Abstract
Renal cell carcinoma (RCC) has been recognized as a cancer responsive to the activation of the immune system. In the 1980s, interferon-alpha and interleukin-2 were shown to prolong survival, but they were not widely used due to toxicities. Then, vascular endothelial growth factor receptor and mammalian target of rapamycin inhibitors demonstrated clinical benefits and became the principal treatment in the first- and second-line setting of metastatic RCC (mRCC). In recent years, the efficacy of immune checkpoint inhibitors (ICIs) is confirmed, either alone or in combination with ICI or antiangiogenic agents. ICI-based immunotherapies have now changed the landscape of treatment of mRCC. In this article, we will review the progress of immunotherapy in clear-cell mRCC.

Keywords: And CTLA-4, immunotherapy, PD-1, renal cell carcinoma

INTRODUCTION
In Taiwan, renal cell carcinoma (RCC) represents the majority of kidney cancers (>90%) with an estimated 1200 newly diagnosed cases in 2016.[1] Clear cell is the most common histological subtype (60%), which is characterized by increased angiogenesis through the activation of the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin pathways.[2] From 2005 to 2017, a number of antiangiogenic agents, mostly VEGF tyrosine kinase inhibitors (TKI), had been approved by the FDA for metastatic RCC (mRCC).[3,4] The prognosis of patients treated with VEGF TKI varied, with a median 2-year survival rate being 75%, 53%, and 7% in favorable-, intermediate-, and poor-risk groups assessed by the International mRCC Database Consortium (IMDC) criteria.[5] Although the first-line antiangiogenic therapies do benefit mRCC patients, the durable response is uncommon for intermediate/poor-risk patients. RCC has historically been recognized as an immunogenic cancer amenable to immune stimulation with interferon-alpha (IFN-α) and high-dose (HD) interleukin-2 (IL-2), which provides a durable complete response rate of 5%.6-8 Recently, immune checkpoint inhibitors (ICIs), which block programmed death 1 (PD-1), PD-ligand 1 (PD-L1), or cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), have been demonstrated to evoke effective anticancer immunity. Many studies have examined the role of these drugs as monotherapies and combination
therapies in mRCC. Herein, we briefly review the progress of immunotherapy in the treatment of mRCC.

**Cytokine Therapies**

**Interferon-alpha**

The role of the immune system in mRCC was first explored through the use of immunoregulatory cytokines, including IFN-α and IL-2. In a multicenter, randomized controlled trial, mRCC patients were randomly assigned to subcutaneous IFN-α or medroxyprogesterone acetate. The study met its primary endpoint, the overall survival (OS), which showed a 28% reduction in the risk of death in the IFN-α group (median OS: 8.5 months vs. 6 months, hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.55–0.94; P = 0.017). The objective response rate (ORR) also favored the IFN-α group (14% vs. 2%). Despite its efficacy, recent Cochrane review reveals that IFN-α monotherapy probably increases 1-year mortality compared with standard targeted therapies with sunitinib or temsirolimus (relative risk: 1.30; 95% CI: 1.13–1.51) and is associated with a higher incidence of Grade 3 or higher treatment-related adverse events (TRAEs) (risk ratio [RR]: 1.17; 95% CI: 1.03–1.32).

IFN-α had also been investigated in combination with other drugs to increase immune response. In the AVOREN and CALGB 90206 studies, the combination of IFN-α and bevacizumab significantly prolonged the progression-free survival (PFS) but not OS. In addition, the combination increased the incidence of Grade 3 hypertension and overall adverse events. In the ARCC trial, the combination of IFN-α and temsirolimus did not significantly extend OS compared with temsirolimus or IFN-α alone. As a result, IFN-α, either alone or combined with bevacizumab or temsirolimus, was not routinely used in treating mRCC patients.

