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Review – Urothelial Cancer

Systematic Review of Immune Checkpoint Inhibition in Urological Cancers

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Abstract

Context: In patients with advanced and metastatic urological cancers, clinical outcome may be improved by immune checkpoint inhibitors (ICIs).
Objective: To systematically review relevant literature on efficacy and safety of ICIs in patients with advanced and metastatic urothelial cell cancer (UCC), renal cell cancer (RCC), and prostate cancer.
Evidence acquisition: Relevant databases, including Medline, Embase, and the Cochrane Library, were searched up to March 16, 2017. A narrative review of randomized clinical trials (RCTs) was performed.
Evidence synthesis: Six RCTs were included for the systematic review. In platinum-pretreated UCC, efficacy of pembrolizumab was superior to chemotherapy, with longer median overall survival (OS; 10.3 vs 7.4 mo), a higher objective response rate (ORR; 21.1% vs 11.4%, $p = 0.001$), and a lower adverse event rate (60.9% vs 90.2%). Three RCTs assessed the safety and efficacy of nivolumab in advanced RCC. The median OS (25.0 vs 19.6 mo) and the ORR (25% vs 5%) were higher in patients treated with nivolumab compared with second-line everolimus. In all three studies, the safety profile of nivolumab was favorable. In patients with metastatic castration-resistant prostate cancer, two RCTs were identified, which did not show significant benefits for ipilimumab over placebo. In UCC and RCC, there was no conclusive association between programmed cell death receptor ligand 1 (PD-L1) expression in tumor tissue and clinical outcome during pembrolizumab and nivolumab treatment, respectively.
Conclusion: In metastatic UCC and RCC, pembrolizumab and nivolumab have superior efficacy and safety to second-line chemotherapy and everolimus, respectively. No beneficial effect of ipilimumab was observed in prostate cancer patients. PD-L1 expression status is currently not suitable as a predictive marker for treatment outcome.
Patient summary: Immune checkpoint inhibitors are able to reactivate the immune system against tumor cells. In second-line setting, pembrolizumab and nivolumab are safe and confer survival benefit in advanced urothelial cell and renal cell cancer, respectively.

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1. Introduction

Immune checkpoint inhibitors (ICIs) have shown efficacy in the treatment of a variety of solid tumors, including advanced urological cancers [1]. Historically, the treatment of urological malignancies included immune modulating agents. In high-risk non–muscle-invasive bladder cancer (NMIBC), adjuvant treatment with intravesical *Bacille Calmette Guérin* (BCG), a therapy that uses mycobacterial components to activate the immune system, provides a 32% risk reduction in recurrence compared with intravesical chemotherapy [2]. In addition, 10–20% of patients with metastatic renal cell cancer (mRCC) experience durable responses upon treatment with high-dose interleukin-2 [3]. The first commercially available autologous cell-based vaccination therapy, sipuleucel-T, was found to be effective in metastatic castration-resistant prostate cancer (mCRPC) [4]. Although immune modulating therapies have shown efficacy in these specific cases, systemic treatment of advanced and metastatic urological cancers thus far mainly comprises chemotherapy (for urothelial cell cancer [UCC] and prostate cancer [PC]), vascular endothelial growth factor (VEGF) pathway inhibitors (for mRCC), and androgen deprivation therapy (for PC).

Over the past 20 yr, standard first-line treatment for advanced and metastatic UCC has been cisplatin-based chemotherapy [5,6]. However, up to 50% of patients are unfit for cisplatin, mainly due to age-associated impaired renal function, cardiovascular comorbidities, and performance status [7]. Furthermore, no effective second-line treatment is available for patients with disease progression after first-line chemotherapy. Single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine) is commonly applied, but only 10% of patients experience a tumor response, and the median overall survival (OS) is around 7 mo [8].

In contrast with UCC, RCC is highly resistant to chemotherapy and, until the introduction of VEGF pathway inhibitors (eg, sunitinib and sorafenib) in 2005–2006, systemic treatment consisted of interferon-alpha and high-dose interleukin-2 [3]. Although VEGF pathway inhibitors, together with mammalian target of rapamycin (mTOR) inhibitors (eg, everolimus), have significantly improved the perspectives of mRCC patients [9], the median OS for mRCC patients remains only 12.5 mo after first-line targeted therapy [10].

In metastatic PC, androgen deprivation therapy is the backbone of treatment and frequently results in durable responses. Nevertheless, eventually all patients experience progression to mCRPC [11]. For the treatment of mCRPC, chemotherapy (docetaxel [12] and cabazitaxel [13]), second-generation antiandrogens such as abiraterone [14] and enzalutamide [15], and radionuclides such as radium-223 [16] have been approved. These agents have improved the survival in mCRPC patients; however, the median OS seems to plateau at about 3 yr [14,15].

The current lack of efficacious treatment options for advanced UCC, mRCC, and mCRPC underscores the clinical need for new well-tolerated treatment modalities that improve the outcome of patients with urological cancers. ICIs may expand the treatment armamentarium for patients with urological malignancies. Currently available ICIs include monoclonal antibodies that block the function of inhibitory receptors on T cells, resulting in a release of T-cell inhibition. Some tumors manage to escape immune surveillance by expressing the programmed cell death receptor ligand 1 (PD-L1) activating the inhibitory receptors on T cells and thereby preventing clearance by the immune system [17]. Interference with this receptor–ligand interaction by ICIs reinvigorates the T-cell–mediated antitumor immune response [18,19]. Thus far, blocking antibodies against programmed cell death 1 (PD-1; eg, nivolumab and pembrolizumab), PD-L1 (eg, atezolizumab), and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4; eg, ipilimumab) have been introduced in the clinic (Fig. 1).

The first hint of antitumor activity of ICIs in urological cancers came from phase I clinical trials, reporting durable responses in metastatic UCC and RCC [19,20]. Since then, several pivotal clinical trials evaluating the efficacy of ICIs in urological cancers have been initiated. In this systematic review, we analyzed the efficacy and safety of ICIs in patients with advanced urological cancers, including UCC, RCC, and PC.

