

REVIEW

The role of immunotherapy in urological cancers

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Summary

Immunotherapy is defined as a therapeutic approach that targets or manipulates the immune system. A deeper understanding of the cellular and molecular composition of the tumour environment, as well as the mechanisms controlling the immune system, has made possible the development and clinical investigation of many innovative cancer therapies. Historically, immunotherapy has played an essential role in treating urologic malignancies, while in the modern era, the development of immune checkpoint inhibitors (ICIs) has been critical to urology.

Urothelial carcinoma is a common type of cancer in the genitourinary system, and treatment strategies in this area are constantly evolving. Intravesical and systemic immunotherapeutic agents have begun to be used increasingly frequently in treating urothelial carcinoma. These agents increase the anti-tumour response by affecting the body's defence mechanisms.

Immunotherapeutic agents used in urothelial carcinoma include various options such as BCG, interferon, anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (atezolizumab, avelumab, durvalumab).

Renal cell carcinoma (RCC) has been known for many years as a tumour with unique sensitivity to immunotherapies. The recent emergence of ICIs that block PD-1/PD-L1 (pembrolizumab, nivolumab, atezolizumab) or CTLA4 (ipilimumab) signalling pathways has reestablished systemic immunotherapy as central to the treatment of advanced RCC. In light of randomized clinical trials conducted with increasing interest in the application of immunotherapies in the adjuvant setting, combination therapies (nivolumab/ipilimumab, nivolumab/cabozantinib, pembrolizumab/axitinib, pembrolizumab/lenvantinib) have become the standard first-line treatment of metastatic RCC.

Prostate cancer is in the immunologically "cold" tumour category; on the contrary, in recent years, immunotherapeutic agents have come to the fore as an essential area in the treatment of this disease. Especially in the treatment of castration-resistant prostate cancer, immunotherapeutic agents constitute an alternative treatment method besides androgen deprivation therapy and chemotherapy. Ipilimumab, nivolumab, pembrolizumab, atezolizumab, and Sipuleucel T (Vaccine-based) are promising alternative treatment options.

Considering ongoing randomized clinical trials, immunotherapeutic agents promise to transform the uro-oncology field significantly. In this review, we aimed to summarize the role of immunotherapy in urothelial, renal and prostate cancer in the light of randomized clinical trials.

KEY WORDS: Urological Cancers; Immunotherapy; Clinical Trials.

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INTRODUCTION

The immune system plays a vital role in preventing and defending against cancer. In recent years, significant advances have been made in understanding the immune system and its role in cancer.

Immunotherapy is the golden child of medical oncology and a new approach to cancer treatment (1). The origin of immunotherapy in urological cancers was found in 1976 by Morales *et al.* It started with the introduction of *Bacillus Calmette-Gueren* (BCG) treatment for superficial bladder cancer (BC) (2). This development was followed by the introduction of cytokines such as interferon and interleukin-2 (IL-2) in the treatment of metastatic renal cell carcinoma (mRCC). One of the first reports demonstrating the potential application of immune modulation in cancer treatment was in 1984, when the administration of IL-2 in a patient diagnosed with melanoma reduced the tumour burden. This report has since led to significant interest in the field of immunology and its role in managing various malignancies (3). In 2010, it joined the field of prostate cancer immunotherapy with the approval of the autologous cancer vaccine Sipuleucel-T. More recently, immune checkpoint inhibitors (ICIs) have been introduced with striking results for urology-specific malignancies.

The introduction of ICIs over the past decade has led to significant advances in cancer treatment. Recent advances in immunotherapy treatment promise to significantly transform the field of uro-oncology. In this review, we aimed to summarize the use of immunotherapeutic agents in treating urothelial, renal and prostate cancer in the light of clinical studies.

Urothelial carcinoma

Urothelial carcinoma can occur along the entire urothelium, which anatomically extends from the kidney to the urethra. Urothelial carcinomas can generally be examined under two main headings: upper urinary tract urothelial carcinomas (UTUC) and lower urinary tract urothelial carcinomas. It is often not possible to evaluate these two main topics independently.

BC accounts for 90-95% of urothelial carcinomas, UTUC accounts for 5-10%, and urethral cancer accounts for 1% (4). Today, in most studies on the role of immunotherapy in urothelial carcinoma, BC and UTUC have been evaluated together. BC is the 10th most common cancer in the entire population and the 7th most common cancer in men. BC is responsible for 2.1% of cancer-related deaths and is the 13th deadliest cancer (5). At the time of initial diagno-

sis, 75% of the patients are diagnosed with *non-muscle-invasive bladder cancer* (NMIBC) (Ta, T1, CIS) and 25% with *muscle-invasive bladder cancer* (MIBC) (T2-T4) (6). UTUC is a malignant change in urothelial cells extending from the renal pelvis and calyces to the ureteral orifice. The exact incidence of UTUC is challenging to determine because it is often associated with renal pelvis and ureteral malignancies; they are reported in a single category as renal tumours (7). The estimated incidence of UTUC in Western countries is 2/100,000 cases per year, and its incidence is highest between the ages of 70 and 90 (8).

Immunotherapeutic Agents Used in Urothelial Carcinoma (Intravesical and Systemic)

The main goal of immunotherapeutic agents is to increase the anti-tumour response by acting on the body's defence cells. The main immunotherapeutic agents used in urothelial carcinoma are;

- BCG } BC (Intravesical Therapy)
- Interferon }
- Anti-PD-1 (pembrolizumab, nivolumab) } BC and UTUC
- Anti-PD-L1 (atezolizumab, avelumab, durvalumab) } (Systemic Treatment)

The most frequently and longest-used method of immunotherapy in urothelial carcinoma is intravesical BCG treatment in BC. BCG stimulates the immune system in two separate ways. First, it enhances the anti-tumour response via Toll-like receptors, inflammatory cytokines, and tumour necrosis factors. Secondly, it increases the immune response against the tumour by stimulating CD4+ T Helper cells.

In addition to these mechanisms, BCG is cytotoxic against tumour cells (9). Interferon is an immunotherapeutic agent that can be used alone or in combination with BCG. Its mechanism of action is lymphocyte activation and strengthening of the T-helper type I immune response (10).

Nowadays, systemic immunotherapeutic agents are increasingly used to treat urothelial carcinoma. This group of drugs acts through PD-1 and PD-L1 receptors. The interaction between PD-1 and PD-L1 triggers immune suppressive mechanisms when T cells encounter tumour cells. In this way, PD-L1 checkpoint blockade may interfere with tumour/immune cell interactions for some tumours and thus improve anti-tumour immune responses. There are four immunotherapeutic agents approved by the *Food and Drug Administration* (FDA) for use in patients diagnosed with *metastatic urothelial carcinoma* (mUC) and progressing following platinum-based *chemotherapy* (CT) (pembrolizumab, nivolumab, atezolizumab, avelumab).