**Interleukin-2**

IL-2 is a cytokine predominantly secreted by antigen-stimulated CD4+ T-cells. The binding of IL-2 and its receptor not only leads to the activation and differentiation of antigen-specific T-cells but also potentiates the cytotoxic activity of natural killer cells. Fyfe et al. reported the efficacy of HD IL-2 in mRCC patients when HD IL-2 was administered by 15-min intravenous (IV) infusion of 600,000 or 720,000 IU/kg every 8 h for 5 days per cycle. The ORR was 14%, including a durable complete response rate of 5%. Nevertheless, HD IL-2 was associated with severe toxicities, with the need of vasopressor support in more than 50% of patients and treatment-related death in 4% of patients. Given the toxicities of HD IL-2, low-dose (LD) IL-2 was studied as monotherapy or in combination with IFN-α. Although LD IL-2-based therapies demonstrated equivalent OS and less toxicities, they exhibited a lower response rate (10% vs. 20%) and a shorter duration of response compared with HD IL-2. Hence, HD IL-2 was approved by the FDA in 1992 in treating mRCC patients who had good performance status and preserved organ functions.

**Immune Checkpoint Inhibitors**

**Ipilimumab (cytotoxic T-lymphocyte–associated antigen-4 inhibitor)**

The interaction between CTLA-4 on T-cells and its ligand, the B-7 family of molecules, on antigen-presenting cells, inhibits proliferation and functions of T-cells. Ipilimumab, a monoclonal antibody blocking CTLA-4, had been used in mRCC treatment. In a Phase II study reported by Yang et al., patients received HD ipilimumab (all doses at 3 mg/kg) or LD ipilimumab (a loading dose of 3 mg/kg with subsequent doses of 1 mg/kg) every 3 weeks. The ORR was 12.5% and 4.7% in HD and LD ipilimumab, respectively, and some patients who failed prior IL-2 therapy still responded. The incidence of Grade 3 or worse TRAE was much higher in the HD ipilimumab group (43% vs. 14%). Notably, there was an association between autoimmune side effects and ORR (30% vs. 0% in patients with or without side effects).

**Nivolumab (programmed death 1 inhibitor)**

PD-1 is an inhibitory receptor expressed by T-cells, and its blockade can overcome the immune tolerance of cancers. Nivolumab had been evaluated in an early Phase I study at a dose of 1 mg/kg or 10 mg/kg every 2 weeks. Nine of thirty-three mRCC patients had a response (27%), and the response was durable. In a Phase II study, a total of 168 clear-cell mRCC patients who failed previous VEGF inhibitors were randomly assigned to nivolumab (0.3 mg/kg, 2 mg/kg, or 10 mg/kg every 3 weeks). About 70% of the patients received more than one prior systemic therapy. The ORR was almost the same in different dosing schedules (20%). The median PFS was 2.7, 4, and 4.2 months, and the median OS was 18.2, 25.5, and 24.7 months, respectively. The most common adverse event was fatigue (22%–35%), and Grade 3 or 4 TRAE occurred in 11% of the patients.

These findings led to the randomized Phase III study, CheckMate 025, which compared nivolumab (3 mg/kg every 2 weeks) with everolimus (10 mg orally once daily) in clear-cell mRCC patients previously treated with more than one antiangiogenic therapy [Table 1].

A total of 821 patients were enrolled, and the primary endpoint was OS. Nivolumab significantly increased the ORR (25% vs. 5%, odds ratio: 5.98; 95% CI: 3.68–9.72; P < 0.001) and prolonged the median OS (25 months vs. 19.6 months, HR 0.73; 98.5% CI, 0.57–0.93; P = 0.002), without difference in the median PFS. Notably, PD-L1 positivity (defined as tumor PD-L1 membrane expression ≥1%) was prognostic rather than predictive. Grade 3 or 4 TRAE occurred in 19% and 37% of the patients who received nivolumab and everolimus, respectively. The most common Grade 3 or 4 TRAE in nivolumab group was fatigue (2%). Nivolumab gained the FDA approval for mRCC patients who were refractory to VEGF inhibitors in November 2015.

**Atezolizumab (programmed death-ligand 1 inhibitor)**

Atezolizumab was studied in a Phase I trial, which enrolled a total of 70 mRCC patients (clear-cell type = 63; nonclear-cell
More than 80% of the patients were of intermediate/poor-risk, and failure at least one prior line of systemic therapy. The ORR was 15%, which differed on the basis of immune cell (IC) PD-L1 status (18% vs. 9% in IC PD-L1-positive and negative patients, respectively). The median PFS was 5.6 months, and the median OS was 28.9 months. According to these findings, atezolizumab was viewed as a promising anticancer therapy and studied in subsequent combination trials.

