key findings and limitations: Eighteen articles met the inclusion criteria. Females had an advantage for RCC-adjuvant treatment for atezolizumab (log OR [SE] = –0.57 ± 0.25, $p = 0.024$) in OS. Males showed a survival advantage in TCC second-line treatment for ADC-Nectin 4 (log OR [SE] = 0.65 ± 0.28, $p = 0.02$). No other significant results were shown.

* Corresponding author. Department of Urology, Hospital Universitario La Ribera, km 1, Ctra. Corbera, 46600 Alzira, Valencia, Spain. Tel. +34 664 454 416; Fax: +34 664 454 416.
E-mail address: mirmare@yahoo.es (M.C. Mir).

https://doi.org/10.1016/j.euo.2024.03.014
2588-9311/© 2024 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Conclusions and clinical implications: The NMA revealed gender-specific variations in ICI and ADC responses for RCC and TCC, offering insights for personalised cancer care and addressing disparities in cancer care and outcomes.
Patient summary: In this systematic review, we looked at the sex differences for metastatic renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) for antibody-drug conjugates and immune checkpoint inhibitors. In our analysis, female and male sex has better overall survival for adjuvant and second-line therapies for RCC and TCC, respectively. Urgent research on gender-specific cancer therapies is imperative.
© 2024 European Association of Urology. Published by Elsevier B.V. All rights reserved.

1. Introduction

Sex discrepancies exist in kidney and urothelial cancers [1]. While urothelial cancers tend to affect men up to four times more frequently, women commonly exhibit more aggressive tumour characterised by unfavourable histology and higher stages upon presentation [1,2]. Conversely, in the case of renal cell carcinoma (RCC), men are usually affected more often and present with higher tumour stage and grade [3]. Indeed, previous in vitro and in vivo studies have demonstrated that sex-related molecular and genetic changes are real game changers in the context of urothelial cancer, thus explaining the different treatment response and cancer-specific mortality rates between women and men even after adjusting for tumour stage [4,5]. The advent of the immune checkpoint inhibitors (ICIs) and antibody-drug conjugate (ADC) has changed the treatment landscape of metastatic urothelial cancers dramatically, marking a pioneering stride in the realm of personalised medicine in transporting chemotherapy drugs to a particular target, exhibiting enhanced therapeutic effectiveness while minimising toxicity [6–9]. European Association of Urology (EAU) guidelines recommend, as the standard of care for International Metastatic RCC Database Consortium favourable- and intermediate-, or poor-risk disease, a combination therapy with an immune-oncology drug (IO) and a tyrosine kinase inhibitor (TKI), according to the immune-enhancement effect, where TKI promotes T-cell infiltration in tumour cells and IO acts by priming, activating, and inducing T-cell–mediated tumour cell death [6,10]. UC guidelines instead recommend IO to selected patients as a first-line therapy or as a second-line treatment for those who progressed during or chemotherapy for metastatic disease; as per the EAU guidelines, IO therapy finds a weak recommendation in the context of adjuvant muscle-invasive bladder cancer (MIBC) because of conflicting results on its efficacy in this setting of patients [7].

Since compelling evidence demonstrated significant improvements in survival outcomes for ICIs and androgen deprivation therapies (ADTs) when compared with standard therapies, we conducted a systematic search of the literature and a network meta-analysis (NMA) to identify the sex-specific differences in the effectiveness of ICI/ADT monotherapy or ICI/ADT-based combination therapies concerning the survival outcomes of RCC and transitional cell carcinoma (TCC), in both the metastatic and the adjuvant setting.

2. Methods

2.1. Search strategy and selection criteria

This study was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42023468632 (https://www.crd.york.ac.uk/PROSPERO/). A systematic search was conducted on PubMed, Cochrane Library, and Web of Science databases up to October 2023. The search terms used included "urothelial carcinoma", "bladder cancer", "UTUC", "kidney cancer", "renal cell carcinoma", "immunotherapy", "immune checkpoint inhibitor", "ICI", "IO", "nivolumab", "ipilimumab", "pembrolizumab", "atezolizumab", "avelumab", "tremelimumab", "durvalumab", "cetrelimab", "antibody-drug conjugate", "ADC", "enfortumab vedotin", "sacituzumab govitecan", "sirtratumab vedotin", "disitamab vedotin", "gender", and "sex". Boolean operators (AND, OR) were used to refine the search. The punctual search of strategy is available in the Supplementary material. A manual review of the reference lists from published systematic reviews was undertaken to prevent overlooking potentially eligible studies. Collaborative efforts were employed between two researchers (C.C. and F.C.) for the literature search, with discrepancies resolved through consultation with a third researcher (M.C.M.).

The inclusion criteria encompassed the following PICOS criteria: (1) population: male and female patients with RCC or TCC treated with ICIs or ADTs; (2) interventions: randomised clinical trials on IO therapies and ADCs for both kidney and urothelial cancers, with data available on sex differences; (3) comparator: patients treated with another systemic therapy (chemotherapy or TKI) or treated with placebo; (4) outcome indicators: primary outcome of overall survival (OS) or disease-free survival (DFS), and secondary outcomes of other survival outcome such as progression-free survival (PFS), overall response rate (ORR), and recurrence-free survival (RFS); and (5) study type: randomised controlled clinical trial. The exclusion criteria comprised (1) animal or cell experiments, case reports, scientific experiment plans, reviews, letters, editorials, and conference papers; (2) literature lacking study data or peer review; and (3) non–English-language papers.

2.2. Data extraction

The initial screening of the titles and abstracts was conducted independently by two investigators (C.C. and F.C.), followed by a second screening of full texts. Disagreements

were resolved through consultation with a third investigator (M.C.M.). Data extraction from the final included studies was carried out independently by two investigators, encompassing information such as the first author, year of publication, country, details on randomisation and blinding, descriptions of intervention and control, as well as details on the number of event/number of patients and significance for OS, DFS, PFS, ORR, and hazard ratios. All the outcomes have been stratified according to sex.