Pembrolizumab

In light of the data obtained from the Keynote-057 trial in phase II, The FDA approved the use of pembrolizumab in 2020 for the treatment of BCG-refractory high-risk, NMIBC-diagnosed patients who are not suitable for radical cystectomy or who refuse radical cystectomy (11). This study showed that pembrolizumab treatment has acceptable response rates in first-line treatment in patients with locally advanced or metastatic urothelial cancer with high comorbidity rates who cannot receive platinum-based CT. Use with this indication was approved by the FDA in 2017 (12).

In a phase II trial (PURE-01) conducted on patients diagnosed with MIBC, regardless of their suitability for platinum-based CT, pembrolizumab neoadjuvant therapy alone has been shown to reduce tumour downstaging at radical cystectomy pathology (13). Another study showed that adding pembrolizumab to platinum-based CT in neoadjuvant treatment improved pathological response rates (14). In another study, the effectiveness of maintenance treatment with pembrolizumab was evaluated in patients who were given platinum-based CT in first-line treatment and stable disease was achieved. There was a benefit in *progression-free survival* (PFS) (5.4 vs 3 mo., $p = 0.04$) (15). In another phase III *randomized controlled trial* (RCT), pembrolizumab monotherapy in second-line treatment showed improvement in *overall survival* (OS) compared to CT (10.3 vs 7.4 mo., $p = 0.002$) (16). However, there are also studies reporting that adding pembrolizumab to standard adjuvant CT in patients with advanced urothelial carcinoma does not increase treatment effectiveness (12).

Nivolumab

According to a phase II single-arm trial results in 270 patients diagnosed with surgically unresectable locally advanced or mUC, an *objective response rate* (ORR) of 19.6% was achieved in patients receiving nivolumab monotherapy. It was shown to provide clinical benefit regardless of PD-L1 expression. Based on the results of this study, the PD-1 inhibitor nivolumab has been approved for second-line treatment in patients diagnosed with mUC who have not received an adequate response to platinum-based CT (17). According to the phase I-II trial results conducted in patients with mUC who did not respond adequately to platinum-based CT, nivolumab/ipilimumab combination therapy had an ORR of up to 38% (18). According to EAU guidelines, adjuvant nivolumab treatment is recommended for patients with pT3, pT4, and pN+ UTUC who cannot receive adjuvant platinum-based CT (19).

In the CheckMate-274 trial, 709 patients with a high risk of recurrence and diagnosed with locally advanced urothelial cancer were randomized. In this study, adjuvant nivolumab was given to one group and placebo to the other group, and a statistically significant improvement in *disease-free survival* (DFS) was detected in the treatment arm (10.8 vs 20.8 mo. $p < 0.001$) (20). Based on data from the study, nivolumab was approved by the FDA for the adjuvant treatment of urothelial carcinoma.

Atezolizumab

Atezolizumab is a monoclonal antibody that inhibits anti-PD-L1. In light of the data from RCTs, the use of atezolizumab in the first-line treatment of patients diagnosed with locally advanced or mUC who are not suitable for platinum-based CT and in the second-line treatment of patients whose disease progresses despite platinum-based CT and who cannot undergo surgical resection has been approved by the FDA and *European Medicines Agency* (EMA) (21, 22). The recently published ABACUS study evaluated the effectiveness of neoadjuvant atezolizumab treatment in patients unsuitable for cisplatin treatment. According to the results of this study, 2-year DFS and OS were reported as 68% and 77%, respectively. In another single-arm phase II clinical study, in the neoadjuvant treatment of patients with cT2-

T4aN0M0 stage tumours, the addition of atezolizumab to gemcitabine-cisplatin combination has been shown to provide a relapse-free survival advantage (23).

In the multicenter randomized controlled phase III study (IMvigor 130), 1213 patients with locally advanced or mUC were divided into three groups. Survival analyses were compared by giving platinum-based CT/atezolizumab to group A, atezolizumab to group B, and platinum-based CT/placebo to group C. The median OS times of patients in groups A and C were reported as 16 mo. and 13.4 mo., respectively, and there was a statistically significant difference between both groups (0.83, 95% CI 0.69-1, p = 0.027). The median OS times of patients in groups B and C were 15.7 mo., and 13.1 mo., respectively, and it was reported that there was no statistically significant difference between the two groups. As a result, it has been reported that adding atezolizumab to platinum-based CT in first-line treatment provides a survival advantage in patients diagnosed with mUC (24).

Avelumab

Avelumab is a humanized monoclonal antibody that acts by binding to PD-L1, similar to atezolizumab and durvalumab. In the JAVELIN Bladder 100 trial, patients with locally advanced/mUC whose disease was stable or had clinical improvement after 4-6 courses of platinum-based CT were divided into two groups. One group was given supportive treatment, and the other group was given avelumab treatment. In the avelumab arm, a statistically significant improvement in OS was detected (14.3 vs 21.4 mo.) (25). Based on the data of this study, the use of avelumab in maintenance therapy in patients with locally advanced or mUC has been approved by the FDA (26). In the EAU 2023 guideline, maintenance avelumab treatment is strongly recommended in patients diagnosed with mUC whose disease is stable after first-line platinum-based CT (19).

Durvalumab

Durvalumab is a humanized monoclonal antibody that

acts by binding to PD-L1 and blocking the PD-1-CD80 interaction. It received accelerated approval from the FDA in 2017 for patients with urothelial carcinoma who did not respond adequately to neoadjuvant or adjuvant treatment (26).

The DANUBE phase III clinical study compared durvalumab monotherapy with durvalumab/tremelimumab and platinum-based CT. The superiority of the tried treatments over CT has not been determined (27). After the report of the DANUBE study was published, the indication of durvalumab in BC was withdrawn (28). Clinical trials of various urothelial cancer immune therapies were summarized in Table 1 (29).

Role of immunotherapy in urothelial carcinoma

Urothelial carcinoma is a common type of cancer in the genitourinary system, and treatment strategies in this area are constantly evolving. Agents used in immunotherapy in urothelial carcinoma include various options such as BCG, interferon, anti-PD-1 (nivolumab, pembrolizumab), anti-PD-L1 (atezolizumab, durvalumab, avelumab). These agents increase the anti-tumour response by affecting the body's defence mechanisms. They show effectiveness at different treatment stages in BC and UTUC.

Cisplatin-based CT has been used as standard therapy in the treatment of urothelial carcinoma for many years. The results of clinical studies with systemic immunotherapeutic agents show that the use of immunotherapeutic agents in treating urothelial carcinoma is becoming increasingly widespread and is considered an effective alternative in patients who are resistant or unsuitable for platinum-based CT. Comparisons between these agents should consider clinical outcomes such as ORR, OS, and DFS. When determining the areas of use and advantages of each agent, the characteristics of the patients and their pre-treatment conditions should be considered. The usage recommendations regarding immunotherapeutic agents employed in urothelial carcinoma in the EAU guidelines are presented in Table 2 (19).

