REVIEW
Urooncology

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Immunotherapy Applications in Urology

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Abstract

Immunotherapy has transformed the management of urological cancers, offering renewed optimism for individuals diagnosed with bladder, kidney, and, to a lesser degree, prostate tumors. Conventional therapies, such as chemotherapy and radiation, frequently demonstrate restricted efficacy. At the same time, immune checkpoint inhibitors (ICIs) have surfaced as promising alternatives, especially in urothelial and renal cell carcinoma (RCC). This review examines immunotherapy mechanisms, focusing on immune checkpoint pathways such as programmed cell death protein 1 and cytotoxic T lymphocyte-associated protein 4, and their contributions to improving immune recognition and eliminating tumor cells. Bacillus Calmette-Guérin immunotherapy is essential for non-muscle-invasive bladder cancer, whereas ICIs have transformed the management of muscle-invasive and metastatic forms of the disease. In RCC, ICIs have markedly enhanced survival outcomes, whether alone or in conjunction with tyrosine kinase inhibitors. Although advancements have been made, the role of immunotherapy in prostate cancer remains in development, with limited efficacy documented thus far. Current research focuses on optimizing combination therapies and identifying biomarkers to improve patient selection. The future of immunotherapy in urology involves its incorporation into earlier treatment stages and its combination with innovative agents, which may enhance outcomes for patients with urological cancers.

Keywords: Immunotherapy, urooncology, bladder cancer, prostate cancer, renal cancer

Introduction

Immunotherapy has transformed the treatment of numerous malignancies, and its use in urology has profoundly altered the management of urological tumors. Conventional therapies for urological malignancies, including chemotherapy and radiation, frequently provide suboptimal results, whereas immunotherapy presents a promising approach for enhancing outcomes, especially in bladder, kidney, and, to a lesser degree, prostate tumors.

In the field of urothelial carcinoma and renal cell carcinoma (RCC), immune checkpoint inhibitors (ICIs) have become crucial components, utilized either as standalone treatments or in conjunction with other therapies. Notwithstanding these developments, their effectiveness in prostate cancer remains limited. This study examines the basic mechanisms of immunotherapy, its present applications in various urological malignancies, and future prospects that may enhance patient outcomes.

Mechanisms of Immunotherapy in Urological Malignancies

Immunotherapy in urological malignancies improves the body's capacity by enhancing the immune system's ability to identify and eliminate malignant cells. The progression of cancer signifies a disruption in the equilibrium between immune surveillance and tumor evasion systems, permitting the unregulated proliferation of aberrant cells. Immunotherapy aims to restore this equilibrium by enhancing the immune system's ability to identify and eliminate tumor cells that have escaped recognition.

Mechanisms of Tumoral Immune Evasion

The microenvironment of the tumor contains several mechanisms that prevent the immune system from effectively combating the tumor, including T-cell exhaustion. Due to prolonged exposure to antigenic stimuli, exhausted T-cells exhibit a loss of normal T-cell functions, and their effector capacities (e.g., cytokine production and cell killing abilities) are reduced. These cells become resistant to reactivation and express high levels of multiple inhibitory surface molecules, such as cytotoxic T

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lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), lymphocyte activation gene-3, and T-cell immunoreceptor with Ig and Immunoreceptor Tyrosine-based Inhibitory Motif (ITIM) domains, T-cell immunoglobulin and ITIM domain. These molecules suppress T-cell activation and help tumor cells evade the immune system (1).

Cancer cells bypass immune detection through many strategies, such as diminished tumor antigen production and the secretion of inhibitory chemicals that provoke T-cell anergy or apoptosis (2). Immune checkpoint molecules, including programmed death ligand 1 (PD-L1), are pivotal in this process. The binding of PD-L1 on tumor cells to the PD-1 receptor on T lymphocytes initiates an inhibitory signal that diminishes T-cell activity, hence promoting immune evasion (3).