**Pembrolizumab (programmed death 1 inhibitor)**
Pembrolizumab had been evaluated in treatment-naive mRCC patients. In the KEYNOTE-427 study, a total of 110 clear-cell mRCC patients were included, and pembrolizumab mono-therapy (200 mg every 3 weeks) demonstrated an ORR of 33.6%.[31] The subgroup analysis showed that an ORR was higher in the intermediate/poor-risk patients than in the favorable-risk patients (37.3% vs. 27.5%). Grade 3 or higher TRAE occurred in 18.2% of the patients, and one patient had Grade 5 pneumonitis. KEYNOTE-427 demonstrated the efficacy and tolerable toxicities of single-agent ICI in the frontline treatment of mRCC.

**Nivolumab plus ipilimumab**
Given the efficacy in melanoma, the combination of nivolumab and ipilimumab was evaluated in patients with mRCC. In the Phase I CheckMate 016 study, mRCC patients were randomized to tri-weekly nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), or nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3) for four doses followed by maintenance bi-weekly nivolumab 3 mg/kg until disease progression or intolerable toxicity.[32] At the time of the analysis, the N3I3 group was non-inferior to the N3I1 group for OS (HR: 0.73; P = 0.002). The ORR was 42% versus 27% (P < 0.001), and the complete response rate was 9% versus 1%, respectively. The median PFS did not differ significantly between the two groups (11.6 months vs. 8.4 months, HR: 0.82, P = 0.38, not met the prespecified level of 0.009). The incidence of Grade 3 or 4 TRAE was 46% in the N3I1 group and 63% in the sunitinib group. TRAE leading to drug discontinuation was documented in 22% and 12% of the patients, respectively. In exploratory analyses of favorable-risk

### Table 1: Published Phase III immune checkpoint inhibitor trials in metastatic renal cell carcinoma

| Trial (patient number) | Treatment | Primary endpoints | Medium follow-up (months) | ORR (CR) | mPFS (months) | mOS (months) |
|------------------------|-----------|------------------|---------------------------|----------|----------------|--------------|
| **Second-line setting** |           |                  |                           |          |                |              |
| CheckMate 025 (n=821)[23] | Nivolumab versus everolimus | OS in ITT patients | 24 | ITT: 25% (1%) versus 5% (<1%) | 4.6 versus 4.4 (HR 0.88; P=0.11) | 25 versus 19.6 (HR 0.73; P=0.002) |
| IMmotion 151 (n=915)[37] | Atezolizumab + bevacizumab versus sunitinib | PFS in PD-L1 + patients | 15 | Intermediate/poor risk: 42% (9%) versus 29% (1%) | Intermediate/poor risk: 8.2 versus 8.3 (HR: 0.77; P=0.0014) | Intermediate/poor risk: NR versus 26.6 (HR: 0.66; P<0.0001) |
| KEYNOTE 426 (n=861)[21] | Pembrolizumab + axitinib versus sunitinib | PFS and OS in ITT patients | 12.8 | ITT: 59.3% (5.8%) versus 55.7% | ITT: 15.1 versus 11.1 (HR: 0.69; P=0.001) | ITT: NR (HR: 0.53; P<0.0001) |
| JAVELIN Renal 101 (n=886)[39] | Avelumab + axitinib versus sunitinib | PFS and OS in PD-L1 + patients | 11.6 | PD-L1+: 55.2% (4.4%) versus 25.5% | PD-L1+: 13.8 versus 7.2 (HR: 0.61; P<0.001) | PD-L1+: NR (HR: 0.82; P=0.38) |

CR: Complete response, HR: Hazard ratio, ITT: Intention to treat, OS: Overall survival, PFS: Progression-free survival, mOS: Median OS, mPFS: Median PFS, NR: Not reached, ORR: Objective response rate

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1. More than 80% of the patients were of intermediate/poor-risk and had failed at least one prior line of systemic therapy. The ORR was 15%, which differed on the basis of immune cell (IC) PD-L1 status (18% vs. 9% in IC PD-L1-positive and negative patients, respectively).
2. The median PFS was 5.6 months, and the median OS was 28.9 months. According to these findings, atezolizumab was viewed as a promising anticancer therapy and studied in subsequent combination trials.
3. Pembrolizumab had been evaluated in treatment-naive mRCC patients. In the KEYNOTE-427 study, a total of 110 clear-cell mRCC patients were included, and pembrolizumab mono-therapy (200 mg every 3 weeks) demonstrated an ORR of 33.6%.[31] The subgroup analysis showed that an ORR was higher in the intermediate/poor-risk patients than in the favorable-risk patients (37.3% vs. 27.5%). Grade 3 or higher TRAE occurred in 18.2% of the patients, and one patient had Grade 5 pneumonitis. KEYNOTE-427 demonstrated the efficacy and tolerable toxicities of single-agent ICI in the frontline treatment of mRCC.
4. Nivolumab plus ipilimumab