Immunotherapy has become an increasingly important

Immunotherapeutic drug	Trial name	Clinical indication	FDA approval	Clinical outcome	References
Atezolizumab	IMvigor210	Second-line mUC, after platinum CT	May 2016	ORR 15%	Rosenberg 2016
Atezolizumab	IMvigor210	First-line mUC, platinum-ineligible	April 2017	ORR 23%	Balar 2017
Nivolumab	CheckMate-275	Second-line mUC	February 2017	RR 19.6%	Sharma 2016
Durvalumab	DANUBE	Second-line mUC		ORR 26%	Powles 2020
Pembrolizumab	Keynote-045	Second-line Advanced UC	May 2017	Median OS 10.3 mo.	Bellmunt 2017
Pembrolizumab	Keynote-052	First-line mUC, platinum-ineligible	May 2017	ORR 24%	Balar 2017 and Vuky 2020
Pembrolizumab	Keynote-057	Recurrent NMIBC	January 2020	CRR 41%	Balar 2021
Avelumab	JAVELIN Bladder 100	Maintenance, mUC	June 2020	Median OS 21 vs 14 mo. of the control	Powles 2020
Nivolumab	Checkmate-274	Adjuvant, MIBC	August 2021	Median DFS 20.8 vs 10.8 mo. of the control	Bajorin 2021

Table 1. Clinical trials of varying treatment plans for urothelial carcinoma (29).

The PD-L1 inhibitors atezolizumab and nivolumab and the PD-1 inhibitor pembrolizumab have been approved for patients whose disease has progressed despite platinum-based CT and who have not received prior immunotherapy.
The PD-L1 inhibitor atezolizumab and the PD-1 inhibitor pembrolizumab are approved for patients with advanced or mUC unsuitable for first-line platinum-based CT.
Offer patients with PD-L1-positive tumours the checkpoint inhibitors pembrolizumab or atezolizumab.
Offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease who are ineligible for or refuse adjuvant cisplatin-based CT.
For patients who achieve stable disease after first-line platinum-based CT, use maintenance treatment with the PD-L1 inhibitor avelumab.

Table 2. Summary of the use of immunotherapeutic agents in the treatment of urothelial carcinoma according to EAU guidelines (19).

treatment modality in urothelial carcinoma. However, further RCTs and long-term follow-up periods will strengthen our knowledge of the effectiveness and safety of these agents. In the future, the role of immunotherapy will be better understood by focusing on more specific treatment strategies and personalized treatments for disease subtypes.

Renal cell carcinoma

Renal cell carcinoma (RCC) accounts for 2-3% of adult cancers, although its incidence is increasing in Western countries (30). According to the *American Cancer Society* data for 2023, it is predicted that approximately 81,800 new cases will be diagnosed in the United States, and 14,890 of the patients will die from kidney cancer (31). Approximately 70% of kidney cancer cases are diagnosed at a localized or locally advanced stage, and the standard of care for these patients is radical or partial nephrectomy (32). Despite this, approximately 35% of patients initially present with advanced or *metastatic RCC* (mRCC), and 30% of patients presenting with localized disease experience recurrence (33).

RCC has been known for many years as a tumour with unique sensitivity to immunotherapies (34). Systemic first-line treatment for mRCC is rapidly evolving, with multiple approved strategies and new clinical trials ongoing. The introduction of mainly new ICIs has led to a paradigm shift in the treatment of this disease (35). RCC immunotherapy agents inhibit receptor-ligand pairs that modulate the congenital or acquired immune system. These molecular pairs, known as immune checkpoints, include PD-1 and PD-L1 and CTLA4 multiple ligands, including *cytotoxic T lymphocyte-associated protein 4* (CTLA4), CD80, and CD86 (36). The recent emergence of ICIs that block the PD-1/PD-L1 or CTLA4 signalling pathways has re-established systemic immunotherapy as central to the medical treatment of advanced RCC, resulting in increasing interest in the application of immunotherapies in the adjuvant setting. Many RCTs are being conducted (34).

Treatment of locally advanced RCC (Neoadjuvant/adjuvant therapy)

Given the recent success of ICIs in mRCC, these therapies are now being studied in the (neo)adjuvant setting to treat localized RCC. The rationale for using neoadjuvant ICIs stems from the hypothesis that intact kidney tissue may provide a source of antigen for the persistent cancer-specific immune response (37). The advantage of adjuvant immunotherapy is that it can maintain efficacy and eliminate micrometastases even after treatment discontinuation (38). This section aims to provide an overview of completed or ongoing clinical trials on adjuvant treatment of RCC, accompanied by the 2023 EAU guideline and current reviews.

Keynote-564 Trial (Pembrolizumab)

Pembrolizumab is a humanized monoclonal IgG4 antibody and is also a PD-1 inhibitor. Keynote-564 study included intermediate-high risk (pT2, grade 4 or sarcomatoid, N0, M0 or pT3, any grade, N0, M0) or high risk of recurrence (pT4, any grade, N0, M0 or any pT, any

grade, pN+, M0, or no evidence of disease after resection of oligometastatic sites < 1 year after nephrectomy or NED). It was a phase III clinical trial in which pembrolizumab (17 cycles of 3 weeks of treatment) was randomized vs placebo as adjuvant therapy in 994 patients (39). In this study, M1 NED was defined as complete resection of oligometastasis simultaneously or within one year after nephrectomy. At a median follow-up of 24 mo., DFS was 77.1% vs 68.1% (HR 0.68, 95% CI: 0.53-0.87; $p = 0.0010$), and this rate was maintained at 30 mo. follow-up. In subgroup analyses of the study, patients with M0 tumours (HR 0.74, 95% CI: 0.57-0.96) and patients with M1 tumours with NED (HR 0.29, 95% CI: 0.12-0.69) DFS benefit was observed and the DFS benefit of pembrolizumab was observed in patients with PD-L1 *combined positive score* (CPS) ≥ 1 (HR 0.67, 95% CI 0.51-0.88) compared to patients with PD-L1 CPS < 1 (HR 0.83, 95% CI 0.45-1.51). In this context, Keynote-564 is the first study of adjuvant ICI to report a positive primary endpoint of DFS. Median OS was not reached in both groups. The most common *adverse effects* (AEs) in the pembrolizumab group were fatigue (1%), diarrhoea (1.6%) and skin rash (0.8%), and grade 4-5 AEs were not observed in both study arms (40).

The study's results led to FDA approval of single-agent pembrolizumab for the adjuvant treatment of patients with resected ccRCC, intermediate-high risk, or high risk of recurrence. In 2021, the EAU RCC guideline issued a weak recommendation for pembrolizumab as adjuvant therapy for ccRCC with intermediate to high risk of recurrence, as defined by the study, until final OS data and results from other studies are available.