The CTLA-4/CD80-CD86 association similarly inhibits T-cell activation, facilitating immunological evasion. The introduction of ICIs, including anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, marks a key advancement in the management of many urological cancers. By obstructing these inhibitory pathways, ICIs can rejuvenate T lymphocytes, enabling them to effectively target and eliminate tumor cells (Figure 1).

Advances in Immuno-Oncology

Recent advancements in immuno-oncology have led to medications that accurately target specific immune pathways, improving precision and reducing off-target effects. ICIs have demonstrated notable effectiveness in RCC and bladder cancer,

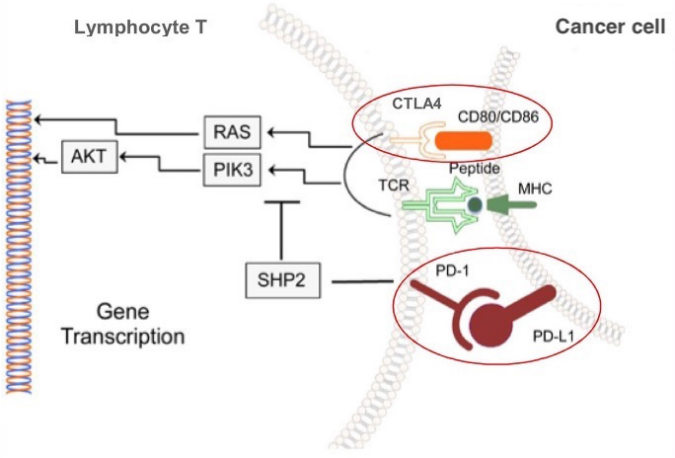

Figure 1. Major immune checkpoints involved in T-cell anergy (4)

CTLA-4, CD80/CD86: Membrane-bound glycoprotein that belongs to the B7 family of immunoglobulin superfamily proteins, PD-1: Programmed death 1 and its ligand (PD-L1), MHC: Major histocompatibility complex, a group of genes that code for proteins responsible for presenting antigens to T-cells, which is a critical step in the immune response, SHP2: Protein tyrosine phosphatase (PTP) encoded by the *PTPN11* gene in humans, RAS: Plays an important role in intracellular signaling. TCR: T-cell receptor, PIK3: Phosphoinositide 3-kinase, a family of enzymes involved in critical cellular processes such as growth, proliferation, survival, metabolism, and motility, AKT: Protein kinase B, is a serine/threonine-specific protein kinase that plays a central role in regulating various cellular processes, including metabolism, growth, survival, and proliferation

leading to their integration into treatment protocols. However, the benefits of immunotherapy for prostate cancer are still under investigation, producing mixed results so far.

The US Food and Drug Administration has approved ICIs for clinical use in certain genitourinary tumor patients (5). Biomarkers are pivotal in early tumor diagnosis, drug development, disease monitoring, and prognosis evaluation. Many methods exist to detect biomarkers, depending on the laboratory and the material to be analyzed (such as tissue or serum). Polymerase chain reaction is a common method for mRNA or DNA-based analysis. ELISA, Western Blot, or immunohistochemical examination may be preferred for a specific analysis at the protein level. Programmed death ligand-1 (PD-L1) expression is a widely used biomarker to predict response to immunotherapy and is evaluated according to expression levels in tumor cells or immune cells (6). Microsatellite instability (MSI) and high tumor mutational burden are other important biomarkers that indicate that immunotherapy may be effective (7). Additionally, the presence of intratumoral $CD8^+$ T-cells may indicate a strong immune response (8). Selecting patients with higher mutational burden, with specific markers, may increase the likelihood of response to immunotherapy.

