HUMAN VACCINES & IMMUNOTHERAPEUTICS
2023, VOL. 19, NO. 2, 2225386
https://doi.org/10.1080/21645515.2023.2225386

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MINI-REVIEW

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First-line ICIs in renal cell carcinoma

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ABSTRACT

Treatment of metastatic renal cell carcinoma (mRCC) has radically changed, switching from interferon alfa (IFN-α) and high-dose interleukin−2 (HD IL−2) to new targeted therapies directed against tumoral neoangiogenesis, the mammalian target of the rapamycin (mTOR) pathway and immune checkpoints. Of note, the inhibition of immune checkpoints restores antitumor immune response, therefore promoting immune-mediated elimination of neoplastic cells. The best example of this targeted treatment is represented by PD-1/PD-L1 inhibition that has become the standard of care in mRCC treatment and has improved mRCC patients' prognoses after failure of other targeted therapies. In this manuscript, we review the main therapeutic protocols adopted for mRCC, based on the use of immune checkpoint inhibitors (ICIs) alone or combined with other drugs.

ARTICLE HISTORY
Received 28 December 2022
Revised 25 May 2023
Accepted 12 June 2023

KEYWORDS
Immune checkpoint inhibition

Introduction

Renal cell carcinoma (RCC) is the seventh most common cancer worldwide, with 330,000 new diagnoses and more than 140,000 deaths every year.[1] It originates from tubular epithelial cells[2] and is typically radio and chemoresistant. Surgical resection is the most effective treatment for early-stage renal cancer, but nearly one-third of patients have distant metastases at the time of diagnosis, and even after surgery, 30% of patients have tumor recurrence or metastasis.[3] In contrast to non-clear cell RCC (nccRCC), which consists of several histological subtypes, including papillary and chromophobe carcinomas, clear cell RCC (ccRCC) is the most prevalent histological subtype and accounts for more than 75% of RCCs.[4] Currently, the International Metastatic Renal Cell Cancer Database Consortium (IMDC) score is used in mRCC to stratify patients into three subgroups (favorable, intermediate, and poor risk), in order to direct treatment choices and to predict prognosis.[5] This prognostic model takes into account anemia, neutrophilia, thrombocytosis, hypercalcemia, Karnofsky performance status of less than 80, and a short time between diagnosis and first-line systemic therapy.[5]

In the last years, treatment of metastatic mRCC has radically changed. In fact, until 2005, the standard of care was represented by interferon alfa (IFN-α) and high-dose interleukin−2 (HD IL−2).[6,7] However, these therapies were often not effective, with many side effects and without an impact on immunological escape mechanisms.[8] In recent years, new targeted therapies have been developed and approved based on a better understanding of the biological and molecular landscape of RCC: the best targets are represented by tumoral neoangiogenesis, the mammalian target of the rapamycin (mTOR) pathway (that plays an important role in the regulation of the cell cycle), immune checkpoints (that downregulate antitumoral immune responses, for example CTLA-4 and the programmed cell death protein 1 [PD-1] and its ligand [PD-L1] pathway). To address tumoral neoangiogenesis, several drugs are available, such as bevacizumab, sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib,[9–13] mainly directed against the vascular endothelial growth factor (VEGF)/VEGF receptors (VEGFRs) pathway; on the other side, the mTOR pathway is targeted by everolimus and temsirolimus,[14,15] CTLA-4 is targeted by ipilimumab and the PD-1/PD-L1 pathway by nivolumab and pembrolizumab (both directed against PD-1).[16,17] Of note, the inhibition of immune checkpoints (with the consequent restoring of antitumor immune response and the promotion of immune-mediated elimination of neoplastic cells) has improved mRCC patients' prognoses after failure of targeted therapy, succeeding in extending their survival.[18] For this reason, they have recently grown in popularity and PD-1/PD-L1 inhibition has become the standard of care in mRCC treatment. On this basis, we performed a systematic review of the available evidence of the efficacy and safety of immune checkpoint inhibitors (ICIs) as first-line therapy for mRCC, alone or combined with other therapeutic agents.