Keynote-564 data should also be interpreted in the context of several significant randomized phase III clinical trials investigating RCC treatment with immunotherapy in the adjuvant setting, pending or ongoing for data to be published. These include clinical studies IMmotion010 (NCT03024996), CheckMate 914 (NCT03138512), and PROSPER (NCT03055013) (Table 3) (41). Not all data published in peer-reviewed journals are available for these clinical studies, but limited data were presented for IMmotion010, CheckMate 914, and PROSPER at the European Society of Medical Oncology (ESMO) Congress in September 2022.

IMmotion010 Trial (Atezolizumab)

IMmotion010 is a randomized placebo-controlled phase III trial evaluating the PD-L1 inhibitor atezolizumab as an adjuvant treatment option in 778 RCC patients with a clear cell or sarcomatoid component and a high risk of recurrence.

IMmotion010 is the first adjuvant ICI study to investigate the efficacy of a PD-L1 inhibitor in terms of DFS and OS in RCC. However, the study did not reach its primary endpoint, with a mean DFS of 57.2 mo. in the atezolizumab arm vs 49.5 mo. in the placebo arm [HR 0.93 95% CI 0.75-1.15; $p = 0.495$] (42). No DFS improvement was detected with atezolizumab in any investigational subgroups. Grade ≥ 3 AEs were reported in 27% and 21% of patients in the atezolizumab and placebo groups, respectively. The most common grade 3-4 AEs were hypertension, hyperglycemia (3% vs 2%), and diarrhoea (1% vs 2%), observed in 2% vs

Table 3.
Clinical trials investigating immunotherapy in the adjuvant setting in RCC (41).

Trial identifier	Therapeutic agent	Inclusion criteria (tumour stage and grade)	Histology	The primary endpoint(s) and results	Estimated primary completion date
Keynote-564 NCT03142334	Pembrolizumab 200 mg IV every 3 weeks for up to 17 cycles	pT2 NO (G4 only), pT3a NO (G3-4), pT3b-T4 NO, pTx N1, M1 NED	ccRCC might include sarcomatoid features	DFS for treatment vs placebo: (HR 0.68, 95% CI 0.53-0.87; P=0.0010)	Dec 2020
IMmotion010 NCT03024996	Atezolizumab 1.200 mg every 21 days for 1 year	pT2 NO (G4 only), pT3a NO (G3-4), pT3b-T4 NO, pTx N1	RCC including clear cell or sarcomatoid component	DFS (assessed through IRF) for atezolizumab vs surgery alone: (HR 0.97, 95% CI 0.74-1.28; P=0.43)	May 2022
CheckMate 914 NCT03138512	Part A: Nivolumab 240 mg IV every 2 weeks, up to 12 doses, ipilimumab 1 mg/kg IV, up to four doses given in cycles 1, 4, 7 and 10 Part B: Nivolumab 240 mg intravenously every 2 weeks, up to 12 doses	pT2a NO (G3-4), pT2b-4 NO, pT(any) N1	ccRCC might include sarcomatoid features	DFS (assessed through BICR) for nivolumab or ipilimumab vs placebo Part A: (HR 0.92, 95% CI 0.71-1.19; P=0.5347) Part B: results pending	July 2024
PROSPER NCT03055013	Nivolumab 480 mg IV, one dose given before surgery, up to nine doses given every 28 days following surgery	pT2-4 NO, pT(any) N1	ccRCC might include sarcomatoid features	EFS for nivolumab (HR 0.97, 95% CI 0.74-1.28; P=0.43)	Nov 2023
RAMPART NCT03288532	Part A: Durvalumab 1.500 mg every 28 days for 1 year Part B: Durvalumab 1.500 mg every 28 days for 1 year + tremelimumab 75 mg on weeks 1 and 4	Leibovich score 3-11	All histological subtypes included	DFS, OS (results pending)	July 2024

BICR: Blinded independent central review; ccRCC: Clear cell renal cell carcinoma; DFS: Disease-free survival; EFS: Event-free survival; G: Tumour grade; IRF: Independent review facility; IV: Intravenously; N: Nodal stage; NED: No evidence of disease; OS: Overall survival; p: Pathological; T: Tumour stage.

15% of patients in the atezolizumab vs the placebo group, respectively (43).

CheckMate 914 Trial (Nivolumab/Ipilimumab)

CheckMate 914 is a phase III randomized placebo-controlled two-part study examining the effectiveness of adjuvant nivolumab and nivolumab/ipilimumab in patients with clear cell RCC at high risk of recurrence after nephrectomy (44). Results of the part A study were reported at ESMO Congress 2022; 816 patients were randomized to nivolumab/ipilimumab or placebo.

The study evaluated 12 cycles of nivolumab at 240 mg every two weeks for six mo. plus ipilimumab at 1 mg/kg every six weeks for four cycles vs placebo as adjuvant therapy for 816 patients. At a median follow-up of 37 mo., DFS was similar between patients in both arms, and the study did not meet its primary endpoint (HR 0.92, 95% CI 0.71-1.91; p = 0.5347). OS analysis could not be performed due to a hierarchical study design. The incidence of treatment-related grade 3 AEs was 29% in the nivolumab/ipilimumab group and 2% in the placebo group, with 4 (1%) deaths considered to be related to combination therapy. The high discontinuation rate of 33% in CheckMate 914 is concerning and may negatively impact the study's effectiveness (45, 46). Based on these data, ICI/ICI combination therapy appears to increase risk rather than benefit and is unlikely to be introduced into clinical practice.

PROSPER Trial (Peroperative Nivolumab)

PROSPER is a perioperative phase III randomized study comparing neoadjuvant nivolumab (1 cycle) followed by radical/partial nephrectomy and postsurgical follow-up with the group receiving nine doses of adjuvant nivolumab (480 mg IV every four weeks).

The study included 819 high-risk patients, defined as \geq T2 or T any pN+ RCC of any histology, for whom radical/partial nephrectomy was planned. Most patients had clear cell histology (78%), 8% had papillary, and 7% had

chromophobe histology. The primary endpoint of the study was relapse-free survival. An interim analysis at 16 mo. of follow-up showed that the addition of perioperative nivolumab did not improve relapse-free survival compared with standard of care surgery, and the study was stopped early due to lack of efficacy (HR 0.97 [95% CI: 0.74-1.28], p = 0.43) (37). As a result, single-agent neoadjuvant immunotherapy does not currently have any role in the treatment of ccRCC.

Treatment of mRCC

(ICI Monotherapy/Combination Therapy)

Several positive phase III trials of ICI/ICI or ICI/tyrosine kinase inhibitor (TKI) dual combinations have established the current treatment paradigm for mRCC, all demonstrating superior clinical benefits, including OS, compared to sunitinib monotherapy (47).