Immunotherapy for Bladder Cancer

Non-muscle invasive bladder cancer (NMIBC) Bacillus Calmette-Guérin (BCG) immunotherapy has long been a fundamental treatment for NMIBC, demonstrating more efficacy than transurethral resection of the bladder alone or in conjunction with intravesical chemotherapy in minimizing recurrence (9,10). A Cochrane review demonstrated the advantage of BCG compared to mitomycin-C in decreasing NMIBC recurrence (11). Moreover, maintenance BCG therapy has been shown to be effective in reducing the risk of progression in high- and intermediate-risk NMIBC (12,13). Intracavitary treatment poses a potential risk for disseminated BCG infection (in less than 5% of patients) and may cause infusion reactions (14). The presence or absence of side effects does not seem to be a prognostic factor for the efficacy of BCG, and maintenance therapy is not associated with a significant increase in toxicity (15).

Recent data on BCG-unresponsive patients with carcinoma *in situ* (16), either alone or with concomitant papillary tumors, have shown promising results with new immunotherapies. Systemic pembrolizumab demonstrated a 40% complete response rate in a phase II prospective study, with 48% of responders maintaining their response for up to 12 months (17). Promising results from a phase III multicenter randomized controlled trial (RCT) demonstrated that intravesical nadofaragene firadenovec achieved a 53.4% complete response rate in patients with BCG-unresponsive carcinoma *in situ* (16). Forty-five percent of responders maintained their response at one year (18). Additional

ongoing studies are exploring the use of combination therapies involving intravesical or systemic immunotherapy to enhance treatment outcomes (19,20).

Muscle-invasive and Metastatic Bladder Carcinoma

In recent years, immunotherapy has emerged as a prominent option for treating muscle-invasive bladder cancer. Traditionally, chemotherapy has remained the first-line treatment for metastatic disease for an extended period; however, it is increasingly being supplanted by immunotherapy approaches. Preliminary studies indicate that the ICI pembrolizumab demonstrates an overall survival advantage of approximately three months compared to second-line chemotherapy. Nevertheless, the current data are insufficient to facilitate its immediate integration into routine clinical practice (21).

The phase III trial Alliance A031501 AMBASSADOR demonstrated that adjuvant pembrolizumab significantly improved disease-free survival (29.6 months *vs.* 14.2 months; hazard ratio: 0.73, p=0.003) compared to observation in patients with high-risk muscle-invasive urothelial carcinoma after radical surgery. These findings support pembrolizumab as an effective adjuvant therapy in this population. However, pembrolizumab was associated with a higher rate of grade 3 or higher adverse events (50.6% *vs.* 31.6%) (22).

Nivolumab, a PD-1/PD-L1 checkpoint inhibitor, is recommended as an adjuvant treatment for patients with tumor cell PD-L1 expression ≥1% who are at high risk of recurrence after surgery in non-metastatic pT3-4 urothelial carcinoma and cannot receive cisplatin-based chemotherapy. The CheckMate 274 trial, which indicated significant improvements in disease-free survival (23), supports this recommendation.

The EV-302/KEYNOTE A39 and Checkmate 901 RCTs have recently revised the first-line treatment algorithm in metastatic disease (24,25). The combination of enfortumab vedotin (EV) and pembrolizumab in metastatic urothelial carcinoma now establishes the new standard of care for patients who are considered eligible for combination therapies. The major eligibility criteria include an Eastern Cooperative Oncology Group performance status of 0-2, a glomerular filtration rate of ≥30 mL/min, and adequate organ function, as determined by the requirements for treatment with EV, and Pembrolizumab. This combination has significantly enhanced progression-free survival (PFS) and overall survival, irrespective of PD-L1 expression. PFS was significantly prolonged with EV+P *vs.* chemo, reducing the risk of progression or death by 55% (median PFS, 12.5 mo *vs.* 6.3 mo, respectively). Additionally, severe side effects were found to be lower than those associated with chemotherapy (24).