2. Evidence acquisition

2.1. Search strategy

Up to March 16, 2017, an electronic search of the Medline, Embase, and Cochrane databases, and relevant websites (Web of Science and Google Scholar) was performed by an expert librarian. The search was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 2) [21]. Search terms included the following: "urinary tract cancer, bladder cancer, kidney cancer, prostate cancer, immune checkpoint inhibitors, atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, tremelimumab, anti-PD1, anti-PD-L1, and anti-CTLA-4" (see Supplementary materials for details). The search was completed by manual screening of reference lists from included studies.

2.2. Inclusion criteria

The study population consisted of patients (>18 yr of age), diagnosed with advanced or metastatic UCC, RCC, or PC, who were treated with one of the ICIs targeting PD-1 (nivolumab and pembrolizumab), PD-L1 (atezolizumab, avelumab, and durvalumab), and CTLA-4 (ipilimumab and tremelimumab). The search was limited to studies executed in humans. No restrictions in publication date or language were imposed. During the systematic review process, only prospective, randomized, phase 1, 2, and 3 clinical trials were included, whereas nonrandomized clinical trials (non-RCTs), case reports, editorials, letters, review articles, and conference abstracts were excluded. If multiple analyses of the same clinical study were performed, the most recent or most relevant publication was selected. Primary outcome measures included OS, progression-free survival (PFS), and

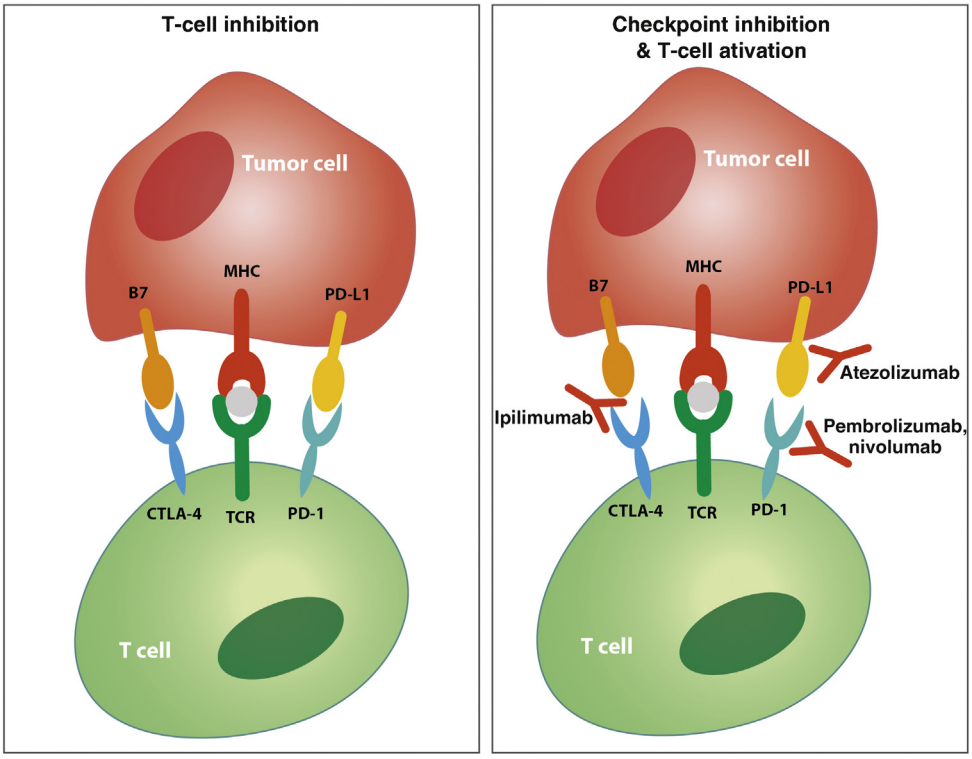

Fig. 1 – T-cell coinhibitory receptor expression and checkpoint inhibition. Tumor cells and antigen presenting cells (APCs) express a specific antigen that is presented to cytotoxic T cells in a peptide major histocompatibility complex (MHC). T cells recognize this presented antigen with their T-cell receptor (TCR) and, together with binding of costimulatory receptors (eg, CD28); this leads to T-cell activation and subsequently elimination of the (tumor) cell. Interaction of coinhibitory receptors on T cells with their ligands on APCs or tumor cells inhibits T-cell activation. Known coinhibitory receptors are PD-1 (that interacts with its ligand PD-L1) and CTLA-4. Blocking antibodies against these coinhibitory receptors or their ligands can prevent their interaction and the subsequent inhibition of T-cell activity. CTLA-4 = cytotoxic T lymphocyte–associated protein 4; PD-1 = programmed cell death 1; PD-L1 = programmed cell death receptor ligand 1.

objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) [22]. Secondary outcomes included adverse events (AEs) and efficacy analyses according to PD-L1 expression status in tumor tissue.

2.3. Data extraction

Two independent reviewers (M.R. and A.A.M.V.) assessed relevant articles for study eligibility, and any disagreement on inclusion was resolved by discussion. Using a standardized data extraction form, the following details were extracted: study design, number of patients, patient characteristics, treatment intervention, median duration of follow-up, survival data, ORR, AEs, and PD-L1 expression status. Data were extracted from all included studies by one reviewer (M.R.) and subsequently checked by a second reviewer (A.A.M.V.) to ensure their accuracy.

2.4. Data analysis

Descriptive analyses were used to present the data. Continuous outcomes were described using mean and standard deviation, or alternatively, median and (interquartile) range. For categorical outcomes, frequencies and proportions were used. If reported, hazard ratios (HRs) with confidence intervals (CIs) were mentioned. Owing to the limited number of available studies, no quantitative analysis (ie, meta-analysis) could be performed.

3. Evidence synthesis

3.1. Study selection

The initial literature search identified 3354 articles. After removing duplicate studies, one reviewer (M.R.) evaluated all titles and abstracts. Finally, 40 publications were identified as potentially relevant and were retrieved for full-text evaluation. According to the inclusion criteria, six randomized phase 1–3 clinical trials were selected for evidence synthesis (one trial on UCC, three trials on RCC, and two trials on PC; Table 1). The literature search identified 16 additional non-RCTs addressing the safety and efficacy of ICIs in urological cancer (Supplementary Tables 1 and 2).