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Molecular background of RCC

The PD-1/PD-L1/CTLA-4 axis in RCC

RCC is highly immunogenic and leads to the mobilization of immune cells into the tumor microenvironment, including Tumor Infiltrating Lymphocytes (TILs) and natural killer cells, supporting tumor progression.[19,20] PD-L1 is widely expressed in RCC, and the PDL-1/PD-L1 checkpoint has a central role in controlling tumor growth in this neoplasm.[20] In particular, PD-1 is present on T cell membrane surface, while PD-L1 is expressed by tumor cells. T cell anergy and downregulation as a result of overexpression of PD-L1 and its interaction with PD-1 inhibitory receptors reduce host immunological response against RCC.[20–22]

For this reason, the inhibition of PD-1 or PD-L1, activating T cells directed against cancer cells, has an important anti-cancer effect. On the other side, there is another molecule that plays a role in immune response against cancer: it is the CTLA-4 coinhibitory receptor, which inhibits T lymphocytes directed against cancer cells when they first become activated and for roughly 48 h following T-cell activation it shows high expression. For this reason, blocking antibodies against CTLA-4 can be used to reactivate immune response against neoplastic cells. However, clinically significant inflammatory or autoimmune toxic effects are seen in 20% to 30% of patients in addition to this response.[2] Generally speaking, PD-1 inhibition is thought to be less harmful and more effective against tumors than CTLA-4 inhibition because PD-1 predominantly regulates the effector phase of T-cell responses and has a stronger selectivity for immune suppressive signals that are directly transmitted by cancer.[23,24]

Neoangiogenesis in mRCC

The growth of new blood vessels is crucial for tumor development, and RCC is well known for having a high blood vessel density. As a result, many strategies used to treat mRCC are designed to inhibit angiogenesis. The tumor suppressor gene von Hippel-Lindau (VHL) is frequently mutated in RCC. VHL participates in the process by which hypoxia-inducible factor (HIF) is degraded. HIF is not broken down when VHL is mutated, which results in the transcription of numerous genes, including VEGF, which causes angiogenesis.[25,26]

Anti-VEGF monoclonal antibodies and tyrosine kinase inhibitors (TKIs) are examples of targeted agents that inhibit VEGF receptors as well as other angiogenesis-related receptors.[27] Clinical trials have demonstrated that the TKIs sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib, as well as the anti-VEGF monoclonal antibody, bevacizumab, improve disease control.

In addition to stimulating angiogenesis, several data suggest that VEGF may contribute to cancer immune evasion. In fact, when VEGF is highly expressed, less differentiated antigen-presenting dendritic cells and more immunosuppressive myeloid cells are found in tumor tissue and peripheral blood, respectively.[28,29] Also, it has been proven that VEGF blockade increases the number of T-cells within a tumor; in fact, Wallin et al. showed an increase in chemokines associated with T-cell migration, in tumor major histocompatibility complex class 1 protein expression and in the presence of tumor-specific T-cells after bevacizumab administration.[30] Moreover, they demonstrated further increases in T-cells with the combination of bevacizumab and atezolizumab, suggesting that the anti-VEGF treatment, bevacizumab, can trigger an antitumor immune response which may be strengthened by the addition of an ICI.[30]

First-line therapies for mRCC

Systemic first-line therapy for mRCC is rapidly evolving with several therapeutic combinations and new clinical trials.

The first targeted therapy to be used in mRCC was sunitinib, a multitarget tyrosine kinase inhibitor with anti-angiogenic effects, an indirect inhibitory effect on tumor growth, and an activity on antitumor immune response. It was approved by the US Food and Drug Administration (FDA) in January 2006 and has represented the cornerstone of mRCC targeted treatment due to the peculiar molecular pathogenesis of this neoplasm. Over the past 15 y, clinical trials have explored the combination of sunitinib with other targeted agents to increase therapeutic efficacy and to reduce the burden of side effects.[18] In fact, the introduction of new ICIs has led to a therapeutic shift in the management of mRCC. Dual checkpoint inhibition with nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor), along with the combination of a PD-(L)-1 ICI and a VEGFR-TKI, was demonstrated to improve response rates, progression-free survival (PFS), and/or overall survival (OS) when compared with sunitinib.[31–33]

After sunitinib, ipilimumab and nivolumab were the most promising therapies to be implemented in mRCC, as they were the only combination therapy that received approval for mRCC.