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patients, sunitinib group demonstrated a higher ORR (52% vs. 29%, *P* < 0.001) and longer median PFS (25.1 months vs. 15.3 months, HR: 2.18, *P* < 0.001). However, the complete response rate was higher in the N311 group than in the sunitinib group (11% vs. 6%). The positive results led to the FDA approval for ipilimumab plus nivolumab in the first-line setting for intermediate/poor-risk mRCC patients in April 2018. After an extended follow-up of 32.4 months, the superior efficacy of combination therapy over sunitinib was maintained.\(^\text{[26]}\)

**Combination of Immune Checkpoint Inhibitors and Antiangiogenic Agents**

VEGF plays an important role in vascular normalization, which facilitates the infiltration of ICs into the tumor microenvironment.\(^\text{[24]}\) The combination of PD-1 blockade and antiangiogenesis was shown to have synergistic antitumor effects.\(^\text{[25]}\) There have been several Phase I/II trials evaluating combination therapy with IC inhibitors and antiangiogenic agents, showing a much higher ORR.\(^\text{[4]}\) Based on these promising results, several randomized Phase III trials compared the efficacy of combination therapy with sunitinib in the first-line setting of mRCC \(^\text{[Table 1]}\).\(^\text{[26]}\)

**Atezolizumab plus bevacizumab**

The activity of atezolizumab plus bevacizumab in treatment-naïve mRCC patients was studied in the Phase II IMmotion 150 trial.\(^\text{[29]}\) A total of 305 patients was randomized to a combination of atezolizumab and bevacizumab, atezolizumab, or sunitinib alone. In PD-L1-positive populations, the combination group had improved PFS (14.7 months vs. 7.8 months in sunitinib, HR: 0.64; 95% CI: 0.38–1.08; *P* = 0.095) and response rate (46% vs. 27%). However, there was no difference in PFS and ORR in the intention-to-treat (ITT) population. Forty percent of the patients with combination therapy had Grade 3 or 4 TRAE (57% in the sunitinib group), and only 9% of the patients discontinued therapy due to treatment-related toxicities. In the exploratory biomarker analyses, the high expression of angiogenesis gene signature was related to better ORR (46% vs. 9%, *P* < 0.001) and longer PFS (19.5 months vs. 3.7 months, HR: 0.31; 95% CI: 0.18–0.55; *P* < 0.001) in the sunitinib group. In addition, the high expression of effector T-cell gene signature (\(T_{\text{eff}}^{\text{high}}\)) correlated with better ORR (49% vs. 16%, *P* = 0.002) and longer PFS (21.6 months vs. 5.6 months, HR: 0.50; 95% CI, 0.30–0.86; *P* = 0.011) in the combination group. Given that myeloid differentiation was related to immunosuppressive activity, its effects on treatment efficacy were also investigated. Atezolizumab monotherapy had worse PFS in the \(T_{\text{eff}}^{\text{high}}\)-Myeloid\(^{\text{high}}\) tumors compared with the \(T_{\text{eff}}^{\text{high}}\)-Myeloid\(^{\text{low}}\) tumors (HR: 3.82; 95% CI: 1.7–8.6; *P* = 0.001). Interestingly, the outcome significantly improved after the addition of bevacizumab (HR: 0.25; 95% CI: 0.10–0.60; *P* = 0.002), suggesting that bevacizumab could possibly reverse the immune escape mechanism of myeloid-mediated immunosuppression.