3.2. Characteristics, efficacy, and PD-L1 status in selected studies

The characteristics, efficacy measures, and PD-L1 status of the included studies are presented in Tables 1, 2, and 3, respectively (see also Supplementary Table 3).

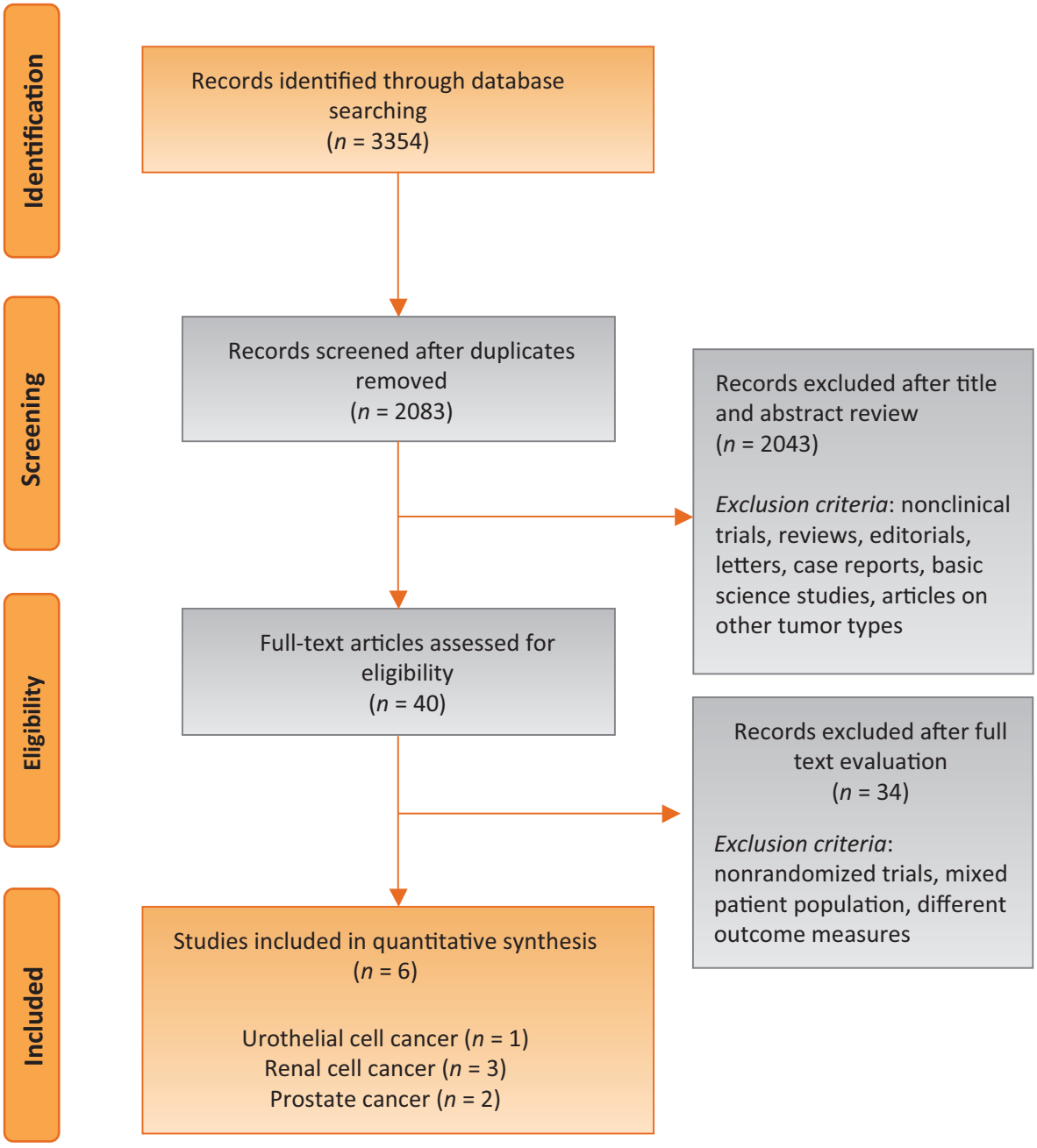

Fig. 2 – Evidence synthesis flowchart according to PRISMA. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.2.1. Urothelial cell cancer

For advanced UCC, one RCT was identified in which 542 patients with disease progression after first-line platinum-based chemotherapy were randomized to receive pembrolizumab (200 mg intravenously every 3 wk) or investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine) [23]. Patients treated with pembrolizumab had significantly longer median OS than those treated with investigator's choice of chemotherapy (10.3 vs 7.4 mo). Although there was no significant between-group difference for PFS (HR for disease progression or death, 0.98 [95% CI, 0.81–1.19], $p = 0.42$), the estimated PFS rate at 12 mo was higher for pembrolizumab-treated patients (16.8% vs 6.2%, no HR reported). The ORR was almost two-fold higher for the pembrolizumab group as compared with the chemotherapy group (21.1% vs 11.4%, $p = 0.001$). Among patients with a tumor response during pembrolizumab treatment, 7% had a complete response and 14.1% had a partial response. In the pembrolizumab group, the median duration of response was not reached, whereas the median response duration was 4.3 mo in the chemotherapy group. PD-L1 expression was determined on pretreatment, mainly archival, tumor tissue. A combined positivity score was used, defined as the

Table 1 – Characteristics of randomized clinical trials on immune checkpoint inhibitors in urological cancer