ICI combination therapies have become the standard first-line treatment of mRCC. These combinations include a dual ICI blockade or a single ICI combined with a TKI (48). A direct comparison between combination regimes is not currently available; therefore, the choice of first-line treatment for each patient is based on numerous individualized variables, including comorbidities, disease location and burden, and psychosocial and economic factors (49). In recent years, advances have been seen in the diagnosis, management, and treatment of the ccRCC subtype resulting from various randomized and prospective phase III clinical studies, including combined therapy effective on immune checkpoints such as PD-1, CTLA-4, and PDL-1 (CheckMate-9ER, Keynote-426, CLEAR and CheckMate-214).

ICI monotherapy in the treatment of mRCC

Nivolumab is a humanized monoclonal PD-1 antibody approved for various metastatic tumours. The use of the drug in treating mRCC was based on data from CheckMate-025 (NCT01668784). In this phase III clinical trial comparing nivolumab with everolimus in the

treatment of mRCC with clear cell subtype refractory to *vascular endothelial growth factor* (VEGFR)-targeted therapy, nivolumab had longer OS, better quality of life and lesser grade 3-4 AEs than everolimus. Despite the OS advantage of nivolumab, no PFS advantage was detected in this study (50). PFS does not appear to be a reliable outcome indicator for PD-1 therapy in RCC. No RCTs supporting single-agent ICIs in treatment-naïve patients have been reported.

Keynote-427 (NCT02853344), published in 2021, is a prospective phase II single-arm clinical study using pembrolizumab in mRCC patients consisting of two cohorts (ccRCC and nccRCC) (51). The nivolumab study included patients who had received prior treatment, while the pembrolizumab study included patients who had not received prior treatment. Moreover, the subtypes included in these clinical studies and their representation percentages differed. Therefore, each study's subtype that responds better to immunotherapy differs because the populations studied are heterogeneous (52). Given these results and without randomized phase III data, single-agent ICI therapy is not recommended as an alternative in the first-line treatment setting (48).

Combination therapy in the treatment of mRCC (ICI/ICI-ICI/TKI)

The beneficial results obtained in clinical trials with immunotherapy treatment have allowed combining such treatments with others using different mechanisms to enhance immunomodulatory effects (53). The contemporary standard of care for metastatic clear cell RCC (cc-mRCC) is the use of TKIs dually (ICI/ICI) or in combination with ICI (54). In the first-line treatment of cc-mRCC, ICI and VEGFR-targeted TKIs have been shown to improve OS compared to TKI monotherapy in randomized studies. However, each combination regimen is thought to be highly effective, with ORR ranging from 42% to 71% (55-58).

Several studies have evaluated combination therapies in cc-mRCC and demonstrated improvement in overall response rate, PFS, and OS compared to standard treatment (sunitinib). These studies were Checkmate-9ER (58) (nivolumab/cabozantinib), Keynote426 (57) (pembrolizumab/axitinib), and CLEAR (55) (pembrolizumab/lenvatinib), all of which focused on ccRCC and did not include less common subtypes of kidney cancer. In recent years, new prospective trials have been conducted to evaluate the effectiveness of ICI/TKI combinations in less common subtypes (Table 4) (59).

CheckMate-9ER Trial (Nivolumab/Cabozantinib)

CheckMate-9ER is a phase III RCT comparing nivolumab/cabozantinib (n = 323) combination therapy with sunitinib (n = 328) in 651 treatment-naïve patients diagnosed with cc-mRCC. During a mean follow-up period of 32.9 mo., the median OS was 37.7 mo. in the group treated with nivolumab/cabozantinib and 34.3 mo. in the patients treated with sunitinib, and as a result, no statistically significant difference was observed. While the median PFS was 16.6 mo. in the group receiving nivolumab/cabozantinib treatment, PFS was 8.3 mo. in sunitinib treatment alone. As a result, a statistically sig-

nificant survival increase in PFS was observed in favour of combination treatment.

Treatment-related AEs (> grade 3) occurred in 61% of patients receiving nivolumab/cabozantinib and 51% receiving sunitinib alone. Treatment-related death was reported in one patient in the nivolumab/cabozantinib arm and two patients in the sunitinib arm (58).

Keynote-426 Trial (Pembrolizumab/Axitinib)

The Keynote-426 trial compared the outcomes of pembrolizumab/axitinib combination therapy with sunitinib monotherapy in 861 treatment-naïve cc-mRCC patients. During a median follow-up of 42.8 mo., pembrolizumab/axitinib combination therapy showed an OS advantage for the intention to treat group (HR: 0.73, 95% CI: 0.60-0.88, p < 0.001).

Median OS was 45.7 months in the pembrolizumab/axitinib arm and 40.1 months in the sunitinib arm, and a PFS advantage was also demonstrated in the combination arm in IMDC subgroups. Treatment-related AEs (> grade 3) occurred in 63% of patients receiving combination therapy and 58% of patients receiving sunitinib. Treatment-related deaths were reported at a rate of approximately 1% in both arms (57).

CLEAR Trial

(Everolimus/Lenvatinib-Pembrolizumab/Lenvatinib)

The CLEAR randomized phase III clinical trial compared everolimus/lenvatinib or pembrolizumab/lenvatinib combination therapy with sunitinib alone in treating advanced RCC. CLEAR randomized a total of 1,069 patients (in a 1:1:1 ratio) to pembrolizumab/lenvatinib (n = 355), everolimus/lenvatinib (n = 357), and sunitinib (n = 357). In the study, the pembrolizumab/lenvatinib arm reached its primary endpoint compared to sunitinib, with a median PFS of 9.2 mo. vs 23.9 mo. (HR: 0.39, 95% CI: 0.32-0.49, p < 0.001). Compared to sunitinib, OS was significantly improved with pembrolizumab/lenvatinib (HR: 0.66, 95% CI: 0.49-0.88, p = 0.005). Efficacy was observed in all IMDC risk groups, regardless of PD-L1 status. Grade 3 or higher AEs associated with treatment with pembrolizumab/lenvatinib were 72%. Treatment-related deaths occurred in four patients in the pembrolizumab/lenvatinib arm and one patient in the sunitinib arm (55).

CheckMate-214 Trial (Ipilimumab/Nivolumab)

The combination of ipilimumab/nivolumab, targeting anti-CTLA4 and anti-PD-1, showed improvements in PFS and OS compared to sunitinib based on data from the phase III CheckMate-214 trial, which led to its approval by the *International Metastatic RCC Database Consortium* (IMDC) for the treatment of low and intermediate risk cc-mRCC. At 60 mo. of follow-up in the CheckMate-214 trial, OS rates were 43% in the ipilimumab/nivolumab arm and 31% in the sunitinib arm, respectively. Grade 3-4 toxicity was reported in 46% and treatment-secondary death in 1.5% in the ipilimumab/nivolumab arm (56). Therefore, immune combination therapy should be applied within the scope of a multidisciplinary team in centres with appropriate supportive care experience (Table 5) (48).