2.3. Statistical analysis

The primary objective was to assess the differences in the treatment efficacy of ICIs and ADCs between males and

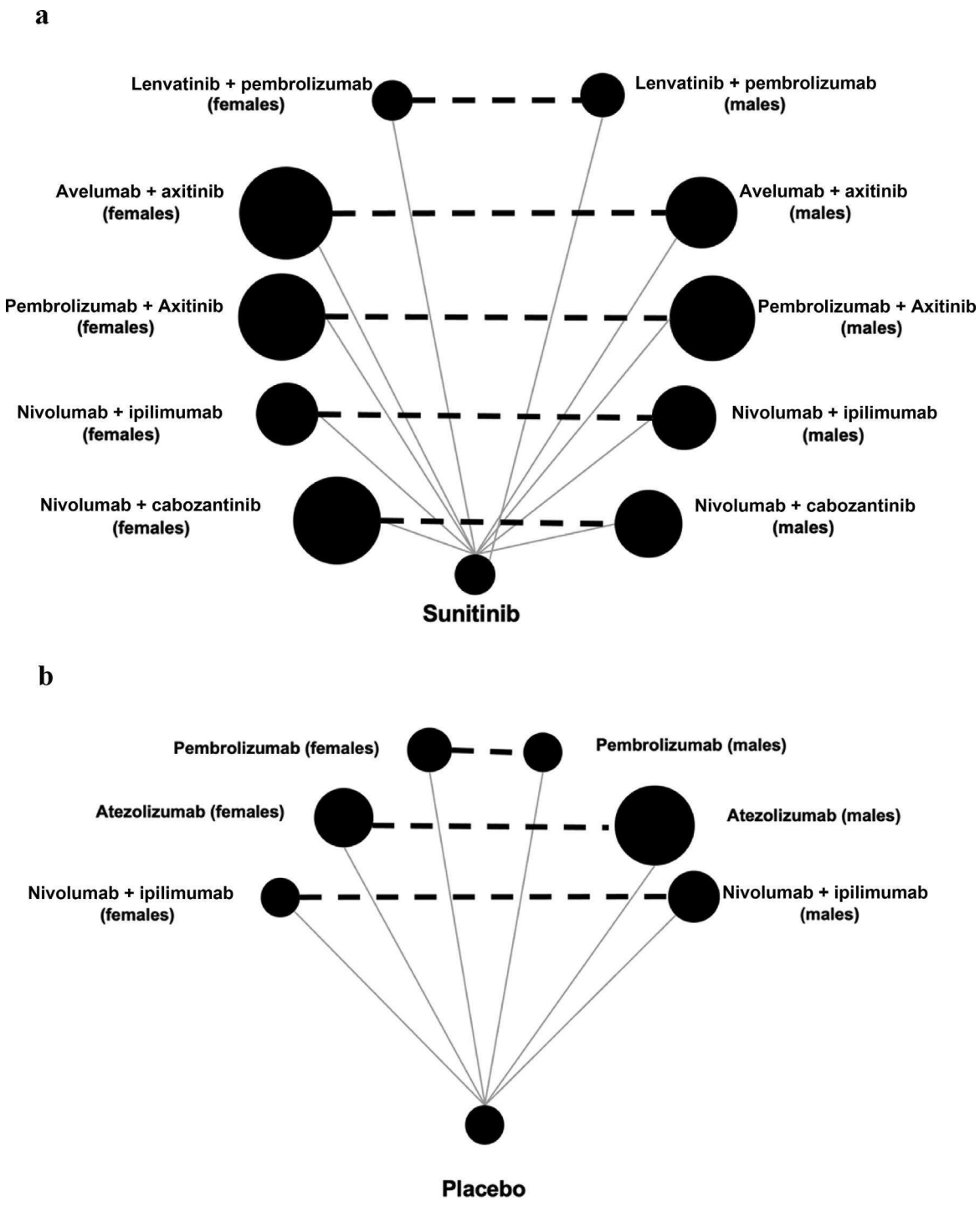


Fig. 1 – Network plots depicting the comparisons that used the same control arm. In the figures, the diameter of the circle is proportional to the number of participants who received the intervention. (A) OS for first-line treatment of RCC. (B) DFS for adjuvant treatment of RCC. (C) OS for first-line treatment of TCC. (D) OS for second-line treatment of TCC. CHT = chemotherapy; DFS = disease-free survival; Gem/Cis = gemcitabine/cisplatin; OS = overall survival; RCC = renal cell carcinoma; TCC = transitional cell carcinoma.