	Trial	Study design	Population	Patients (*n*)	Histology subgroups	Line	Previous therapy	Experimental arm	Comparator
Urothelial cell cancer									
Bellmunt et al (2017) [23]	Keynote-045 NCT02256436	Phase 3	Advanced UCC	542	Pembrolizumab 68.9% and chemotherapy 73.0% pure transition cell features	Second	Platinum-based chemotherapy	200 mg pembrolizumab IV, every 3 wk	Investigator's choice of chemotherapy
Renal cell cancer									
Motzer et al (2015) [26]	CheckMate 025 NCT01668784	Phase 3	Advanced and metastatic RCC	821	100% clear cell RCC	Second	Antiangiogenic therapy	3 mg/kg nivolumab IV, every 2 wk	10 mg everolimus, orally, once daily
Motzer et al (2015) [25]	NCT01354431	Phase 2	Metastatic RCC	168	100% clear cell RCC	Second	Antiangiogenic therapy	0.3, 2, or 10 mg/kg nivolumab IV, every 3 wk	Other experimental arms
Choueiri et al (2016) [24]	NCT01358721	Phase 1b	Metastatic RCC	91	100% clear cell RCC	First, second	Systemic therapy, not specified	0.3, 2, or 10 mg/kg nivolumab, every 3 wk [a]	Other experimental arms
Prostate cancer									
Beer et al (2017) [27]	NCT01057810	Phase 3	mCRPC	602	NA	Second	Antiandrogenic therapy, no chemotherapy for mCRPC	10 mg/kg ipilimumab IV, every 3 wk for up to four doses, followed by maintenance treatment every 12 wk	Placebo IV, every 3 wk for up to four doses, followed by maintenance treatment every 12 wk
Kwon et al (2014) [28]	NCT00861614	Phase 3	mCRPC	799	Adenocarcinoma	Second	Antiandrogenic therapy, docetaxel-based chemotherapy for mCRPC	Single-dose bone-directed radiotherapy (8 Gy) followed by 10 mg/kg ipilimumab IV, every 3 weeks for up to 4 doses	Single-dose bone-directed radiotherapy (8 Gy) followed by placebo IV, every 3 wk for up to four doses

UCC = urothelial cell cancer; RCC = renal cell cancer; mCRPC = metastatic castration-resistant prostate cancer; NA = not available; IV = intravenously.
[a] Previously treated population is subdivided into three dosage subgroups of 0.3, 2, or 10 mg/kg nivolumab; all treatment-naive patients received 10 mg/kg nivolumab.

Table 2 – Efficacy of immune checkpoint inhibitors in randomized clinical trials in urological cancer

	Treatment	Patients (*n*)	Median follow-up (mo) (CI)	Median OS (mo) (CI)	Median PFS (mo) (CI)	ORR (CI)	CR	PR	SD	PD	NE	Median duration of response (mo) (CI)	Other
Urothelial cell cancer													
Bellmunt et al (2017) [23]	Pembrolizumab 200 mg	270	14.1 (9.9–22.1) [a]	10.3 (8.0–11.8) [b]	2.1 (2.0–2.2) [b]	21.1% (16.4–26.5) [b]	19 (7%)	38 (14.1%)	47 (17.4%)	131 (48.5%)	35 (13.0%)	NR (1.6+ to 15.6+) [a]	
	Chemotherapy	272	14.1 (9.9–22.1) [a]	7.4 (6.1–8.3) [b]	3.3 (2.3–3.5) [b]	11.4% (7.9–15.8) [b]	9 (3.3%)	22 (8.1%)	91 (33.5%)	90 (33.1%)	60 (22.1%)	4.3 (1.4+ to 15.4+) [a]	
Renal cell cancer													
Motzer et al (2015) [26]	Nivolumab 3 mg/kg	410	NA	25.0 (21.8–NR) [b]	4.6 (3.7–5.4) [b]	25%	4 (1%)	99 (24%)	141 (34%)	143 (35%)	23 (6%)	12.0 (0–27.6) [a]	
	Everolimus 10 mg	411	NA	19.6 (17.6–23.1) [b]	4.4 (3.7–5.5) [b]	5%	2 (1%)	20 (5%)	227 (55%)	114 (28%)	48 (12%)	12.0 (0–22.2) [a]	
Motzer et al (2015) [25]	Nivolumab 0.3 mg/kg	60	NA	18.2 (16.2–24.0) [c]	2.7 (1.9–3.0) [c]	20% (13.4–28.2) [c]	1 (2%)	11 (18%)	22 (37%)	24 (40%)	2 (3%)	NR (NR–NR) [c]	
	Nivolumab 2 mg/kg	54	NA	25.5 (19.8–28.8) [c]	4.0 (2.8–4.2) [c]	22% (15.0–31.1) [c]	1 (2%)	11 (20%)	23 (43%)	18 (33%)	1 (2%)	NR (4.2–NR) [c]	
	Nivolumab 10 mg/kg	54	NA	24.7 (15.3–26.0) [c]	4.2 (2.8–5.5) [c]	20% (13.4–29.1) [c]	0 (0%)	11 (20%)	24 (44%)	17 (32%)	2 (4%)	22.3 (4.8–NR) [c]	
Choueiri et al (2016) [24]	All patients	91	NA	NA	NA	15% (8.7–24.5) [b]	2 (2%)	12 (13%)	42 (46%)	27 (30%)	8 (9%)	NA	
Previously treated group	Nivolumab 0.3 mg/kg	22	NA	16.4 (10.1–NR) [b]	NA	9% (1.1–29.2) [b]	0 (0%)	2 (9%)	8 (36%)	9 (41%)	3 (14%)	NA	
	Nivolumab 2 mg/kg	22	NA	NR	NA	18% (5.2–40.3) [b]	0 (0%)	4 (18%)	10 (46%)	5 (23%)	3 (14%)	NA	
	Nivolumab 10 mg/kg	23	NA	25.2 (12.0–NR) [b]	NA	22% (7.5–43.7) [b]	0 (0%)	5 (22%)	11 (48%)	6 (26%)	1 (4%)	NA	
Treatment-naive group	Nivolumab 10 mg/kg	24	NA	NR	NA	13% (2.7–32.4) [b]	2 (8%)	1 (4%)	13 (54%)	7 (29%)	1 (4%)	NA	