The introduction of biological and immunological drugs in the therapeutic armamentarium of metastatic renal cell carcinoma, on the one hand, has led to remarkable results in terms of efficacy and , on the other hand, has documented a series of new or unusual side effects that deserve proper management. The main side effects related to tyrosine kinase inhibitors are represented by diarrhea, fatigue, nausea, hypertension, congestive heart failure, thyroid dysfunction, cutaneous alterations, gastrointestinal toxicity, hepatitis, nephritis, and hematological alterations such as neutropenia and thrombocytopenia. According to the Common Terminology Criteria for Adverse Events (CTCAE), immune-related adverse events can range in severity from grade 1 to grade 5 (mild/asymptomatic, moderate, severe, life-threatening, and fatal).[34] It should be noted that with combination ICI therapy, immune-related adverse events are more frequent and severe, with a higher prevalence of high-grade side effects than with single-agent therapy. However, most immune-related adverse events resolve with temporary or permanent withdrawal of immunotherapy and with the use of immunosuppressive drugs. The time required for side effects to resolve depends on the type of toxicity. Gastrointestinal, hepatic, and renal adverse events typically improve rapidly upon initiation of immunosuppressive therapy. Conversely, the resolution of cutaneous and, above all, endocrine toxicity may take longer and may leave

behind an endocrine insufficiency which may require replacement therapy indefinitely.[35–38]

Herein, we describe in greater detail the first-line therapeutic regimens currently in use in mRCC.

ICIs in mRCC (dual-type combination)

Nivolumab + ipilimumab

The phase 3 CheckMate 214 trial assessed this association in comparison to sunitinib in 847 patients with metastatic ccRCC.[31,39,40] In intermediate-poor IMDC risk groups, first-line treatment with nivolumab and ipilimumab was associated with higher response rates (41.9% vs. 26.8%, $p < .001$), PFS, and an increase in 12-month OS rate (80% vs. 72%, $p < .001$). At a minimum follow-up of 4 y, nivolumab plus ipilimumab has shown to be more effective than sunitinib in terms of both overall responses ($RR^{ORR\ [objective\ response\ rates]}$ 1.56; 95% CI: 1.29–1.90) and complete responses (RR 7.28; 95% CI: 3.14–16.91), with both progression risk and mortality risk, respectively, of 26% (HR [hazard ratio]^{PFS} .74; 95% CI [confidence interval]: 0.62–0.88) and 35% (HR^{OS} .65; 95% CI: 0.54–0.78). Additionally, only 1.4% and 6.5% of sunitinib treated patients showed a full response in the intermediate-poor risk and favorable risk groups, respectively, compared to 10% of patients under combined therapy (across all IMDC risk categories).[41] Nevertheless, in favorable risk IMDC group, ORRs were less than in the control arm (sunitinib) (29.6 vs. 51.6%, $p = .0005$), PFS was lower (12.4 vs. 28.9 months, HR 1.84, 95% CI: 1.29–2.62), and also OS was reduced (HR 0.93; 95% CI 0.62–1.4; OS not reached).

Moreover, PD-L1 expression was not predictive of either response to treatment or to survival. Regarding adverse events, the combination of nivolumab and ipilimumab was linked to a lower incidence of serious adverse events compared to sunitinib (RR of G3–5 adverse events: 0.73; 95% CI: 0.65–0.81), even if the incidence of adverse events in general was significantly higher (especially tiredness, pruritus, rash, nausea, diarrhea, and increases in transaminase levels), increasing the likelihood of treatment termination (RR 1.76; 95% CI: 1.34–2.32). However, the rate of such adverse events was comparable to those seen in immune checkpoint inhibitor trials in other solid cancers. Nevertheless, grade ≥3 adverse events occurred in a high percentage of patients (46%) and high-dose corticosteroids were necessary in 36% of them (a higher percentage if compared to therapy with immune checkpoint inhibitor associated with an anti-VEGF drug).

Regarding patients' reported outcomes, there have been decreases (ranging from 25% to 43%) in the probability of a significant decline in health-related quality of life scores, underlining reported better levels of such parameter. Therefore, given the outcomes for tolerability and quality of life, FDA approved such first-line therapy for intermediate or poor-risk mRCC in April 2018.

This trial has shown a significant impact on clinical practice, since the association of nivolumab and ipilimumab has become the standard-of-care first-line therapy for the aforementioned mRCC risk groups.