On the basis of promising results in IMmotion 150 study, the Phase III IMmotion 151 trial evaluated the efficacy of combination therapy (atezolizumab [1200 mg] plus bevacizumab [15 mg/kg] IV every 3 weeks) versus sunitinib (50 mg orally once daily, 4 weeks on, 2 weeks off) in the first-line setting of mRCC.\(^\text{[27]}\) This study enrolled 915 patients with clear-cell or sarcomatoid histology. Co-primary endpoints were investigator-assessed PFS in the PD-L1-positive population and OS in the ITT population. In PD-L1-positive patients, the PFS was longer (11.2 months vs. 7.7 months, HR: 0.74; 95% CI: 0.57–0.96; *P* = 0.0217) and the ORR was higher (43% vs. 34%) in the combination group than in the sunitinib group. In the subgroup analysis for PFS, patients with sarcomatoid differentiation had longer survival time (HR: 0.46; 95% CI: 0.28–0.78). For the other co-primary endpoints of OS in the ITT population, there was no difference between the two groups at the second interim analysis (33.6 months vs. 34.9 months, HR: 0.93; 95% CI: 0.76–1.14; *P* = 0.4751). Forty percent of the patients in the combination group and 54% of the patients in the sunitinib group had Grade 3 or 4 TRAE, with 5% and 8% of patients leading to treatment discontinuation, respectively.

**Pembrolizumab plus axitinib**

Atkins et al. reported a Phase Ib study which evaluated the combination of pembrolizumab and axitinib in mRCC patients.\(^\text{[37]}\) A total of 52 patients were enrolled, and the regimen showed an extremely high ORR of 73% (complete response rate: 8%). Grade 3 or worse TRAE occurred in 65% of the patients, the most frequent being hypertension (23%), diarrhea (10%), and fatigue (10%). Due to the inspiring results, subsequent randomized Phase III study was conducted.

In the KEYNOTE-426 study, a total of 861 treatment-naïve clear-cell mRCC patients were randomly assigned to receive pembrolizumab (200 mg intravenously every 3 weeks for up to 35 weeks) plus axitinib (5 mg orally twice daily), or sunitinib monotherapy (50 mg orally once daily, 4 weeks on, 2 weeks off).\(^\text{[28]}\) The primary endpoints were OS and PFS in the ITT population. After a median follow-up of 12.8 months, pembrolizumab plus axitinib showed an increased 12-month survival rate (89.9% vs. 78.3%, HR: 0.53; 95% CI: 0.38–0.74; *P* < 0.0001), longer PFS (15.1 months vs. 11.1 months, HR: 0.69; 95% CI, 0.57–0.84; *P* < 0.001), and a higher ORR (59.3% vs. 35.7%, *P* < 0.001). The benefit of combination therapy was shown across all IMDC-risk groups and different PD-L1 expression status. Grade 3 or higher adverse events of any cause occurred in 75.8% and 70.6% of the patients in the combination arm and sunitinib arm, respectively. The combination arm led to the discontinuation of both the drugs in 10.7% of the patients and dose reduction of axitinib in 20.3%. On the other hand, the sunitinib arm led to the discontinuation in 13.9% of the patients and dose reduction in 30.1%. Given the promising results, the FDA approves pembrolizumab plus axitinib for first-line treatment of advanced RCC in April 2019.


**Table 2: Selected ongoing immune checkpoint inhibitor combination trials in renal cell carcinoma**

| Trial | Phase | Study design |
|-------|-------|--------------|
| ICI + anti-VEGF | III | Nivolumab + cabozantinib versus sunitinib in treatment-naïve mRCC (CheckMate 9ER) |
| NCT03141177 | III | Atezolizumab + cabozantinib in advanced/metastatic solid tumors |
| NCT03179069 | I/II | Atezolizumab + bevacizumab in advanced nonclear-cell RCC |
| NCT02724878 | II | Pembrolizumab + lenvatinib versus lenvatinib + everolimus in advanced RCC |
| NCT02811861 | III | Pembrolizumab + lenvatinib versus lenvatinib + everolimus versus sunitinib in treatment-naïve mRCC (CLEAR) |
| ICI + cytokines | I/II | Nivolumab +/- ipilimumab + NKTR-214 (pegylated IL-2 prodrug) in advanced/metastatic solid tumors (PIVOT-02) |
| NCT02983045 | I/II | Nivolumab + IL-2 in clear-cell mRCC |
| NCT02989714 | II/II | Pembrolizumab + PEGylated IFN alpha-2b or ipilimumab in advanced melanoma or RCC (KEYNOTE-29) |
| NCT02964078 | II | Pembrolizumab+IL2 in mRCC |
| ICI + immune modulator | I | Nivolumab + APX005M (CD40 agonist) + cabiralizumab (CSF1R inhibitor) in advanced melanoma, NSCLC, or RCC |
| NCT03502330 | I | Atezolizumab + CPI-444 (adenosine receptor inhibitor) or CPI-444 alone in advanced cancers |
| NCT02655822 | I | Pembrolizumab + itacitinib (JAK1 inhibitor) or INCB050465 (PI3K-delta inhibitor) in advanced solid tumors |
| NCT03598816 | II | Durvalumab + tremelimumab + vaccine-orchestrated treatment in advanced/metastatic RCC (PIVOT-RCC) |
| ICI + others | I/II | Atezolizumab + entinostat (HDAC inhibitor) in advanced RCC |
| NCT03024437 | I/II | Pembrolizumab + vorinostat (HDAC inhibitor) in advanced RCC or UC |
| NCT03483883 | I | Pembrolizumab + IL-2 in advanced RCC |