Table 4.
First-line immune checkpoint inhibitor combination trials for clear-cell RCC (59).

Study	N	Experimental arm	Primary endpoint	Risk groups	PFS (mo) Median (95% CI) HR	OS (mo) Median (95% CI) HR
CheckMate 9ER NCT03141177 Median follow-up of 23.5 mo.	651	NIVO 240 mg fixed dose IV every 2 wk plus CABO 40 mg PO daily vs SUN 50 mg PO QD 4/2 wk	PFS in the ITT by BICR	IMDC FAV 22% IMD 58% POOR 20% MSKCC Not determined	(ITT) NIVO + CABO: 17.0 (12.6-19.4) SUN: 8.3 (6.9-9.7) HR: 0.52 (95% CI: 0.43-0.64) p < 0.0001	(ITT) NIVO + CABO: NR (NE) SUN: 29.5 (28.4-NE) HR: 0.66 (98.9% CI: 0.50- 0.87) p = 0.0034
Keynote-426 NCT02853331 Median follow-up of 42.8 mo.	861	PEMBRO 200 mg, IV Q3W plus AXI 5 mg, PO BID vs SUN 50 mg PO QD 4/2 wk	PFS and OS in the ITT by BICR	IMDC FAV 31% IMD 56% POOR 13% MSKCC Not determined	(ITT) PEMBRO + AXI: 15.7 (13.6-20.2) SUN: 11.1 (8.9-12.5) HR: 0.68 (95% CI: 0.58-0.80) p < 0.0001	(ITT) PEMBRO + AXI: 45.7 (43.6-NR) SUN: 40.1 (34.3-44.2) HR: 0.73 (95% CI: 0.60-0.88) p = 0.001
CLEAR NCT02811861 Median follow-up of 33.4 mo.	712	PEMBRO 200 mg IV Q3W plus LEN 20 mg PO QD vs SUN 50 mg PO QD 4/2 wk	PFS in the ITT by BICR	IMDC FAV 31% IMD 59% POOR 9% NE 1% MSKCC FAV 27% IMD 64% POOR 9%	(ITT) PEMBRO + LEN: 23.9 (20.8-27.7) SUN: 9.2 (6.0-11.0) HR: 0.39 (95% CI: 0.32-0.49) p > 0.001	(ITT) PEMBRO + LEN: NR (41.5-NE) SUN: NR (38.4-E) HR: 0.72 (95% CI: 0.55-0.93) p = 0.005
Checkmate 214 NCT02231749 Median follow-up of 60 mo.	1096	NIVO 3 mg/kg plus IPI 1 mg/kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W vs SUN 50 mg PO QD 4/2 wk	PFS and OS in the IMDC intermediate and poor risk population by BICR	IMDC FAV 23% IMD 61% POOR 17% MSKCC Not determined	(IMDC IMD/poor) NIVO + IPI: 11.6 (8.4-16.5) SUN: 8.3 (7.0-10.4) HR: 0.73 (95% CI: 0.61-0.87)	(IMDC IMD/poor) NIVO + IPI: 47.0 (35.4-57.4) SUN: 26.6 (22.1-33.5) HR: 0.68 (0.58-0.81) p < 0.0001
JAVELIN 101 NCT02684006 Median follow-up 19 mo.	886	AVE 10 mg/kg IV Q2W plus AXI, 5 mg PO BID vs SUN 50 mg PO QD 4/2 wk	PFS in the PD-L1+ population and OS in the ITT by BICR	IMDC FAV 22% IMD 62% POOR 16% MSKCC FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI: 13.8 (10.1-20.7) SUN: 7.0 (5.7-9.6) HR: 0.62 (95% CI: 0.49-0.78) p < 0.0001	(PD-L1+) AVE + AXI: NR SUN: 28.6 (27.4-NE) HR: 0.83 (95% CI: 0.60-1.15) p = 0.1301
IMmotion151 NCT02420821 Median follow-up 24 mo.	915	ATEZO 1200 mg fixed dose IV plus BEV 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs SUN 50 mg PO QD 4/2 wk	PFS in the PD-L1+ population and OS in the ITT by IR	IMDC Not determined MSKCC FAV 20% IMD 69% POOR 12%	(PD-L1+) ATEZO + BEV: 11.2 (8.9-15.0) SUN: 7.7 (6.8-9.7) HR: 0.74 (95% CI: 0.57-0.96) p = 0.0217	(ITT) ATEZO + BEV: 36.1 (31.5-42.3) SUN: 35.3 (28.6-42.1NE) HR: 0.91 (95% CI: 0.76-1.08) p = 0.27

BATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; LEN = lenvatinib; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = progression-free survival; PITT = PFS intention-to-treat; PO = by mouth; Pts = patients; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; wk = weeks.

Table 5.
Updated EAU Guidelines recommendations for the first-line treatment of cc-mRCC (48).

	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	nivolumab/cabozantinib ^[1b] pembrolizumab/axitinib ^[1b] pembrolizumab/lenvatinib ^[1b]	sunitinib* ^[1b] pazopanib* ^[1b]
IMDC intermediate and poor risk	nivolumab/cabozantinib ^[1b] pembrolizumab/axitinib ^[1b] pembrolizumab/lenvatinib ^[1b] nivolumab/ipilimumab ^[1b]	cabozantinib* ^[2a] sunitinib* ^[1b] pazopanib* ^[1b]

IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium.
*pazopanib for intermediate-risk disease only.
[1b] = based on one randomised controlled phase III trial.
[2a] = based on a well-designed study without randomisation or subgroup analysis of a randomised controlled trial.

Immunotherapy in Metastatic Non-clear cell RCC

Among diagnosed renal tumours, clear cell RCC is the most common type (80%); the remaining 20% is *non-clear cell renal cell carcinoma* (nccRCC), a rare and histopathologically heterogeneous group of tumours (31). In most kidney cancer trials, nccRCC tumours are not included or only marginally represented. Therefore, little is known about the best management of nccRCC types. Treatment options for nccRCC are limited as few specific studies are available. Although nccRCC subtypes have not been included in pivotal ccRCC clinical trials, their treatments are based on data from ccRCC clinical trials. No phase III clinical trials have been reported for patients diagnosed with metastatic nccRCC (60). The EAU 2023 guideline made a weak recommendation for pembrolizumab alone or pembrolizumab/lenvatinib or nivolumab/cabozantinib treatment for papillary RCC patients based on small single-arm studies.

Conducting clinical trials on more patients with different histologies and investigating new biomarkers that will help predict response to treatment remain questions that researchers need to answer in the treatment of nccRCC. Undoubtedly, future clinical trials will play a key role in treating these patients (61).