However, it should be noted that EV has not yet been included in the reimbursement scope of the social security institution in our country. Li et al. (27) evaluated the cost-effectiveness of EV plus pembrolizumab as a first-line treatment for metastatic urothelial carcinoma compared to chemotherapy. While EV plus pembrolizumab improved survival, providing an additional 2.10 life-years (26) and 1.72 quality-adjusted life-years (QALYs), the incremental cost-effectiveness ratio was $558,973 per QALY-well above the willingness-to-pay threshold of $150,000 per QALY. Subgroup analysis suggested that the combination was slightly more cost-effective in cisplatin-ineligible patients, but overall, the therapy is not considered cost-effective from the perspective of U.S. payers (27).

Numerous combinations are currently being studied in various clinical studies. The JAVELIN bladder 100 study evaluated the efficacy of ongoing treatment with the PD-L1 inhibitor avelumab following platinum-gemcitabine chemotherapy. After four to six cycles of platinum-gemcitabine chemotherapy, an increase in overall survival was noted among patients treated with avelumab, with respective survival rates of 21.4 and 14.3 months for those who received and did not receive avelumab (28).

Currently, phase I, II, and III studies indicate that ICIs, including pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab, exhibit comparable efficacy and safety in patients who have progressed during or following platinum-based chemotherapy (21,29-32). Sacituzumab govitecan is a humanized monoclonal antibody that targets trophoblast cell surface antigen 2 (Trop-2). Research indicates that it enhances progression-free and overall survival prior to chemotherapy (33). As a result of new molecules or combinations, it is anticipated that standard treatment algorithms will undergo changes in the near future.

Adverse events can affect any organ in the body and range in severity from mild to severe. The most affected organs include the skin, gastrointestinal tract, liver, lungs, thyroid, adrenal glands, and pituitary gland. Other potentially impacted systems include the musculoskeletal, renal, nervous, hematologic, ocular, and cardiovascular systems. Any new symptoms or changes observed during immunotherapy should prompt consideration of a potential connection to the treatment (34).

Immunotherapy in Renal Carcinoma

The majority of immunotherapy studies in RCC focus on clear cell RCC (ccRCC), as it is the most prevalent subtype, accounting for approximately 70-80% of all RCC cases (35). As a result, there is limited knowledge regarding the optimal management of non-clear cell RCC (nccRCC) subtypes. Treatment options for nccRCC remain scarce due to the lack of specific studies focused on these variants. For these reasons, our review primarily focuses on clear cell RCC.

Before the introduction of ICIs, the primary treatments for metastatic RCC included tyrosine kinase inhibitors (TKIs), mTOR inhibitors, and vascular endothelial growth factor (VEGF) inhibitors. CheckMate trials 025 and 214 demonstrated that nivolumab, both alone and in combination with ipilimumab, enhanced overall survival in metastatic ccRCC, resulting in a significant shift in treatment approaches (36,37).

As a monotherapy, nivolumab has demonstrated superiority over everolimus in terms of overall survival for patients with VEGF-refractory ccRCC. However, no advantage in PFS has been observed in this patient population (38). Currently, no RCTs support the use of single-agent ICIs in metastatic kidney cancer.

To date, numerous combination treatments have been investigated in the context of kidney cancer. Combining immunotherapy with interventions explicitly targeting the VEGF pathway has demonstrated significant efficacy. First-line ICI combination trials for clear-cell RCC are presented in Table 1. The Keynote 426 phase III clinical trial indicates that the combination of pembrolizumab and axitinib outperforms first-line sunitinib in terms of overall survival among treatment-naïve patients, irrespective of PD-L1 expression (39).

A comprehensive five-year analysis of the Keynote 426 study revealed that combination therapy offers a PFS advantage. In the study, for pembrolizumab + axitinib *vs.* sunitinib, the 60-month overall survival rates were 41.9% *vs.* 37.1%, and the 60-month PFS rates were 18.3% *vs.* 7.3%. Furthermore, no significant differences were identified in treatment-related side effects compared to standard treatments (40).

Randomized controlled phase III trials evaluating the combinations of nivolumab with cabozantinib, as well as lenvatinib with pembrolizumab, demonstrated a PFS advantage, compared with sunitinib. These studies assessed efficacy without regard to risk group or PD-L1 status (41,42).