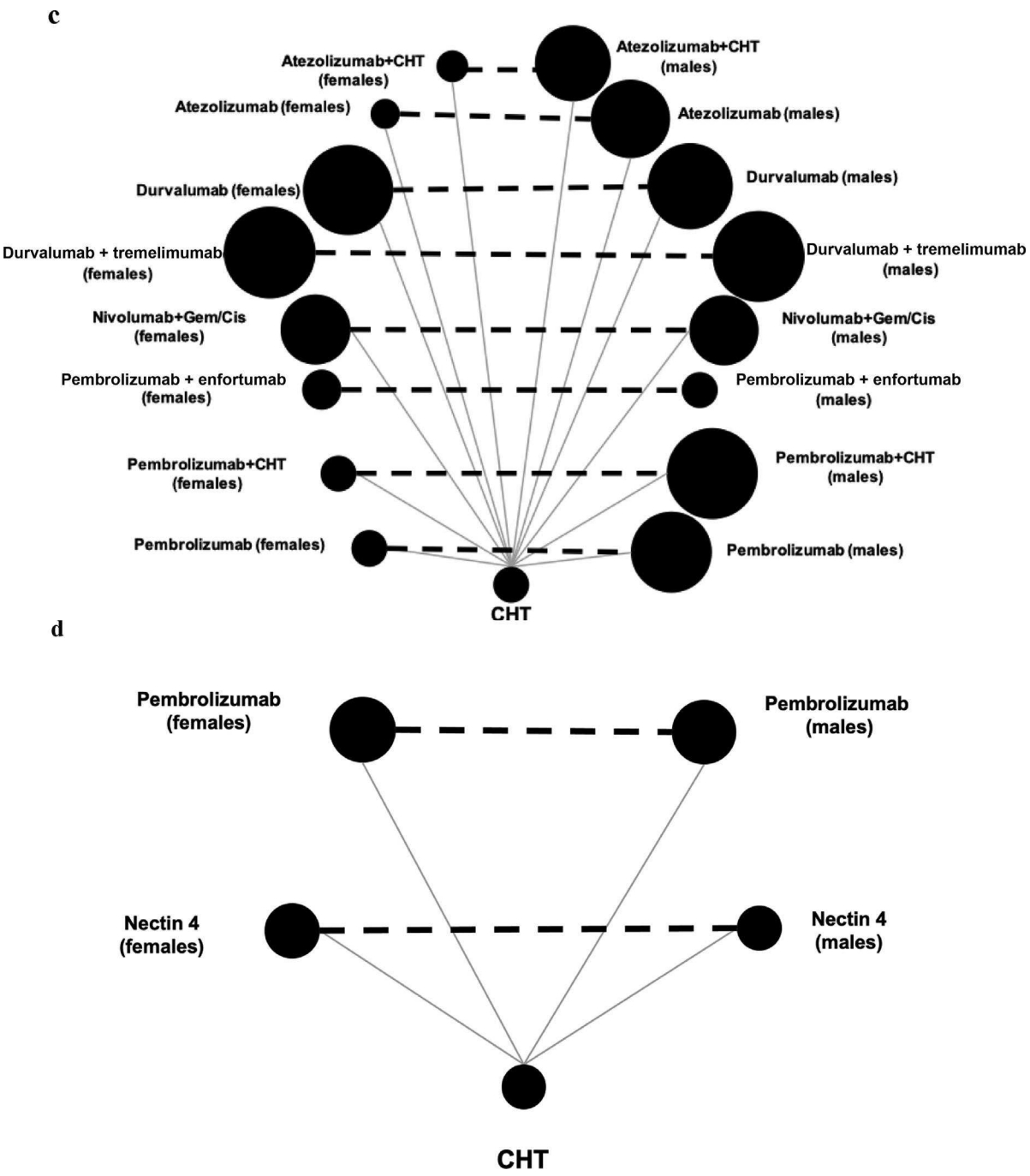


Fig. 1 (*continued*)

females in terms of OS or DFS. An analysis of the secondary outcomes PFS and ORR was conducted when available or in the absence of OS data. In the case of adjuvant treatments for RCC, DFS and RFS were considered to represent the same outcome, albeit used interchangeably across the original studies.

The considered treatment regimens included the following: ICIs in first-line treatment for RCC, ICIs in adjuvant treatment for RCC, ICIs and ADCs in first-line treatment for TCC, and ICIs and ADCs in second-line treatment for TCC. Although both adjuvant therapies for RCC and MIBC present conflicting results regarding their efficacy [6,7], we focused on adjuvant therapy for RCC rather than MIBC based on the emerging evidence suggesting a tangible benefit in OS rather than solely in DFS with adjuvant therapy for RCC [11].

For each treatment regimen, treatment efficacy was assessed separately for males and females using the odds ratio (ORs) and confidence intervals relative to the corresponding control arm. The log transformation of the ORs along with their respective standard errors (SEs) was employed to preserve the assumption of normality. Log ORs were then used as parameters for creating a frequentist NMA conceived as a system of three interconnected nodes, each representing a different sex and the control arm.

Specifically, the three nodes included the male node, the female node, and the control node, while the connections between nodes were established through ORs relative to the control arm, thus allowing for an indirect comparison between treatment responses in males and females. A fixed-effect model was selected since the cohorts originated from the same study, maintaining identical protocols, follow-up strategies, doses, and durations. The inverse variance method was applied within the R environment by the netmeta package (version 2.8.2; R Foundation for Statistical Computing, Vienna, Austria). Transitivity was considered sound by default, as all effect modifiers present in the data and suspected to differ in distribution between males and females should have already been accounted for by the randomisation process. No homogeneity/consistency checks were conducted, as no study compared treatment efficacy between sexes directly.

The results of indirect treatment comparisons between nodes were presented in tabular form, reporting the log OR ± SE of the differences in treatment efficacy between sexes. The results of direct and indirect comparisons with other nodes (eg, among different treatments within the same sex) were not reported, as these were beyond the scope of the present study.