														PSARR (CI) [b]
Prostate cancer														
Beer et al (2017) [27]	Ipilimumab	400	24–48	28.7 (24.5–32.5) [b]	5.6 (5.3–6.3) [b]	NA	NA	NA	NA	NA	NA	NA	23% (19–27) [b]	
	Placebo	202	24–48	29.7 (26.1–34.2) [b]	3.8 (2.8–4.1) [b]	NA	NA	NA	NA	NA	NA	NA	8% (5–13) [b]	
Kwon et al (2014) [28]	Radiotherapy with ipilimumab	399	9.9 (4.3–16.7) [d]	11.2 (9.5–12.7) [b]	4.0 (3.6–4.3) [b]	NA	NA	NA	NA	NA	NA	NA	13.1% (9.5–17.5) [b]	
	Radiotherapy with placebo	400	9.3 (5.4–14.6) [d]	10.0 (8.3–11.0) [b]	3.1 (2.9–3.4) [b]	NA	NA	NA	NA	NA	NA	NA	5.2% (3.0–8.4) [b]	

CI = confidence interval; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; PSARR = prostate-specific antigen response rate; NA = not available; NR = not reached.

[a] Range.

[b] CI 95%.

[c] CI 80%.

[d] Interquartile range.

Table 3 – Efficacy of immune checkpoint inhibitors in randomized clinical trials in urological cancer according to tumor PD-L1 expression status

Study	Assessment of PD-L1 expression	Treatment	PD-L1 expression	Patients (*n*)	Median OS (mo) (95% CI)	Median PFS (mo) (95% CI)	ORR (95% CI)	CR	PR	SD	PD	NE
Urothelial cell cancer												
Bellmunt et al (2017) [23]	Combined positive score of tumor cells and tumor-infiltrating immune cells	Pembrolizumab	All patients	270	10.3 (8.0–11.8)	2.1 (2.0–2.2)	21.1% (16.4–26.5)	19 (7%)	38 (14.1%)	47 (17.4%)	131 (48.5%)	35 (13.0%)
			PD-L1 ≥10%	74	8.0 (5.0–12.3)	NA	21.6% (12.9–32.7)	5 (6.8%)	11 (14.9%)	9 (12.2%)	37 (50%)	12 (16.2%)
		Chemotherapy	All patients	272	7.4 (6.1–8.3)	3.3 (2.3–3.5)	11.4% (7.9–15.8)	9 (3.3%)	22 (8.1%)	91 (33.5%)	90 (33.1%)	60 (22.1%)
			PD-L1 ≥10%	90	5.2 (4.0–7.4)	NA	6.7 (2.5-13.9)	2 (2.2%)	4 (4.4%)	35 (35.6%)	38 (31.1%)	24 (26.7%)
Renal cell cancer												
Motzer et al (2015) [26]	Tumor membrane expression	Nivolumab	PD-L1 <1%	276	27.4 (21.4–NR)	NA	NA	NA	NA	NA	NA	NA
			PD-L1 ≥1%	94	21.8 (16.5–28.1)	NA	NA	NA	NA	NA	NA	NA
			PD-L1 <5%	326	24.6 (21.4–NR)	NA	NA	NA	NA	NA	NA	NA
			PD-L1 ≥5%	44	21.9 (14.0–NR)	NA	NA	NA	NA	NA	NA	NA
		Everolimus	PD-L1 <1%	299	21.2 (17.7–26.2)	NA	NA	NA	NA	NA	NA	NA
			PD-L1 ≥1%	87	18.8 (11.9–19.9)	NA	NA	NA	NA	NA	NA	NA
			PD-L1 <5%	345	20.0 (17.7–24.7)	NA	NA	NA	NA	NA	NA	NA
			PD-L1 ≥5%	41	18.1 (10.3–NR)	NA	NA	NA	NA	NA	NA	NA
Motzer et al (2015) [25]	Tumor membrane expression	Nivolumab	≥1% or <5%	78	18.2 (12.7–26.0)	2.9 (2.1–4.2)	18% (10.2–28.3)	NA	NA	NA	NA	NA
		Nivolumab	≥5%	29	NR (13.4–NR)	4.9 (1.4–7.8)	31% (15.3–50.8)	NA	NA	NA	NA	NA
Choueiri et al (2016) [24]	Not determined											

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; PD-L1 = programmed cell death receptor ligand 1; NE = not evaluable; NA = not available; NR = not reached.

percentage of PD-L1 expressing tumor and tumor-infiltrating immune cells relative to the total number of tumor cells. Patients in all subgroups experienced benefit from pembrolizumab treatment irrespective of PD-L1 expression. In both pembrolizumab- and chemotherapy-treated patients, shorter OS was observed in those with high PD-L1 expression, defined as a combined positive score of ≥10%.

3.2.2. Renal cell cancer

For advanced RCC and mRCC, three RCTs evaluating the efficacy of nivolumab were identified, including two dose-controlled trials (phases 1b and 2) and one active comparator-controlled phase 3 trial with everolimus. In these three trials, only clear cell histology was allowed and patients were mainly pretreated with antiangiogenic therapy.

In the two dose-controlled trials, patients were randomized to nivolumab at a dose of 0.3, 2, or 10 mg/kg every 3 wk. These phase 1b and 2 trials were different in patient population, design, and objectives. The phase 1b study demonstrated immune pharmacodynamic effects (eg, changes in circulating chemokines and tumor-associated lymphocytes) irrespective of dose [24], whereas the phase 2 study did not show a significant dose–response effect [25].

In the phase 3 trial, 821 patients with previously treated advanced RCC or mRCC were randomized to everolimus or nivolumab at a dosage of 3 mg/kg every 2 wk [26]. Nivolumab treatment was associated with significantly improved median OS (25.0 vs 19.6 mo, HR 0.73 [98.5% CI, 0.57–0.93], $p = 0.002$). Although the ORR was significantly higher in the nivolumab group than in the everolimus group (25% vs 5%, odds ratio 5.98 [95% CI, 3.68–9.72], $p < 0.001$), there was no difference in PFS (4.6 vs 4.4 mo, HR 0.88 [95% CI, 0.75–1.03], $p = 0.11$). Overall, eight out of 1080 (<1%) nivolumab-treated patients in the three RCTs (phases 1b, 2, and 3) had a complete response.