VEGF inhibitors + ICIs in mRCC

Pembrolizumab + axitinib

In the phase 3 KEYNOTE−426 trial, 861 patients with metastatic ccRCC were randomly assigned to receive either pembrolizumab and axitinib or sunitinib as their first line of treatment.[33,42] In terms of both PFS and OS, this combination has been demonstrated to be effective throughout a follow-up period of at least 30 months.

In particular, the combination of pembrolizumab and axitinib demonstrated greater activity in the subgroup of 269 patients with favorable IMDC risk (RR^{ORR} 1.38; 95% CI: 1.13–1.69) and better control of progression (HR^{PFS} .79; 95% CI: 0.57–1.09) compared to sunitinib, but with similar OS (HR^{OS} 1.06; 95% CI: 0.60–1.86). In the 592 IMDC intermediate-high risk category patients, the combination of pembrolizumab and axitinib demonstrated greater activity (RR^{ORR} 1.58; 95% CI: 1.32–1.90) than sunitinib, with a reduction in the risk of progression by 31% (HR^{PFS} .69; 95% CI: 0.56–0.84) and death by 37% (HR^{OS} .63; 95% CI: 0.50–0.81). Overall, the treatment based on pembrolizumab plus axitinib showed statistically significant improvements in ORR (59.3% vs. 35.7%, $p < .001$), PFS (15.4 vs. 11.1 months, $p < .0001$), and OS (HR 0.68, 95% CI: 0.55–0.85, $p = .0003$) regardless of PD-L1 expression and IMDC risk group (except for OS in favorable IMDC risk group, as reported above).

In the entire population, the incidence of serious adverse events was similar (RR 1.07; 95% CI: 0.97–1.18); however, the combined therapy group had a greater incidence of adverse events that resulted in treatment termination (RR of G3–5 adverse events 2.56; 95% CI: 1.85–3.54) as well as adverse immuno-related events (RR 6.27; 95% CI: 3.14–12.51). However, there were no unexpected therapy-related side effects, and diarrhea and hypertension were frequent toxicities in both groups.

At long-term follow-up, pembrolizumab plus axitinib therapy appeared to provide a durable antitumor response, as evidenced by ORRs of 85%, PFS rates of 94.7%, and OS rates of 74.8% at 36 months.[43] The FDA authorized pembrolizumab plus axitinib as a combination in April 2019 for the first-line treatment of mRCC, hence the findings from KEYNOTE−426 have a significant impact on clinical practice.

Pembrolizumab + lenvatinib

The efficacy of the anti-VEGFR TKI lenvatinib in combination with either everolimus or pembrolizumab has been compared with sunitinib in patients with metastatic ccRCC in the phase 3 randomized CLEAR-KN581 trial.[44]

Compared to lenvatinib plus everolimus and sunitinib, treatment with lenvatinib plus pembrolizumab was linked with a greater ORR (71% vs. 53.5% vs. 36.1%). In particular, pembrolizumab plus lenvatinib was administered to 355 individuals, and sunitinib was given to 357 of them. The median period without evidence of disease progression after a median follow-up of 22.3 months was 23.9 months (95% CI: 20.8–27.7) in the pembrolizumab + lenvatinib arm versus 9.2 months (95% CI: 6.0–11.0) in the control arm, and these data showed statistical significance ($p < .001$). The combination of pembrolizumab and lenvatinib was associated with

a 61% relative reduction of progression risk compared to sunitinib (HR 0.39; 95% CI: 0.32–0.49; $p < .001$). Moreover, when compared to sunitinib, lenvatinib with pembrolizumab substantially improved also OS (HR 0.66; 95% CI: 0.49–0.88, $p = .005$, OS not reached) and reduced the risk of mortality by 28% (HR 0.72; 95% CI: 0.55–0.93). These benefits were independent from both PD-L1 expression and IMDC risk group. When compared to sunitinib, lenvatinib plus everolimus also provided prolonged PFS (14.7 vs. 0.2 months, $p < .001$) but this did not result in an improvement in OS (although this last data is not statistically significant). After 33.7 months of follow-up, it is still impossible to estimate the median survival for both treatment modalities in terms of OS.

Regarding adverse events, 82.4% of patients receiving lenvatinib plus pembrolizumab, 83.1% of patients receiving lenvatinib plus everolimus, and 71.8% of patients receiving sunitinib experienced grade ≥3 side effects: for example, hypertension, diarrhea, and increased lipase levels were present in at least 10% of patients in any group.