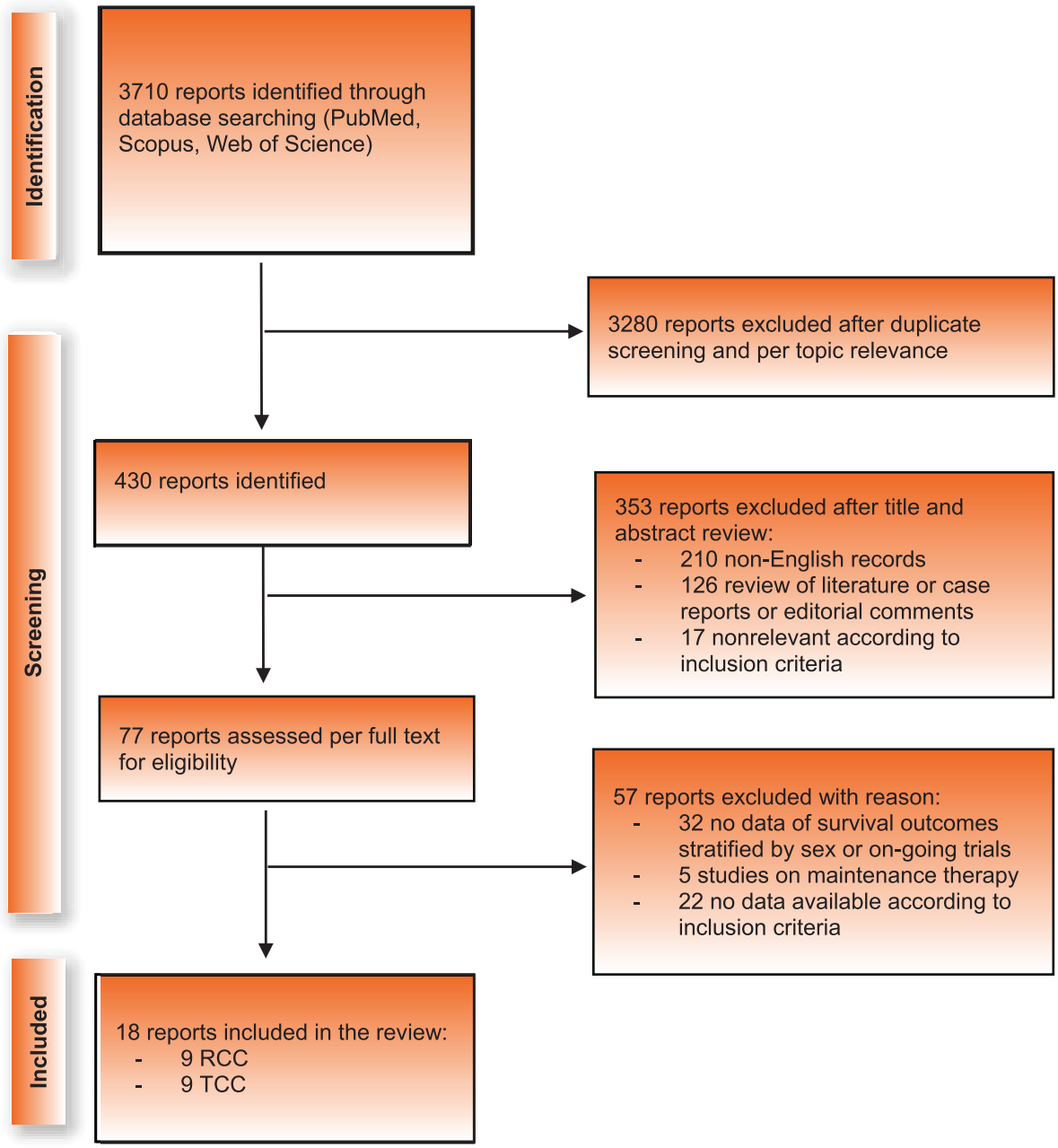


Fig. 2 – The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart for the inclusion of the studies in the systematic review. RCC = renal cell carcinoma; TCC = transitional cell carcinoma.

Table 1 – Essential characteristics of the included literature

Study	Year	Population	Treatment	Control	Outcome	Cases/overall	
						Males	Females
CLEAR Motzer et al [17]	2021	1st line M+ RCC	Lenvatinib + pembrolizumab	Sunitinib	OS PFS	59/255 125/255	21/100 40/100
Javelin Renal 101 Haanen et al [16]	2023	1st line M+ RCC	Avelumab + axitinib	Sunitinib	OS PFS	117/316 205/316	55/126 92/126
CLEAR – East Asian subset Rha et al [18]	2023	1st line M+ RCC	Lenvatinib + permbrolizumab	Sunitinib	PFS	24/54	9/21
CheckMate 214 Motzer et al [14]	2019	1st line M+ RCC	Nivolumab + ipilimumab	Sunitinib	OS	104/314	36/111
KEYNOTE-426 Plimack et al [15]	2023	1st line M+ RCC	Pembrolizumab + axitinib	Sunitinib	OS PFS	137/308 197/308	56/124 89/124
CheckMate 9ER Motzer et al [13]	2022	1st line M+ RCC	Nivolumab + cabozantinib	Sunitinib	OS PFS	104/314 160/249	36/111 47/74
KEYNOTE 564 Powles et al [20]	2022	Adjuvant RCC	Pembrolizumab	Placebo	DFS	76/347	38/149
IMmotion010 Pal et al [21]	2022	Adjuvant RCC	Atezolizumab	Placebo	DFS	129/287	35/103
CheckMate 914 Motzer et al [19]	2023	Adjuvant RCC	Nivolumab + ipilimumab	Placebo	DFS	84/286	26/119
IMvigor130 Galsky et al [22]	2020	1st line M+ TCC	1st arm: atezolizumab + CHT 2nd arm: atezolizumab	CHT	OS	337/451 271/360	114/451 89/360
DANUBE Powles et al [23]	2020	1st line M+ TCC	1st arm: durvalumab 2nd arm: durvalumab + tremelimumab	CHT	OS	112/153 190/256	39/56 65/86
KEYNOTE-361 Powles et al [24]	2021	1st line M+ TCC	1st arm: pembrolizumab + CHT 2nd arm: pembrolizumab	CHT	OS	191/272 80/122	54/79 25/38
EV 302 Powles et al [28]	2023	1st line M+ TCC	Pembrolizumab + enfortumab	CHT	OS	101/344	32/98
CheckMate 901 van der Heijden et al [25]	2023	1st line M+ TCC	Nivolumab + gemcitabine + cisplatin	CHT	OS PFS	133/236 163/236	39/68 48/68
KEYNOTE-052 Balar et al [29]	2023	1st line M+ TCC	Pembrolizumab	Placebo	ORR	83/286	24/48
EV 103 – Cohort K O'Donnell et al [26]	2023	1st line M+ TCC	Pembrolizumab + enfortumab	Enfortumab	ORR	36/54	13/22
EV 302 Hoimes et al [27]	2023	1st line M+ TCC	Pembrolizumab + enfortumab	–	ORR	27/36	06/09
KEYNOTE-045 Balar et al [29]	2023	2nd line M+ TCC	Pembrolizumab	CHT	OS	246/402	88/140
EV 103 Powles et al [30]	2021	2nd line M+ TCC	Nectin 4	CHT	OS	101/238	33/63

CHT = chemotherapy; DFS = disease-free survival; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma; TCC = transitional cell carcinoma.