The COSMIC-313 study is the first RCT aimed at evaluating the efficacy of the cabozantinib-nivolumab-ipilimumab triple combination treatment against the nivolumab-ipilimumab standard treatment combination, with a cohort of 855 patients (22). Although the study has not yet yielded long-term results, initial findings suggest that the triple combination provides a significant advantage in PFS (43).

In light of these findings pertaining to the metastatic stage, new prospective studies are underway to assess the potential impact of immunotherapy, whether administered as neoadjuvant or adjuvant treatment, in patients with localized kidney cancer who are deemed to be at high risk of recurrence. Currently, evaluating PD-L1 expression status is not a standard procedure. Combination therapies, which include immunotherapy, have now been established as the standard treatment for metastatic kidney cancer. It is anticipated that modifications to the treatment algorithm may occur in the future due to numerous RCTs that are currently in progress.

The meta-analysis of 95 RCTs involving 40,552 participants evaluated the risk of renal adverse events (RAE) (11) associated with ICIs. The overall incidence of RAE and acute kidney injury was low, but anti-CTLA-4 monotherapy showed higher toxicity, particularly for grade 3-5 RAE, compared to other ICIs like anti-PD-1 and anti-PD-L1. Combination therapies, such as anti-CTLA-4 plus anti-PD-1 and ICI plus chemotherapy, were associated with higher risks of RAE and AKI compared to monotherapies or traditional therapies, with ICI plus chemotherapy being the most toxic regimen. These findings emphasize the need for careful monitoring of renal function in patients receiving ICI-based treatments (44).

There is certainly a need for studies reporting the cost-effectiveness of immunotherapy. The study evaluated the cost-effectiveness of seven treatment strategies for metastatic renal cell carcinoma, including immunotherapy-TKI combinations and sunitinib, using public-payer costs in the United States. Nivolumab + ipilimumab provided the highest QALYs at 3.6. Still, it was not cost-effective at a willingness-to-pay threshold of $150,000 USD/QALY because of its high incremental cost-effectiveness ratio of $297,465 to $348,516 USD compared to sunitinib. Sunitinib, as the least expensive option, emerged as the most cost-effective treatment, while cost reductions of 22-38% in NI could improve its cost-effectiveness (45).

Immunotherapy in Prostate Cancer

Unlike in bladder and kidney cancers, the use of immunotherapy has not yet gained widespread acceptance in prostate cancer due to limited efficacy.

In the context of castration-resistant prostate cancer (CRPC), sipuleucel-T immunotherapy has undergone extensive investigation. This therapeutic approach involves cultivating the patient's serum mononuclear cells with the PA2024 fusion protein, which comprises a prostate antigen linked to granulocyte-macrophage colony-stimulating factor. Sipuleucel-T, formulated using the patient's blood cells, has demonstrated an overall survival advantage of 4.1 months for CRPC patients exhibiting no or minimal symptoms. However, it has not shown an impact on disease progression (46). Many similar prostate cancer vaccine studies have been conducted (47,48).

Research indicates that ICIs exhibit minimal efficacy in the treatment of prostate cancer. While some studies demonstrate a response to immunotherapy, the treatment for prostate cancer may require a more tailored approach for each patient. This

necessity arises from the substantial variation in mutation burden and spectrum observed among patients with CRPC (49).

MSI arises from the insufficient functionality of DNA repair mechanisms. This deficiency within cancer cells can result in tumors being more readily identified by the immune system, thereby exhibiting an enhanced response to immunotherapy. Although individuals with high MSI in prostate cancer are infrequent, pembrolizumab has received FDA approval for patients with metastatic CRPC and may represent a beneficial supplementary treatment option (50,51).