When sunitinib was employed as a comparator, the risk of a major adverse event rose by 15% in patients receiving lenvatinib plus pembrolizumab (RR 1.15; 95% CI: 1.06–2.05). With a relative increase in risk of permanent treatment interruption of more than two times and a half (RR 2.58; 95% CI: 1.93–3.46) when compared to sunitinib, the cumulative incidence of adverse events leading to treatment interruption was 37.2% in the pembrolizumab + lenvatinib arm as opposed to 14.4% in the control arm. Lenvatinib and pembrolizumab were given FDA approval in 2021 for the treatment of mRCC. However, further follow-up data are needed.

Nivolumab + cabozantinib

This drug combination has been compared with sunitinib in patients with metastatic ccRCC in the phase 3 randomized CheckMate−9ER trial.[45] Sunitinib (328 patients) or nivolumab + cabozantinib (323 patients) has been given to a total of 651 patients. Nivolumab plus cabozantinib treatment was associated with significantly higher response rates (55.7% vs. 27.1%, $p < .0001$), longer PFS (16.6 vs. 8.3 months; HR 0.51; 95% CI: 0.41–0.64; $p < .0001$), and 12-month OS (85.7% vs. 75.6%, $p = .001$) compared to sunitinib. About 55.7% of patients who received nivolumab + cabozantinib and 27.1% of patients who received sunitinib had an objective response. These benefits were independent from both PD-L1 expression and IMDC risk. Grade ≥3 adverse events occurred in 75.3% of nivolumab + cabozantinib patients and in 70.6% of sunitinib patients. Although rates of hepatotoxicity were greater in the nivolumab + cabozantinib group, there were no unexpected treatment-related side effects. Due to immune-related toxicities, 19.1% of the patients in the nivolumab + cabozantinib group required high dosage corticosteroid therapy. Additionally, 19.7% of patients overall stopped at least one drug due to negative outcomes. However, patients treated with nivolumab + cabozantinib reported a higher quality of life than those treated with sunitinib.

Based on the findings of this study, the FDA authorized first-line nivolumab and cabozantinib for mRCC in January 2021. However, further follow-up data are needed.

Table 1 summarizes key statistics for each approved first-line combination treatment compared to sunitinib.

Table 1. Clinical trials for ICIs as first-line treatment of mRCC.

Trial (study name)	Targeting agents and comparison	ORR stratified according to IMDC risk groups	PFS stratified according to IMDC risk groups	OS stratified according to IMDC risk groups	G3–5 adverse events according to IMDC risk groups (RR compared to sunitinib)
CheckMate 214	Nivolumab + ipilimumab vs. sunitinib	Favourable: 29.6 vs. 51.6% ($p = .0005$) Intermediate-poor: 41.9 vs. 26.8% ($p < .0001$)	Favourable: 12.4 vs. 28.9 months; HR 1.84; 95% CI 1.29–2.62 Intermediate-poor: 11.2 vs. 8.3 months; HR 0.74; 95% CI 0.62–0.88	Favourable: HR 0.93; 95% CI: 0.62–1.4; OS not reached Intermediate-poor: 48.1 vs. 26.6 months; 50% vs. 35.8%; HR 0.65; 95% CI 0.54–0.78	Intermediate-poor risk group: RR 0.73; 95% CI: 0.65–0.81
KEYNOTE−426	Pembrolizumab + axitinib vs. sunitinib	All risk groups: 59.3% vs. 35.7%; $p < .001$	All risk groups: 15.4 vs. 11.1 months; $p < .0001$	All risk groups: HR 0.68; 95% CI 0.55–0.85; $p = .0003$; median OS not reached	All risk groups: RR 2.56; 95% CI: 1.85–3.54
CLEAR-KN581	Pembrolizumab + lenvatinib (1st group) or everolimus + lenvatinib (2nd group) vs. sunitinib (control)	All risk groups: 71% (1st group) vs. 53.5% (2nd group) vs. 36.1% (control); p value not available	All risk groups: 23.9 vs. 9.2 months, $p < .001$ (1st group vs. control); 14.7 vs. 9.2 months, $p < .01$ (2nd group vs. control)	All risk groups: HR 0.66; 95% CI 0.49–0.88; $p = .005$; OS not reached (1st group vs. control; exception observed in patients with favorable risk features) All risk groups: HR 1.15; 95% CI 0.88–1.5; $p = .3$; OS not reached (2nd group vs. control)	All risk groups: RR 1.15; 95% CI: 1.06–2.05 (1st group); incidence of G3–5 adverse events: 82.4% of lenvatinib + pembrolizumab patients vs. 83.1% of lenvatinib + everolimus patients vs. 71.8% of sunitinib patients
CheckMate−9ER	Nivolumab + cabozantinib vs. sunitinib	55.7% vs. 27.1%; $p < .001$	All risk groups: 16.6 vs. 8.3 months; HR 0.51; 95% CI 0.41–0.64; $p < .0001$	All risk groups: 85.7% vs. 75.6% at 12 months; HR 0.6; 98% CI 0.4–0.89; $p = .001$	All risk groups (incidence of G3–5 adverse events): 75.3% of nivolumab + cabozantinib patients vs. 70.6% of sunitinib patients