Role of Immunotherapy in RCC

Immunotherapy is the cornerstone of mRCC treatment. These agents are currently used in clinical trials in the (neo)adjuvant setting for high-risk localized RCC to achieve primary tumour response, reduce the risk of recurrence, and improve long-term oncological outcomes. In addition to shrinking the primary tumour and enabling nephron-sparing surgeries, neoadjuvant ICIs could theoretically generate a durable immune response given the presence of antigens in intact kidney tissue (32). However, whether neoadjuvant ICI/TKI use is associated with long-term DFS or OS benefit is not yet known.

Immunotherapy treatment in the adjuvant setting is promising, but the risk of disease recurrence remains high. In the Keynote-564 (39) trial, relapse was observed in 22.7% of patients in the pembrolizumab group. The heterogeneity observed between adjuvant ICI studies may include differences in study groups (e.g., the inclusion of M1 NED in Keynote-564 and IMmotion010 and no inclusion in CheckMate 914), drug tolerability, and factors that may affect adequate drug distribution (e.g., Checkmate 914). (43% medication discontinuation rate) may contribute to this heterogeneity. Additionally, including T2a/grade 3 patients in the CheckMate 914 study, who were assumed to have lower malignancy than the other two, may have significantly affected the study results. These differences in inclusion criteria between ongoing clinical trials may affect the risk of disease recurrence and, ultimately, negatively contribute to disease progression. Additionally, differences in treatment-limiting toxicity rates across studies may alter the treatment received and impact DFS results. One of the reasons why the IMmotion010 (43) trial failed to meet the primary endpoint compared to the Keynote-564 study may be that the anti-PD-1 and PD-L1 antibodies used in the studies showed a difference in efficacy. Liu *et al.* discuss the incidence of *renal adverse events* (rAEs) for ICI-based reg-

imens vs targeted or chemotherapies, including 95 RCTs totalling more than 40,000 patients (62). Grade 3 or higher rAEs incidence was 4.3%. Among ICI monotherapies, anti-CTLA4 was found to have a higher risk of \geq grade 3 rAEs compared to anti-PD-1/PD-L1. Diagnostic and management challenges for ICI-associated toxicities highlight the value of a multidisciplinary approach to the management of high-grade rAEs.

Currently, there are no standard or validated biomarkers to help treat RCC. Discovering one or more of these biomarkers is probably at the top of every researcher's wish list. If biomarkers can be identified in patients who have not received CT or at an earlier time when cancer is diagnosed, opportunities for the use of neoadjuvant or early adjuvant immunotherapy will increase.

Although DFS benefit in the adjuvant setting is a meaningful primary endpoint supported by the FDA and the European Medical Association, treatment-related toxicities should not be ignored by patients and clinicians. While the DFS benefit of pembrolizumab was maintained in long-term follow-up, against the background of many negative adjuvant clinical trials, clinicians await the study's long-term OS data before recommending adjuvant pembrolizumab to patients. In the meantime, adjuvant pembrolizumab remains a reasonable option for patients with high-risk RCC in light of the EAU 2023 guideline. When discussing adjuvant treatment options with a patient with high-risk RCC, clinicians should discuss available data supporting the use of adjuvant ICIs and outline questions that will be answered over time. Until we get answers to these crucial questions, adjuvant immunotherapy application appears to be a personalized decision.

Prostate cancer

Prostate cancer is the 2nd most common type of cancer in men and ranks 5th among cancer-related deaths. Prostate cancer is the most frequently diagnosed cancer in 112 countries in the world, followed by lung cancer in 36 countries and colorectal cancer in 11 countries (63). The widespread use of *prostate-specific antigen* (PSA) has led to a significant increase in the incidence of prostate cancer. This has resulted in increased detection of indolent disease and decreased detection of metastatic prostate cancer (64). The most important risk factors in the aetiology of prostate cancer are, as many studies have shown, advanced age, geography, ethnicity, family history and genetic predisposition (65-67).

In recent years, immunotherapy has emerged as an essential field in the treatment of prostate cancer. Prostate cancer is an immunological tumour to a lesser extent compared to other types of urological cancer. The reasons for this are that prostate cancer has a low rate of tumour mutation, PD-L1 expression and T-cell infiltration (68). Therefore, although immunotherapy has a limited place in prostate cancer, some immunotherapeutic agents have become part of standard treatment in the past few years. It provides an alternative treatment method, especially for *castration-resistant prostate cancer* (CRPC), in addition to standard methods such as androgen deprivation therapy and CT (69, 70). A particular subgroup of patients, including mismatch repair (dMMR) deficient, CDK12-mutated tumours in addition to high PD-L1 tumour expression, tumour muta-

tional burden, and *microsatellite instability* (MSI), have recently shown good responses to ICI therapy (68, 71). The main immunotherapeutic agents used in prostate cancer are:

- Ipilimumab
- Nivolumab
- Pembrolizumab
- Atezolizumab
- Sipuleucel-T (Vaccine based)

Ipilimumab

Ipilimumab is a monoclonal antibody that increases the immune system's response to tumour cells by targeting the CTLA-4 receptor. It is the first FDA-approved ICI for prostate cancer. When administered as monotherapy, ipilimumab has been shown to significantly increase the proportion of regulatory effector T lymphocytes present in the *tumour microenvironment* (TME) (72).

In the literature, phase I trials have shown that ipilimumab and its combinations provide PSA reduction in patients and prolong the PSA doubling time (73-76). *Slovin et al.* shared the results of 50 patients diagnosed with *metastatic CRPC* (mCRPC) who received ipilimumab alone or ipilimumab/*radiotherapy* (RT) combination therapy. A more than 50% decrease in PSA was observed in eight patients, a complete response was achieved in 1 patient, and no progression was observed in 6 patients (77). *Kwon et al.*, in a randomized controlled phase III study, 799 mCRPC patients received palliative RT therapy. Then, the patients were divided into two groups, one receiving ipilimumab and the other receiving placebo. Although a significant improvement in PFS was detected in the ipilimumab arm between the two groups, no significant difference was detected in OS data (70). After three years, an approximately two- to three-fold higher OS benefit was detected in the ipilimumab arm (78). *Beer et al.* reported increased PFS and a higher PSA response rate (23% vs 8%) in the ipilimumab arm (5.6 mo.) compared to the placebo arm (3.8 mo.) in mCRPC (79).

Nivolumab

The interaction of PD-1 with its ligand prevents the activation of T cells, and, as a result, the destruction of can-

cer cells by the immune system is prevented. Nivolumab is an IgG4 monoclonal antibody that demonstrates anti-tumor response by blocking PD-1 (80, 81).

In the CheckMate 650 phase II clinical trial investigating the combined effects of ipilimumab and nivolumab in patients with mCRPC, combination therapy demonstrated an ORR of 25% (81).