Network plots were generated to depict the comparisons that used the same control arm (Fig. 1A–D). In the figures, the diameter of the circles is proportional to the number of participants who received the intervention.

All the analyses were performed using the R software environment for statistical computing and graphics (version 4.3.2; R Foundation for Statistical Computing, htttp://www.r-project.org/). The statistically significant level was set at $p < 0.05$.

2.4. Quality assessment

The evaluation of the risk of bias in the included studies was performed using the Cochrane Risk of Bias Assessment Tool (RoB2.0) [12]. The assessment covered six domains: inadequate randomisation process, deviation from defined interventions, missing outcome data, outcome measurement, selective reporting of outcomes, and other potential sources of bias. Two reviewers (C.C. and F.C.) independently assigned ratings of low risk, high risk, or some concerns to each domain. Any discrepancies were resolved through consultation with a third investigator (M.C.M.). The results of the quality assessment are shown in Supplementary Figure 1.

3. Results

3.1. Search results and study characteristics

The initial search identified 3710 articles. Following a preliminary review of titles and abstracts, 3633 studies were excluded. Subsequently, the full texts of the remaining studies were retrieved and examined to exclude the ineligible ones. Ultimately, 18 articles met the inclusion criteria. A detailed depiction of the screening process is illustrated in Figure 2.

The overall study population comprised 8496 patients: 2556 female and 5940 male patients, respectively. For kidney cancer, the intervention group utilised combined and single ICI treatment in, respectively, seven [13–19] and two studies [20,21]; for TCC, intervention groups utilised combined therapies with IO/chemotherapy/ADC in seven studies [22–28], and IO or ADC alone in five studies [22–24,29,30]. In the control group, participants received a placebo in four studies [19–21,29], chemotherapy in seven studies [22–25,28–30], sunitinib in six studies [13–18], and an ADC in two studies [26,27]. The essential characteristics of the included literature are summarised in Table 1.

3.2. Outcomes of the NMA

3.2.1. First-line treatment of RCC

Six studies reported OS data for six therapeutic lines (Supplementary Table 1) [13–18]. The results showed that the combinations lenvatinib + permbrolizumab (log OR [SE] = –0.26 ± 0.34, $p = 0.45$), pembrolizumab + axitinib (log OR [SE] = –0.29 ± 0.22, $p = 0.19$), and nivolumab + ipilimumab (log OR [SE] = –0.31 ± 0.25, $p = 0.21$) were marginally more effective in improving OS in women than in men, while the combinations avelumab + axitinib (log OR [SE] = 0.47 ± 0.29, $p = 0.10$) and nivolumab + cabozantinib (log OR [SE] = 0.17 ± 0.27, $p = 0.51$) were marginally more effective in improving OS in men; however, these differences did not reach statistical significance.

Five studies reported PFS data (Supplementary Table 2) [13,15–18]. There were no statistically significant differences in treatment efficacy between males and females for the combinations lenvatinib + pembrolizumab (log OR [SE] = 0.07 ± 0.24, $p = 0.76$), avelumab + axitinib (log OR [SE] = 0.3 ± 0.23, $p = 0.20$), pembrolizumab + axitinib (log OR [SE] = –0.11 ± 0.2, $p = 0.59$), and nivolumab + cabozantinib (log OR [SE] = 0.25 ± 0.23, $p = 0.26$).

3.2.2. Adjuvant treatment of RCC

Three studies were included (Supplementary Table 3) [19–21]. Pembrolizumab (log OR [SE] = 0.2 ± 0.26, $p = 0.5$), nivolumab + ipilimumab (log OR [SE] = –0.12 ± 0.31, $p = 0.7$), and everolimus (log OR [SE] = –0.02 ± 0.19, $p = 0.9$) outperformed placebo in improving DFS, with no statistically significant differences between sexes. The treatment efficacy of atezolizumab (log OR [SE] = –0.57 ± 0.25, $p = 0.024$) was in favour of female sex when compared with the male one.

3.2.3. First-line treatment of TCC

OS data were available for eight therapies in five studies (Supplementary Table 4) [22–25,28]. Atezolizumab alone (log OR [SE] = –0.38 ± 0.24, $p = 0.11$), durvalumab alone (log OR [SE] = –0.15 ± 0.27, $p = 0.57$), the combination of pembrolizumab + chemotherapy (log OR [SE] = –0.18 ± 0.21, $p = 0.39$), or pembrolizumab alone (log OR [SE] = –0.22 ± 0.32, $p = 0.49$) was slightly more effective in women. The combinations of atezolizumab + chemotherapy (log OR [SE] = 0.06 ± 0.15, $p = 0.70$), f durvalumab + tremelimumab (log OR [SE] = 0.07 ± 0.21, $p = 0.74$), pembrolizumab + enfortumab (log OR [SE] = 0.08 ± 0.27, $p = 0.76$), and nivolumab + gemcitabine + cisplatin (log OR [SE] = 0.08 ± 0.25, $p = 0.76$) were instead slightly favouring males. However, these differences did not prove to be statistically significant.