In the phase 2 and 3 trials with nivolumab, pretreatment tumor PD-L1 expression was determined as the percentage of PD-L1–positive tumor cells relative to the total number or tumor cells [25,26]. In the phase 2 dosing study, a beneficial effect of higher PD-L1 expression (≥5%) was observed, with a higher ORR and longer OS [25], whereas the phase 3 study showed shorter OS in nivolumab-treated patients with high PD-L1 expression (≥1%; 27.4 vs 21.8 mo) [26].

3.2.3. Prostate cancer

For mCRPC, two RCTs were selected in which chemotherapy-naive ($n = 602$) and docetaxel-pretreated patients ($n = 799$) were randomized to ipilimumab or placebo [27,28]. In one study, single-dose bone-directed radiotherapy (8 Gy) was given prior to administration of ipilimumab or placebo [28]. In both studies, ipilimumab failed to show survival benefit over placebo. However, there was a trend toward improved PFS and a prostate-specific antigen response in ipilimumab-treated patients [27,28], suggesting some efficacy.

3.3. Safety of ICIs in urological cancer

AEs reported in the selected randomized studies are presented in Table 4.

3.3.1. Urothelial cell cancer

Compared with chemotherapy-treated UCC patients, patients treated with pembrolizumab experienced fewer AEs (90.2% vs 60.9% AEs of any grade) [23]. In addition, the incidence of grade 3–4 AEs was more than three times higher in chemotherapy-treated patients. In pembrolizumab-treated patients, grade 3–4 immune-related AEs were observed in 4.5% of the patients, including pneumonitis, colitis, and nephritis. In both treatment groups, four treatment-related AEs resulted in patient death. Treatment-related deaths in the pembrolizumab group resulted from pneumonitis ($n = 1$), urinary tract obstruction ($n = 1$), malignant neoplasm progression ($n = 1$), and unspecified cause ($n = 1$).

3.3.2. Renal cell cancer

In mRCC patients treated with nivolumab, fewer treatment-related AEs were reported compared with those in patients in the everolimus group (79% vs 88%) [26]. In nivolumab-treated patients, the most common grade 3–4 AEs were fatigue, nausea, and diarrhea. Overall, the incidence of immune-related AEs was limited. In the phase 2 study, there was no association between nivolumab dosage and the number of AEs [25].

3.3.3. Prostate cancer

In the RCT without radiotherapy, the incidence of grade 3–4 AEs in mCRPC patients treated with ipilimumab was approximately 40%, including 31% grade 3–4 immune-related AEs and nine (2%) treatment-related deaths [27]. The most frequently reported AEs included diarrhea (15%), rash (3%), and fatigue (3%). In the RCT with single-dose radiotherapy, grade 3–4 immune-related AEs were reported both in the ipilimumab and in the placebo group (26% vs 11%) [28].

3.4. Discussion

3.4.1. Principal findings

Although UCC and RCC have totally different tumor characteristics, varying from a high mutational load in UCC [29] to high vascularization and chemotherapy resistance in RCC [3], immune modulating therapies have a great potential in at least a subgroup of both populations. In patients with advanced UCC and RCC, the ICIs pembrolizumab and nivolumab, respectively, have shown proven efficacy as evidenced by survival improvement, as well as a favorable AE profile in randomized comparator controlled trials, thereby changing treatment paradigms in second-line treatment. Immune checkpoint blockade with the anti-CTLA-4 antibody ipilimumab, though, did not show survival benefit combined with a relatively high risk of toxicity in mCRPC patients.

3.4.2. Efficacy and future perspectives

3.4.2.1. Urothelial cell cancer. The success of ICIs in UCC is likely associated with its high mutational load [29], thereby potentially sensitizing UCC to immune checkpoint blockade [30]. Based on an almost 3 mo OS benefit [23], the U.S. Food

Table 4 – Treatment-related adverse events in randomized clinical trials on immune checkpoint inhibitors in urological cancer