Conclusion

Recent advancements in immunotherapy have notably enhanced its application in urology, especially concerning the treatment of bladder and kidney cancers. ICIs are critical elements in the treatment protocols for these malignancies, providing significant enhancements in survival rates. Despite these advancements, the application of immunotherapy in prostate cancer is still limited, necessitating additional research to identify predictive biomarkers and enhance combination strategies for optimal benefit.

Table 1. First line immune checkpoint inhibitor combination trials for clear-cell RCC (52)

Study	n	Experimental arm	Primary endpoint	Risk groups	PFS (22) median (95% CI) HR	OS (22) Median (95% CI) HR
KEYNOTE-426 NCT02853331 Median follow-up 67 months (39,40,53,54)	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: 0.69 (95% CI: 0.59-0.81) p<0.0001	(ITT) PEMBRO + AXI: 47.2. (43.6-54.8) SUN: 40.8 (34.3-47.5) HR: 0.84 (95% CI: 0.71[0.99) p=0.001
JAVELIN 101 NCT02684006 Median follow-up 34.1 months (16,55,56)	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: 13.9 (11.0-17.8) SUN: 8.2 (6.9-9.4) HR: 0.67 (95% CI: 0.57-0.79) p<0.0001	(PD-L1+) AVE + AXI: NR (40.0-NR) SUN: 36.2 (30.0-NE) HR, 0.81 (95% CI: 0.62-1.04) p=0.0498
IMmotion151 NCT02420821 Median follow-up 24 months (57,58)	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
CheckMate214 NCT02231749 Median follow-up of 60 months (37,59)	1096	NIVO 3 mg/kg plus ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/ kg IV Q2W vs. SUN 50 mg PO QD 4/2 wk.	PFS and OS in the IMDC inter- mediate 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
CheckMate9ER NCT03141177 Median follow-up of 44 months (26,41,60)	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: 16.6 (12.8-19.5) SUN: 8.4 (7.0-9.7) HR: 0.59 (95% CI: 0.49-0.71) p<0.0001	(ITT) NIVO+CABO: 49.5 (40.3-NE) SUN: 35.5 (29.2- 42.3) HR: 0.70 (98.9% CI: 0.56-0.87) p=0.0034
CLEAR NCT02811861 Median follow-up of 49.8 months (42,61,62)	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 BIRC	**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: 0.47 (95% CI: 0.38-0.57) p>0.001	(ITT) PEMBRO+LEN: 53.7 (48.7-NE) SUN: 54.3 (40.9-NE) HR: 0.79 (95% CI: 0.63-0.99) p=0.005

Table 1. Continued

Study	n	Experimental arm	Primary endpoint	Risk groups	PFS (22) median (95% CI) HR	OS (22) Median (95% CI) HR
COSMIC-313 Median follow-up of 20.2 months (43)	855	NIVO 3 mg/kg plus IPI 1 mg/ kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W + CABO 40mg PO QD vs. NIVO 3 mg/ kg plus IPI 1 mg/ kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W	PFS in the PITT population (first 550 pts. randomised)	**IMDC** IMD 75% POOR 25%	(PITT) NIVO+IPI+CABO: NR (14.0-NE) NIVO+IPI: 11.3 (7.7- 18.2) HR: 0.73 (95% CI: 0.57-0.94) p=0.013	NR

CI: Confidence interval, RCC: Renal cell carcinoma, PFS: Progression-free survival, HR: Hazard ratio, OS: Overall survival

Current clinical trials are investigating the application of immunotherapy in both neoadjuvant and adjuvant contexts, with potential outcomes that may broaden its utilization in early-stage cancers. The advancement of knowledge regarding tumor biology and immune interactions is expected to lead to the development of innovative agents and combination therapies, thereby significantly altering the treatment landscape for urological cancers and providing new hope for patients.

Footnotes

Authorship Contributions

Concept: Y.Ş., B.Ş., Design Y.Ş., B.Ş., Data Collection or Processing: Y.Ş., Analysis or Interpretation: Y.Ş., B.Ş., Literature Search: Y.Ş., Writing: Y.Ş., B.Ş.

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