Three studies [26,27,29] reported ORRs for pembrolizumab (log OR [SE] = –0.01 ± 0.21, $p = 0.95$) and the combination of pembrolizumab + enfortumab (log OR [SE] = –0.14 ± 0.18, $p = 0.45$), but our analysis did not reveal any statistically significant result (Supplementary Table 5).

Two studies [25,29] reported PFS for the combination of pembrolizumab + enfortumab (log OR [SE] = 0.11 ± 0.21, $p = 0.61$) and the combination of nivolumab + chemotherapy (log OR [SE] = –0.06 ± 0.24, $p = 0.81$), with no statistically significant differences between sexes (Supplementary Table 6).

3.2.4. Second-line treatment of TCC

Two studies reported OS data (Supplementary Table 7) [29,30]. The results revealed a nonstatistically significant difference between sexes in the effect of immune ICIs on improving OS considering pembrolizumab (log OR [SE] = 0.07 ± 0.27, $p = 0.81$). The ADT versus Nectin 4 favoured instead the male gender (log OR [SE] = 0.65 ± 0.28, $p = 0.02$).

3.3. Assessment of the risk of bias

The results of the risk-of-bias assessment for the 20 included studies are depicted in Supplementary Figure 1. Concerning the randomisation process, two studies were evaluated as having a high risk of bias, while the remaining 18 studies were deemed to have a low risk of bias. Regarding the risk of bias in deviation from defined interventions, seven studies were assessed as "having some concerns". All studies demonstrated a low risk of bias in terms of missing outcome data and outcome measurement. The risk of selective reporting was a moderate risk of bias. The risk of other sources of bias was low across all included studies. In summary, the overall risk of bias in the included literature was deemed to be moderate.

4. Discussion

The sex specificity of cancer represents a crucial aspect in the landscape of disease management. As our understanding of cancer biology deepens, it becomes increasingly evident that the interplay between biological sex and sex-related factors significantly influences disease incidence, progression, and treatment outcomes [31,32]. Several potential mechanisms and theories have been investigated to explain sex-related disparities. Sex chromosomes and sex hormones drive differential adaptive immunity across malignancies, which persist even after accounting for established risk factors, such as carcinogenic environment exposures and unhealthy lifestyle [33–35]. Recently, in vitro and in vivo studies and systematic reviews have demonstrated that sex-related molecular and genetic disparities are real game changers in the context of urothelial cancer and renal cancers, thus explaining the different treatment response and cancer-specific mortality rates between women and men even after adjusting for tumour stage [4,36,37]. For example, considering the PD-1/PD-L1 pathway, Abdel-Hafiz et al [5], using genomic and transcriptomic studies, demonstrated that loss of Y chromosome tumours (Y^- tumours) was more aggressive than that of Y^+ tumours in immune-competent hosts in a T-cell–dependent manner, promoting the dysfunction or exhaustion of $CD8^+$ T cells in the tumour microenvironment. The exhaustion of $CD8^+$ cells of the Y^- tumours in turn exhibited an increased response to anti–PD-1 immune checkpoint blockade therapy in both mice and patients with cancer.

In this systematic review and NMA, we evaluated the impact of sex on oncological outcomes in both RCC and TCC patients treated with ICI-based treatments or ADC. Even if in literature it is demonstrated that ICI- and ADC-based treatments improve survival outcomes significantly compared with standard therapies, and despite previous hypothesis demonstrating that sex plays a central role in tumorigenesis and development, our analysis revealed only two statistically significant difference between sexes [21,30].

As general trends, female patients showed better OS outcomes than male patients when treated with a combination of ICI therapies for first-line metastatic RCC, while male sex showed better PFS in the same setting. The result of better OS for females treated with ICI therapies for renal cancer has been confirmed in the setting of the adjuvant therapies, where females showed significantly improved OS when treated with atezolizumab alone when compared with the male gender ($p = 0.024$) [21]. This result is in line with similar trend outcomes. In their meta-analysis, Yanagisawa et al [38] demonstrated that ICI-based combination therapies reduced the risk by 37% in female patients when compared with sunitinib alone, and that females seemed to have a larger benefit of ICI therapy in the metastatic RCC as well as the adjuvant RCC setting.

Oestrogen effects on RCC have previously been studied widely. Tulchiner et al [39] previously investigated the role of E2 levels in metastatic RCC patients when treated with nivolumab. They found that male patients had a significant increase in E2 levels, associated with an increase in the luteinising hormone/follicle-stimulating hormone ratio, and that this ratio correlated with a response to therapy in males at 6/8 wk [39]. However, no differences were evident in OS between males and females. More recently, in vivo studies demonstrated that female sex is a significant predictor of poor renal cancer mortality for advanced disease but only in the postmenopausal period, probably for E2 changes [40,41], while another in vitro study showed that E2 has some inhibition on RCC [42].

In the setting of TCC, females seem to respond better to first-line ICI-based monotherapies, while males show a more favourable trend for combination therapies with chemotherapies. Recent evidence suggested that oestrogen could contribute to increase the PD-L1 expression [36], reinforcing what a recent meta-analysis demonstrated, so as to say that female sex is generally associated with worse survival outcomes in terms of OS and cancer-specific survival [43,44]. In our meta-analysis, we did not find significant differences. This is in line with a previous meta-analysis, which reveals that first-line ICI-based combination therapies reduced the risk of death by the same margin in male and female patients, compared with chemotherapy alone [38].

For second-line therapies, no differences were found regarding ICI-based therapies, while males showed a significant improvement in OS when considering the ADC versus Nectin 4 [30].