**ICI + other**

- NCT03024437: Atezolizumab + entinostat (HDAC inhibitor) in advanced RCC
- NCT02619253: Pembrolizumab + vorinostat (HDAC inhibitor) in advanced RCC or UC
- NCT03483883: Pembrolizumab + IL-2 in advanced RCC

**ICI + immune modulator**

- NCT03502330: Nivolumab + APX005M (CD40 agonist) + cabiralizumab (CSF1R inhibitor) in advanced melanoma, NSCLC, or RCC
- NCT02655822: Atezolizumab + CPI-444 (adenosine receptor inhibitor) or CPI-444 alone in advanced cancers
- NCT02646748: Pembrolizumab + itacitinib (JAK1 inhibitor) or INCB050465 (PI3K-delta inhibitor) in advanced solid tumors
- NCT03598816: Durvalumab + tremelimumab + vaccine-orchestrated treatment in advanced/metastatic RCC (PIVOT-RCC)

**ICI + cytokines**

- NCT02983045: Nivolumab +/- ipilimumab + NKTR-214 (pegylated IL-2 prodrug) in advanced/metastatic solid tumors (PIVOT-02)
- NCT02989714: Nivolumab + IL-2 in clear-cell mRCC
- NCT02964078: Pembrolizumab+IL2 in mRCC

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- NCT03598816: Durvalumab + tremelimumab + vaccine-orchestrated treatment in advanced/metastatic RCC (PIVOT-RCC)

**ICI + cytokines**

- NCT02983045: Nivolumab +/- ipilimumab + NKTR-214 (pegylated IL-2 prodrug) in advanced/metastatic solid tumors (PIVOT-02)
- NCT02989714: Nivolumab + IL-2 in clear-cell mRCC
- NCT02964078: Pembrolizumab+IL2 in mRCC

**ICI + other**

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- NCT02619253: Pembrolizumab + vorinostat (HDAC inhibitor) in advanced RCC or UC
- NCT03483883: Pembrolizumab + IL-2 in advanced RCC

CSF1R: Colony-stimulating factor 1 receptor, HDAC: Histone deacetylase, ICI: Immune checkpoint inhibitor, IL-2: Interleukin 2, JAK1: Janus kinase 1, NSCLC: Non-small cell lung cancer, PI3K: Phosphoinositide 3-kinase, RCC: Renal cell carcinoma, mRCC: Metastatic RCC, UC: Urothelial carcinoma, VEGF: Vascular endothelial growth factor
Identification of predictive biomarkers is urgently required to balance the benefit and toxicities. Second, whether we should treat mRCC patients with ICI and anti-VEGF agents or in sequence in first-line setting remains elusive. Third, there are patients who have primary or acquired resistance after the treatment of ICI. Further investigation to potentiate the efficacy of current immunotherapy agents is mandatory. On the other hand, adjuvant cytokines had been studied to prevent a recurrence, which revealed no additional benefit. Nevertheless, given the success of newer immunotherapy agents, there are ongoing clinical trials to evaluate the role of ICIs in the adjuvant setting.

**Conclusions**

The landscape of the treatment of mRCC has shifted from anti-VEGF therapy to ICI and their combination with antiangiogenic agents. Further studies about biomarker identification, drug sequencing, and research of innovative combinations are needed. With the advance of immunotherapy-based treatment, the survival time of mRCC is expected to be longer and the potential cure rate to be higher.

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**Conflicts of interests**

There are no conflicts of interests.

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