	Treatment	Patients (*n*)	Any grade AEs	Grade 3–4 AEs	Types of grade 3–4 AEs	Grade 3–4 IR AEs	Types of grade 3–4 IR AEs	AEs leading to discontinuation [a]	AEs leading to death [b]
Urothelial cell cancer									
Bellmunt et al (2017) [23]	Pembrolizumab	270	162 (61%)	40 (15%)	Fatigue (1.1%), diarrhea (1.1%), anemia (0.8%), nausea (0.4%), asthenia (0.4%), decreased neutrophil count (0.4%)	12 (4.5%)	Pneumonitis (2.3%), colitis (1.1%), nephritis (0.8%), severe skin reaction (0.4%), adrenal insufficiency (0.4%)	12 (4.5%)	4 (1.5%)
	Chemotherapy	272	230 (90%)	126 (49%)	Neutropenia (13.3%), decreased neutrophil count (12.2%), anemia (7.8%), fatigue (4.3%), constipation (3.1%), asthenia (2.7%), peripheral sensory neuropathy (2.0%), nausea (1.6%), decreased appetite (1.2%), diarrhea (0.8%), peripheral neuropathy (0.8%), alopecia (0.8%), pruritus (0.4%)	4 (1.6%)	Severe skin reaction (1.2%), myositis (0.4%)	28 (11%)	4 (1.6%)
Renal cell cancer									
Motzer et al (2015) [26]	Nivolumab	406	319 (79%)	76 (19%)	Fatigue (2%), anemia (2%), diarrhea (1%), dyspnea (1%), pneumonitis (1%), hyperglycemia (1%), decreased appetite (<1%), rash (<1%), nausea (<1%)	NA	NA	31 (8%)	0
	Everolimus	397	349 (88%)	145 (37%)	Anemia (8%), hypertriglyceridemia (5%), hyperglycemia (4%), stomatitis (4%), fatigue (3%), pneumonitis (3%), mucosal inflammation (3%), nausea (1%), diarrhea (1%), decreased appetite (1%), rash (1%), dyspnea (1%), peripheral edema (1%)	NA	NA	52 (13%)	2
Motzer et al (2015) [25]	Nivolumab 0.3 mg/kg	59	44 (75%)	3 (5%)	Nausea (2%)	NA	Increased AST (2%), increased ALT (2%)	1 (2%)	0
	Nivolumab 2 mg/kg	54	36 (67%)	9 (17%)	Nausea (2%), pruritus (2%)	NA	Pruritus (2%), hypothyroidism (2%), gastrointestinal (2%), increased AST (2%), increased ALT (2%)	6 (11%)	0
	Nivolumab 10 mg/kg	54	42 (78%)	7 (13%)	Arthralgia (2%)	NA	0	4 (7%)	0
Choueiri et al (2016) [24]	Nivolumab 0.3 mg/kg	22	22 (100%)	15 (68%)	Constipation (5%), increased AST (5%), increased ALT (5%), acute renal failure (5%), pneumonitis (5%)	0	0	NA	NA
	Nivolumab 2 mg/kg	22	22 (100%)	8 (36%)	Fatigue (9%), constipation (5%)	0	0	NA	NA
	Nivolumab 10 mg/kg	23	23 (100%)	13 (57%)	Increased AST (9%), colitis (4%), diarrhea (4%), increased ALT (4%), increased blood bilirubin (4%), acute renal failure (4%), pneumonitis (4%), skin (4%)	1 (4%)	Skin (4%)	NA	NA
Treatment naive	Nivolumab 10 mg/kg	24	24 (100%)	12 (50%)	Colitis (8%), fatigue (4%), diarrhea (4%), endocrine (4%), hypersensitivity/infusion reaction (4%), infusion-related reaction (4%)	0	0	NA	NA
Prostate cancer									
Beer et al (2017) [27]	Ipilimumab	399	325 (82%)	158 (40%)	Diarrhea (15%), rash (3%), fatigue (3%), nausea (2%), decreased appetite (1%), vomiting (1%), pruritus (<1%)	125 (31%)	NA	114 (29%)	9 (2%)
	Placebo	199	98 (49%)	11 (6%)	Fatigue (1%), pruritus (<1%)	3 (2%)	NA	5 (3%)	0
Kwon et al (2014) [28]	Radiotherapy with ipilimumab	393	295 (75%)	NA	NA	101 (26%)	NA		4 (1%)
	Radiotherapy with placebo	396	180 (45%)	NA	NA	11 (3%)	NA		0

AEs = adverse events; IR = immune related; NA = not available; AST = aspartate aminotransferase; ALT = alanine aminotransferase; NA = not available.

[a] Treatment-related events of any grade leading to treatment discontinuation.

[b] Treatment-related events of any grade leading to patient death.

and Drug Administration (FDA) has lent priority review for pembrolizumab as second-line treatment of UCC, and the file has also been submitted to the European Medicine Agency. Previous phase 2 clinical trials have already resulted in FDA approval of atezolizumab and nivolumab for second-line therapy of UCC (Supplementary Tables 1 and 2) [31,32]. Meanwhile, after obtaining approval in second-line treatment of UCC, ICIs are currently moving toward earlier treatment lines and disease stages.

In a recent phase 2 study, cisplatin-ineligible patients with advanced UCC were treated with first-line atezolizumab (1200 mg intravenously every 3 wk), resulting in an ORR of 23% (9% complete response rate) and median OS of 15.9 mo (Supplementary Tables 1 and 2) [30]. Similar results from a phase 2 study with pembrolizumab showed a comparable ORR in this patient population [33]. Since the median OS in patients unfit for cisplatin, who receive mostly carboplatin–gemcitabine as first-line chemotherapy, is around 9 mo at best [34], the extrapolated median OS of more than 12 mo in these studies seem encouraging for ICIs, having prompted applications for the additional indication as first-line treatment in the frail cisplatin-unfit patient population. In addition, several phase 3 studies are currently evaluating the efficacy of ICIs as first-line treatment in cisplatin-eligible patients. In several ongoing first-line RCTs, immune checkpoint blockade (monotherapy, in combination with platinum-based chemotherapy, or combination of anti-PD-1 and anti-CTLA-4) is compared with conventional platinum-based chemotherapy [35,36]. Likewise, studies addressing the use of ICIs in the adjuvant setting are in progress in patients at high risk for disease progression following radical cystectomy [35]. BCG-unresponsive high-risk NMIBC has high recurrence rates and also a significant risk of progression to muscle-invasive disease. At present, radical cystectomy is the only available treatment option for BCG-unresponsive NMIBC [37]. The use of ICIs as a treatment strategy and potential means to avoid bladder cancer surgery would be of great potential. This is further supported by the observation that PD-L1 expression seems to be higher following BCG treatment [38] and that, like in muscle-invasive disease, a high mutational load is present in BCG-unresponsive NMIBC [39]. An ongoing international multicenter phase II clinical trial explores the efficacy of pembrolizumab in BCG-unresponsive NMIBC [35].

3.4.2.2. Renal cell cancer. With an almost 6 mo OS benefit [26], nivolumab has been approved by the FDA, thereby replacing everolimus as second-line treatment of advanced clear cell RCC. Cost per responder analysis of the CheckMate 025 trial showed that nivolumab is also cost effective compared with everolimus, with a monthly cost per responder of $54 315 for nivolumab compared with $224 711 for everolimus [40]. However, large studies on the efficacy of ICIs for nonclear cell RCC are still lacking. Furthermore, the place of nivolumab as second-line treatment of clear cell RCC is currently shared with cabozantinib, since this tyrosine kinase inhibitor has been approved more recently as another second-line treatment option [41,42].

In resemblance with UCC, immune checkpoint blockade is also moving toward earlier treatment lines and disease stages of RCC, including the neoadjuvant and adjuvant settings. Current clinical trials mainly focus on several combination strategies, including the combination nivolumab–ipilimumab [35]. From a historical perspective, combining immune checkpoint blockade with antiangiogenic therapy is a logical step in the treatment of RCC. It has been shown that bevacizumab increases the migration of cytotoxic T cells into RCC, thereby potentially enhancing the local immune response induced by atezolizumab [43]. At present, several clinical trials have been initiated in which ICIs are combined with the monoclonal antibody bevacizumab or a tyrosine kinase inhibitor such as axitinib [35].