Shenderov et al., in patients with AR-V7 positive mCRPC, which is associated with poor prognosis, investigated the effectiveness of nivolumab/ipilimumab combination therapy. Although this study showed that combination therapy may benefit AR-V7 positive PCa patients, sufficient evidence was not obtained for routine use (82).

Pembrolizumab

Pembrolizumab is an anti-PD-1 antibody that acts similarly to nivolumab. In the Keynote-365 study, CT-refractory mCRPC patients receiving abiraterone or enzalutamide were given pembrolizumab/docetaxel and prednisone combination therapy. The PSA response rate was 34%, the radiological mean PFS was 8.5 mo., and the OS was 20.2 mo. (83).

In a phase II clinical study (Keynote-199) involving multiple cohorts, pembrolizumab monotherapy was administered to 258 patients diagnosed with mCRPC who had bone-predominant metastases measurable by *Response Evaluation Criteria In Solid Tumors* (RECIST) and received docetaxel and targeted endocrine therapy. Patients with positive PD-L1 expression showed an ORR of 5%, and patients with negative expression showed an ORR of 3%. Median OS was reported as 9.5 mo. in PD-L1 expression-positive patients and 7.9 mo. in negative patients (84). With these results, it is thought that pembrolizumab treatment may be more effective in tumours with high PD-L1 expression.

Atezolizumab

Atezolizumab, avelumab and durvalumab, which target PD-L1, work by blocking the interaction of PD-L1 with PD-1. These agents have been investigated as an option in the treatment of advanced prostate cancer (85-89).

In IMbassador 250 study, 759 patients with mCRPC or locally advanced CRPC refractory to abiraterone and docetaxel were treated with the combination of atezolizumab

Table 6.
Clinical trials of varying treatment plans for mCRPC (91).

Treatment	N	Target	Dosing Interval	Results	Article
Ipilimumab	799	mCRPC	One dose of RT followed by 10 mg/kg ipilimumab every 3 weeks	Overall increased survival rates for patients given ipilimumab	<i>Fizazi et al.</i>
Pembrolizumab	258	mCRPC	200 mg every 3 weeks	OS of 14.1 mo. with acceptable safety	<i>Antonarakis et al.</i>
Pembrolizumab	23	Advanced prostate adenocarcinoma	10 mg/kg every 2 weeks	OS of 7.9 mo.	<i>Hansen et al.</i>
Pembrolizumab plus Docetaxel and Prednisone	104	mCRPC	200 mg pembrolizumab and 75 mg/m ² docetaxel every 3 weeks, 5 mg prednisone BID	OS of 29.2 mo. with acceptable safety	<i>Yu et al.</i>
Pembrolizumab plus Enzalutamide	28	mCRPC	200 mg pembrolizumab every 3 weeks with 4 doses of enzalutamide	OS of 41.7 mo.	<i>Graff et al.</i>
Atezolizumab	35	mCRPC	Every 3 weeks	OS of 14.7 mo. with acceptable safety	<i>Petrylak et al.</i>
Atezolizumab with Sipuleucel-T	37	mCRPC	1200 mg atezolizumab every 3 weeks, sipuleucel-T every 2 weeks	OS of 23.6 mo.	<i>Dorff et al.</i>
Avelumab	15	mCRPC	10 mg/kg every 2 weeks	OS of 7.4 mo.	<i>Brown et al.</i>
Nivolumab plus Ipilimumab	90	mCRPC	1 mg/kg nivolumab and 3 mg/kg ipilimumab IV followed by 480 mg nivolumab every 4 weeks	OS of 19.0 mo.	<i>Sharma et al.</i>

and enzalutamide or enzalutamide alone. Similar OS rates were detected in both treatment arms. Subgroup analyses reported that combination therapy may benefit patients with high PD-L1 expression (86).

Sipuleucel-T

There are also immunotherapeutic vaccines used in the treatment of prostate cancer. However, many of these vaccines are still in the experimental stage.

FDA approval of Sipuleucel-T is considered the first application of immunotherapy in prostate cancer. Sipuleucel-T is the only FDA-approved vaccine approved for use against prostate cancer. It has been shown in the literature that Sipuleucel-T is effective in mCRPC (69, 90). According to a study conducted by *Kantoff et al.* in mCRPC patients, sipuleucel-T treatment prolonged OS by an average of 4.1 mo. and resulted in a 22% reduction in the risk of death (69). These results may guide new immunotherapeutic vaccine trials. Clinical trials of various prostate cancer immune therapies were summarized in Table 6 (91).

Role of Immunotherapy in Prostate Cancer

As it is known, prostate cancer is in the category of immunologically "cold" tumours, so patients must be evaluated according to their individual immunogenicity status in order to receive effective immunotherapy treatment (91).

More successful treatment results can be achieved in larger patient populations with combination treatments with different agents. Another critical issue is that immunological interventions are generally applied only to those with advanced disease, although, as the disease progresses, the number of T cells decreases. Therefore, applying immunotherapy at the early stage of the disease may provide a more effective response to treatment.

Immunotherapy is a promising alternative treatment option, especially in some CRPC patients. ICI treatment success is higher in prostate cancer patients with high MSI/dMMR or CDK12 mutations. A better understanding of TME and ICI mechanisms through high-volume prospective RCTs may pave the way for new immunotherapeutic approaches in advanced prostate cancer.

CONCLUSIONS

Given the limited research experience to date, it remains unclear whether the persistence of the primary tumour will impact attempts to modulate the metastatic cascade or whether different immunotherapy agents have different degrees of efficacy in adjuvant or neoadjuvant settings.

Cisplatin-based CT has long been used as standard therapy in the treatment of urothelial carcinoma. With the promising results obtained in locally advanced and mUC, systemic immunotherapeutic agents have begun to take their place in the standard treatment of the disease. However, more RCT evidence and extended follow-up periods are needed.

Data from large clinical trials to evaluate immunotherapy and TKIs for treating RCC in the adjuvant setting remain largely conflicting regarding the DFS benefit of either

treatment modality. However, a comprehensive biological rationale exists for administering TKIs and immunotherapy agents in the adjuvant setting. However, questions regarding the optimal adjuvant treatment regimen and appropriate method in RCC still remain to be answered. Prostate cancer, which is considered an immunological "cold" tumour, is not as sensitive to immunotherapy as other urological malignancies. However, promising results have been obtained in some identified prostate cancer patients. In the light of new prospective RCTs, treatment procedures that reach sufficient evidence levels do not seem far away.

To make an informed decision about the individualized use of adjuvant immunotherapy, clinicians should discuss the available data with patients and actively make the decision. Further research and development of biomarkers are needed to answer these questions and improve outcomes for uro-oncology. Although it is challenging to stay up to date on innovations in immunotherapy, given the ongoing RCTs, there is no doubt that we will have more options available to our patients who need this treatment in the next decade.

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