Enfortumab vedotin is an ADC developed to target Nectin 4, a type I transmembrane polypeptide member that in normal tissues allows proper adhesion of cell junction held together with cadherin [9]. Conflicting evidence exists concerning the association of Nectin 4 overexpression and male sex in the setting of different cancers [45,46]. However, studies included in these reviews were mainly retrospective, had all small sample size, and had a high degree of heterogeneity. From a biochemical point of view, it has been demonstrated that ADCs act on the immune system by altering the tumour microenvironment [47] and that these are influenced by sex hormones, which have regulatory effects acting on mediators for regulating immune cytokines in mononuclear phagocytes (interleukin [IL]-1, IL-6, and tumour necrosis factor alpha) and T lymphocytes (IL-2 and interferon gamma). These effects may be more prominent in tissues with higher pharmaceutically relevant

concentrations, influencing cellular immune response [47]. Therefore, different sex hormones might influence tissue-specific cytokine expression, which in turn express higher or lower expression of ADC activators. The real problem is that since the clinical use of ADCs is relatively new, we lack granular information and a punctual analysis of male and female subpopulations.

Our study has several limitations. First, this is a review of randomised controlled trials, including heterogeneous populations, and as such our results should be interpreted carefully. Second, many of the included studies involved combinations of treatment, thus making a direct comparison between the treatments not possible. When chemotherapy protocols were associated with the immunotherapy, these were heterogeneous too, limiting furthermore the single-treatment analysis. Third, sex-related treatments can be influenced by many other factors such as hormonal changes, microbiome [33], or adaptive immunity. Fourth, our study is constrained by the limited data available for an analysis. In fact, we were able to demonstrate a significant difference between sexes in the only paper that reports on OS with ADCs in urothelial cancers and similarly only in one study with IO in the adjuvant RCC setting.

However, our analysis was conducted with the data currently accessible, aiming to illuminate and emphasise an aspect—sex disparities—that is often overlooked in clinical trials. Future research efforts may focus on conducting trials with more homogeneous patient populations or considering stratified analyses to provide more nuanced insights into treatment efficacy across sex-specific subgroups, considering even that recent retrospective studies conducted on large populations demonstrated that sex differences exist in immune-related adverse events [48,49]. This is of major clinical importance, to prevent treatment discontinuation and potential disease relapses.

5. Conclusions

The proposed NMA provides a comprehensive framework for understanding the differences in checkpoint inhibitor responses between genders, contributing valuable insights for optimising personalised approaches to cancer care in renal tumours and upper tract urothelial carcinomas. Research endeavours that focusing on unravelling the intricacies of how cancer manifests differently in males and females is not just desirable but is reaching a point of utmost urgency.

Author contributions: Maria Carmen Mir 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: Cerrato, Mir.
Acquisition of data: Cerrato, Crocerossa.
Analysis and interpretation of data: Crocerossa, Marchioni.
Drafting of the manuscript: Cerrato, Crocerossa, Mir.
Critical revision of the manuscript for important intellectual content: Giannarini, Gupta, Albiges, Brouwer, Albersen, Fankhauser, Grimm, Gandaglia, Roupret, Mir.
Statistical analysis: Crocerossa, Marchioni.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Mir.
Other: None.

Financial disclosures: Maria Carmen Mir 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: None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.03.014.

References

[1] Radkiewicz C, Edgren G, Johansson ALV, et al. Sex differences in urothelial bladder cancer survival. Clin Genitourin Cancer 2020;18:26–34.
[2] Richters A, Dickman PW, Witjes JA, Boormans JL, Kiemeney LALM, Aben KKH. Bladder cancer survival: women only fare worse in the first two years after diagnosis. Urol Oncol 2019;37:853–61.
[3] Lucca I, Klatte T, Fajkovic H, de Martino M, Shariat SF. Gender differences in incidence and outcomes of urothelial and kidney cancer. Nat Rev Urol 2015;12:585–92.
[4] Hamade A, Li D, Tyryshkin K, et al. Sex differences in the aging murine urinary bladder and influence on the tumor immune microenvironment of a carcinogen-induced model of bladder cancer. Biol Sex Differ 2022;13:19.
[5] Abdel-Hafiz HA, Schafer JM, Chen X, et al. Y chromosome loss in cancer drives growth by evasion of adaptive immunity. Nature 2023;619:624–31.
[6] Ljungberg B, Albiges L, Bedke J, et al. EAU guidelines on renal cell carcinoma. 2023. European Association of Urology Web site. https://uroweb.org/guidelines/renal-cell-carcinoma.
[7] Witjes JA, Bruins HM, Carrión A, et al. Guidelines on muscle-invasive and metastatic bladder cancer. 2023. European Association of Urology Web site. https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer.
[8] Sganga S, Riondino S, Iannantuono GM, Rosenfeld R, Roselli M, Torino F. Antibody–drug conjugates for the treatment of renal cancer: a scoping review on current evidence and clinical perspectives. J Pers Med 2023;13:1339.
[9] Ungaro A, Tucci M, Audisio A, et al. Antibody-drug conjugates in urothelial carcinoma: a new therapeutic opportunity moves from bench to bedside. Cells 2022;11:803.
[10] Wang HK, Zhu Y, Yao XD, et al. External validation of a nomogram using RENAL nephrometry score to predict high grade renal cell carcinoma. J Urol 2012;187:1555–60.
[11] Choueiri T, Tomczak P, Park S, et al. Overall survival results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab versus placebo for the treatment of clear cell renal cell carcinoma (ccRCC). J Clin Oncol 2024;42(4_suppl):LBA359.
[12] Higgins J, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions version 6.3. London, UK: Cochrane; 2022.
[13] Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an