3.4.2.3. Prostate cancer. In contrast with UCC and RCC, data on the efficacy of ICIs in mCRPC are limited. Although the phase 3 trials did not show benefit for ipilimumab in mCRPC patients [27,28], immune checkpoint blockade may still play a role in a subset of mCRPC patients. In enzalutamide-resistant mCRPC patients, early phase 2 studies have shown efficacy of pembrolizumab when added to enzalutamide [44]. The survival benefit conferred by sipuleucel-T also indicates that immunotherapy-boosting T-cell activity can exert effects in PC patients [4]. In order to enhance T-cell activity in mCRPC, several combination strategies are currently under development, including ICIs combined with anticancer vaccination, PARP inhibition, radium-223, chemotherapy, or enzalutamide [35].

3.4.3. Tumor PD-L1 expression as a predictive marker for efficacy

Overall, the results on the value of PD-L1 expression in UCC and RCC are somewhat conflicting. In the phase 3 trial in advanced UCC patients, the beneficial effect of pembrolizumab over chemotherapy was observed irrespective of PD-L1 expression, which is underscored by the results of previous phase 2 trials with either atezolizumab or nivolumab as second-line treatment in UCC [31,32]. However, high PD-L1 expression, defined as a combined positive score of $\geq$10%, was associated with shorter OS in both chemotherapy- and pembrolizumab-treated UCC patients [23]. In advanced RCC, high PD-L1 expression ($\geq$1%), determined as the percentage of PD-L1–positive tumor cells relative to the total number of tumor cells, was also associated with an unfavorable outcome in both nivolumab- and everolimus-treated patients. These findings suggest that higher PD-L1 expression may be associated with more aggressive tumor behavior [38] and may be a prognostic instead of a predictive marker.

Conflicting results on PD-L1 status in different studies may be related to different targets of the administered agents (PD-1 and PD-L1) and different methods to determine PD-L1 expression including differences in assays, measurements, definition of PD-L1 expression (tumor cells, tumor-infiltrating immune cells, or combined), semiquantitative analyses, and cutoffs. In addition, archival tissue from primary tumors, often collected years prior to metastatic disease, was mostly used to determine PD-L1 expression, whereas PD-L1 expression is a dynamic marker

that may change during several disease stages and sequential therapies. To better understand PD-L1 dynamics, future studies will focus on fresh biopsies from metastatic lesions sequentially obtained during treatment with ICIs.

In clinical practice, tools are needed to select patients for immune checkpoint blockade. In particular, stratification for combination strategies is required, as a number of patients have already benefited from monotherapy and may not benefit from an additional therapy with regard to antitumor effect and higher risk of toxicity. Alternative tools to stratify patients may include genomic subtype, interferon-γ gene expression signature, chemokine expression signature, and mutational load. In addition, positron emission tomography (PET) using ^{89}Zr-labeled ICIs may be valuable, as this noninvasive technique enables drug uptake measurements in tumors, thereby revealing intertumor heterogeneity [45]. Future studies will show whether PET using ^{89}Zr-labeled ICIs may be useful to select patients for treatment with ICIs.

3.4.4. Safety

In UCC and RCC, anti-PD-1 therapy with pembrolizumab and nivolumab, respectively, was associated not only with fewer AEs [23,26], but also with better quality of life than the comparator treatment, that is, chemotherapy and everolimus, respectively [46,47]. However, ipilimumab was associated with a high risk of grade 3–4 toxicity in approximately 40% of mCRPC patients [28], which is specifically associated with inhibition of CTLA-4 signaling. Although blockade of PD-1 and PD-L1 signaling is associated with less toxicity, awareness and expertise for immune-related toxicity such as colitis, endocrinopathies (eg, hypothyroidism, type 1 diabetes), nephritis, and pneumonitis are required as immune-related toxicities can develop rapidly and severely, and, although rare, can even be fatal. In addition, immune-related toxicities can even develop after discontinuation of treatment. Early recognition and treatment are necessary, as these toxicities can be treated adequately with immune-suppressive agents, including high-dose steroids, tumor necrosis factor-alpha blockers (eg, infliximab), and, in case of endocrinopathies, hormone replacement therapy [48]. Although combination strategies with ICIs may enhance efficacy, they are also associated with a higher risk of toxicity.

In rare cases, rapid disease progression is observed after the initiation of ICIs, indicating that ICIs may be harmful for some patients. Hyperprogressive disease during ICIs develops independently of tumor histology and is associated with a poorer OS. So far, no predictive markers for hyperprogressive disease have been identified [49].

For optimal patient selection and counseling, there is a need for tools to identify patients with a high risk of severe toxicity. Since antitumor activity of ICIs has also been observed at low dosages [25] and may even last after early discontinuation of treatment, further optimization of dosage and administration schedules is required, potentially reducing toxicity and costs. To reduce the economic burden of ICIs, future studies should focus on the optimal treatment duration, value of treatment beyond disease progression [50], and development of predictive tools for both tumor response and toxicity.

3.4.5. Strengths and limitations of review

The strengths of this review are the prespecified and systematic literature search, selecting only published RCTs. As a result, only high-quality studies were selected. However, an important limitation is the lack of unpublished results from other phase 3 studies. To overcome this limitation, potential landmark studies, which are not published yet, are mentioned in the Discussion section. In addition, early phase 1 and 2 studies, including those potentially leading to FDA approval, and phase 3 studies are mentioned in the Discussion section and presented in Supplementary Tables 1 and 2.

4. Conclusions

In conclusion, ICIs show superior efficacy and safety outcomes compared with conventional second-line treatment in patients with advanced UCC and RCC. To date, treatment paradigms with ICIs have not shown clinical benefit in mCRPC patients. Ongoing studies, also assessing novel combination strategies with ICIs, may further enhance efficacy in earlier treatment lines and disease stages of urological cancers. Since PD-L1 expression thus far seems to be inconclusive as a predictive marker, future research needs to focus on alternative markers.

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Appendix A. Supplementary data

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