Discussion

The selection of first-line therapy for mRCC is primarily based on the IMDC prognostic risk model. In fact, first-line therapeutic options in the favorable risk group include ICIs alone or in association with antiangiogenic agents, while ipilimumab and nivolumab, as well as combinations of an ICI and a TKI, represent choices for diseases with an intermediate or poor prognosis. Patients with a high disease burden and severe symptoms may benefit from treatment with ICI and TKI since the TKI may provide a quick response to therapy. Moreover, nowadays, we have long-term follow-up periods showing the advantages of therapy with ipilimumab and nivolumab in terms of lasting response and high survival, while the majority of clinical trials examining combinations of ICIs and TKIs have shorter follow-up periods and insufficient long-term data, making it unclear whether these treatments can provide comparable responses. Nevertheless, given the greater rates of immune-related toxicities and demand for high dosage corticosteroids associated with ipilimumab and nivolumab treatments compared to ICI and TKI treatments, toxicity is also a crucial factor to take into account. For such reason, treatment choice should depend on patients' features and underlying co-morbidities: for example, immunotherapy combinations should be avoided in cases of underlying autoimmune diseases and the association of lenvatinib plus pembrolizumab may be a serious problem in the presence of cardiovascular comorbidities, since it has been linked to increased rates of hypertension and hyperlipidemia. Moreover, hepatotoxicity represents an important contraindication for mRCC patients who also suffer from liver disease: in this subset, in fact, both pembrolizumab + axitinib and nivolumab + cabozantinib therapies are not recommended.[46] Of note, even if many clinicians feel that the anti-PD-1 agents are not as effective in mRCC, a recent meta-analysis showed that combination therapy with anti-PD-1/PD-L1 inhibitors reduced the risk of death and progression by 26% and 32%, respectively, compared to sunitinib alone (HR^{OS} .74, 95% CI 0.67–0.81, $p < .001$; HR^{PFS} .68, 95% CI 0.54–0.85, $p = .001$). The complete response rate and overall response rate of immuno-based combination treatment were both improved (respectively OR 3.04, 95% CI 2.31–3.99, $p = .001$ and OR 2.53, 95% CI 1.77–3.62, $p < .03$).[47] Moreover, results from KEYNOTE −564 phase 3 trial showed that pembrolizumab improved both OS and disease-free survival (DFS) in ccRCC patients at high risk for recurrence following nephrectomy (this study also included mRCC patients who underwent radical local and secondary localization surgery).[48] Based on these results, pembrolizumab was authorized for RCC treatment in 2021. All of these data denote the substantial efficacy of anti-PD-1 drugs and its biological rationale could lie in the fact that, being PD-1 present on T cell membrane surface, anti-PD-1 drugs can activate T cells even when PD-L1 expression by tumor cells is low or absent.[49]

Conclusions

In the past 10 y, the introduction of new TKIs and the increasing use of ICIs have changed the therapeutic landscape of mRCC. As a result, patients with mRCC now have better prognoses and longer survivals. However, most of them experience disease relapse after resistance development. Treatment with ICIs, both in a dual-type combination and in combination with a TKI, has given better results than sunitinib alone, and more combined treatments are being studied to broaden treatment options. Nonetheless, there is a critical need to identify new biomarkers and to develop novel targeted agents to overcome tumor resistance and to guide treatment decisions.

Authors' contributions

VF and FP wrote the original draft and produced the table; PT, LML, CP, and MM reviewed and edited the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported that there is no funding associated with the work featured in this article.

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