open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:888–98.
[14] Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol 2019;20:1370–85.
[15] Plimack ER, Powles T, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib as first-line treatment of advanced renal cell carcinoma: 43-month follow-up of the phase 3 KEYNOTE-426 study. Eur Urol 2023;84:449–54.
[16] Haanen JBAG, Larkin J, Choueiri TK, et al. Extended follow-up from JAVELIN Renal 101: subgroup analysis of avelumab plus axitinib versus sunitinib by the International Metastatic Renal Cell Carcinoma Database Consortium risk group in patients with advanced renal cell carcinoma. ESMO Open 2023;8:101210.
[17] Motzer R, Alekseev B, Rha S-Y, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 2021;384:1289–300.
[18] Rha SY, Choueiri TK, Matveev VB, et al. Efficacy and safety of lenvatinib plus pembrolizumab vs sunitinib in the East Asian subset of patients with advanced renal cell carcinoma from the CLEAR trial. Int J Cancer 2023;153:1241–50.
[19] Motzer RJ, Russo P, Grünwald V, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. Lancet 2023;401:821–32.
[20] Powles T, Tomczak P, Park SH, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2022;23:1133–44.
[21] Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. Lancet 2022;400:1103–16.
[22] 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.
[23] 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.
[24] 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.
[25] van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine–cisplatin. N Engl J Med 2023;389:1778–89.
[26] O'Donnell PH, Milowsky MI, Petrylak DP, et al. Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer. J Clin Oncol 2023;41:4107–17.
[27] Hoimes CJ, Flaig TW, Milowsky MI, et al. Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer. J Clin Oncol 2023;41:22–31.
[28] Powles TB, Perez Valderrama B, Gupta S, et al. LBA6 EV-302/KEYNOTE-A39: Open-label, randomized phase III study of enfortumab vedotin in combination with pembrolizumab (EV+P) vs chemotherapy (Chemo) in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC). Ann Oncol 2023;34:S1340.
[29] Balar AV, Castellano DE, Grivas P, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. Ann Oncol 2023;34:289–99.
[30] Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384:1125–35.
[31] Irelli A, Sirufo MM, D'Ugo C, Ginaldi L, De Martinis M. Sex and gender influences on cancer immunotherapy response. Biomedicines 2020;8:232.
[32] Webb K, Peckham H, Radziszewska A, et al. Sex and pubertal differences in the type 1 interferon pathway associate with both X chromosome number and serum sex hormone concentration. Front Immunol 2019;9:3167.
[33] Koti M, Ingersoll MA, Gupta S, et al. Sex differences in bladder cancer immunobiology and outcomes: a collaborative review with implications for treatment. Eur Urol Oncol 2020;3:622–30.
[34] Schafer JM, Xiao T, Kwon H, et al. Sex-biased adaptive immune regulation in cancer development and therapy. iScience 2022;25:104717.
[35] Gakis G, Stenzl A. Gender-specific differences in muscle-invasive bladder cancer: the concept of sex steroid sensitivity. World J Urol 2013;31:1059–64.
[36] Carè A, Bellenghi M, Matarrese P, Gabriele L, Salvioli S, Malorni W. Sex disparity in cancer: Roles of microRNAs and related functional players. Cell Death Differ 2018;25:477–85.
[37] Peired AJ, Campi R, Angelotti ML, et al. Sex and gender differences in kidney cancer: clinical and experimental evidence. Cancers (Basel) 2021;13:4588.
[38] Yanagisawa T, Kawada T, Quhal F, et al. Impact of sex on the efficacy of immune checkpoint inhibitors in kidney and urothelial cancers: a systematic review and meta-analysis. World J Urol 2023;41:1763–74.
[39] Tulchiner G, Pichler R, Ulmer H, et al. Sex-specific hormone changes during immunotherapy and its influence on survival in metastatic renal cell carcinoma. Cancer Immunol Immunother 2021;70:2805–17.
[40] Qu Y, Chen H, Gu W, Gu C, Zhang H, Xu J, et al. Age-dependent association between sex and renal cell carcinoma mortality: a population-based analysis. Sci Rep 2015;5:9160.
[41] Yu CP, Ho JY, Huang YT, et al. Estrogen inhibits renal cell carcinoma cell progression through estrogen receptor-β activation. PLoS One 2013;8:e56667.
[42] Sun L, Gao Z, Luo L, Tan H, Zhang G. Estrogen affects cell growth and IGF-1 receptor expression in renal cell carcinoma. Onco Targets Ther 2018;11:5873–8.
[43] Mori K, Mostafaei H, Enikeev DV, et al. Differential effect of sex on outcomes after radical surgery for upper tract and bladder urothelial carcinoma: a systematic review and meta-analysis. J Urol 2020;204:58–62.
[44] Mori K, Yanagisawa T, Katayama S, et al. Impact of sex on outcomes after surgery for non-muscle-invasive and muscle-invasive bladder urothelial carcinoma: a systematic review and meta-analysis. World J Urol 2023;41:909–19.
[45] Murata M, Ito T, Tanaka Y, Kaku-Ito Y, Furue M. Nectin4 expression in extramammary Paget's disease: implication of a new therapeutic target. Int J Mol Sci 2020;21:5891.
[46] Liu R, Zhao K, Wang K, et al. Prognostic value of nectin-4 in human cancers: a meta-analysis. Front Oncol 2023;13:1081655.
[47] Lucas AT, Price LSL, Schorzman AN, et al. Factors affecting the pharmacology of antibody-drug conjugates. Antibodies 2018;7:10.
[48] Wahli MN, Hayoz S, Hoch D, et al. The role of immune checkpoint inhibitors in clinical practice: an analysis of the treatment patterns, survival and toxicity rates by sex. J Cancer Res Clin Oncol 2023;149:3874–958.
[49] Chen C, Zhang C, Jin Z, Wu B, Xu T. Sex differences in immune-related adverse events with immune checkpoint inhibitors: data mining of the FDA adverse event reporting system. Int J Clin Pharm 2022;44:689–97.