Heliyon 10 (2024) e29215

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Rationale for immune checkpoint inhibitors plus targeted therapy for advanced renal cell carcinoma

Siwei Yang [a,1], Xianrui Yang [a,1], Zekai Hou [a,1], Liang Zhu [a,1], Zhili Yao [a,1], Yifei Zhang [b], Yanzhuo Chen [a], Jie Teng [c], Cheng Fang [d], Songmao Chen [e,f], Mingfei Jia [g], Zhifei Liu [h], Shaosan Kang [g], Yegang Chen [a], Gang Li [a], Yuanjie Niu [a], Qiliang Cai [a,*]

[a] Department of Urology, Tianjin Institute of Urology, Second Hospital of Tianjin Medical University, Tianjin, China
[b] Tianjin Medical University, Tianjin, China
[c] Affiliated Hospital of Hebei University, Baoding, China
[d] Taihe County People's Hospital, Anhui, China
[e] Department of Urology, Fujian Provincial Hospital, Fujian, China
[f] Provincial Clinical Medical College of Fujian Medical University, Fujian, China
[g] Department of Urology, North China University of Science and Technology Affiliated Hospital, Hebei, China
[h] Department of Urology, Tangshan People's Hospital, Hebei, China

ARTICLE INFO

Keywords:
Renal cell carcinoma
Targeted therapy
Immune checkpoint inhibition
Combination therapy

ABSTRACT

Renal cell carcinoma (RCC) is a frequent urological malignancy characterized by a high rate of metastasis and lethality. The treatment strategy for advanced RCC has moved through multiple iterations over the past three decades. Initially, cytokine treatment was the only systemic treatment option for patients with RCC. With the development of medicine, antiangiogenic agents targeting vascular endothelial growth factor and mammalian target of rapamycin and immunotherapy, immune checkpoint inhibitors (ICIs) have emerged and received several achievements in the therapeutics of advanced RCC. However, ICIs have still not brought completely satisfactory results due to drug resistance and undesirable side effects. For the past years, the interests form researchers have been attracted by the combination of ICIs and targeted therapy for advanced RCC and the angiogenesis and immunogenic tumor microenvironmental variations in RCC. Therefore, we emphasize the potential principle and the clinical progress of ICIs combined with targeted treatment of advanced RCC, and summarize the future direction.

1. Introduction

Renal cell carcinoma (RCC) is the most frequent renal malignancy and the third urological malignancy in the world. A total of 431,288 new cases and 179,368 deaths were reported worldwide in 2020, with a trend that has deepened in recent years [1]. About 85% of renal tumors are RCC, of which clear cell renal cell carcinoma (ccRCC) is the most common, representing 70% of the cases. Papillary RCC and chromophobe RCC are another two common subtypes [2]. Early symptoms of RCC are not obvious; approximately

* Corresponding author.
E-mail address: caiqiliang@tmu.edu.cn (Q. Cai).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e29215
Received 11 September 2023; Received in revised form 2 April 2024; Accepted 2 April 2024
Available online 4 April 2024

half of the patients diagnosed with RCC are found incidentally, with about 25% of them progressing to metastatic disease and the remaining patients may recur and advance to metastatic RCC (mRCC) after local surgical resection [3]. Unlike prostate cancer and bladder cancer, RCC is insidious and not susceptible to chemoradiotherapy [4]. Sarcomatoid elements are present in about 20% of tumors from patients with advanced RCC (aRCC), making it more aggressive and leading to rapid metastasis and poor clinical prognosis with a five-year survival rate of only 18% [5,6].

Treatment options for aRCC have changed dramatically in the past decades. Until 2005, cytokine therapy has been the major modality of advanced mRCC. Cytokine therapy, consisting of interleukin-2 (IL-2) and interferon-α (IFN-α) and so on, shows benefits in a limited proportion of patients with aRCC, but such therapy involves high toxicity and low response efficiency [7]. Augmented vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) signaling and mammalian target of rapamycin (mTOR) activity are critical contributors to dysregulation of angiogenesis responsible for oncogenic spread in RCC [8]. Targeted therapy is a drug therapy aimed at the tumor cell proliferation or diffusion at the molecular level to prevent the growth of cancer cells [9]. With the further research of abnormal angiogenesis in RCC and the development of antiangiogenesis agents, tyrosine kinase inhibitors (TKIs) targeting the VEGF + growth pathway and mTOR pathway were approved for related drug developments, such as sunitinib, cabozantinib, axitinib, lenvatinib, bevacizumab, everolimus, and temsirolimus. Subsequent trials demonstrated that these drugs are far more effective compared with cytokine therapy. However, nearly all patients end up being resistant to these targeted molecular therapies or antiangiogenic treatments [10].

The advent of immune checkpoint inhibitor (ICI) therapy has not only revolutionized the therapeutic landscape of RCC but also reawakened interest in immune-based therapies [11,12]. ICIs negatively regulate programmed cell death protein 1 (PD-1) receptor, programmed death receptor ligand 1 (PD-L1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and other immune checkpoints proteins, thus achieving immune activation and anti-tumor response [13,14]. ICIs offer superior safety and oncologic efficacy compared with cytokines and targeted therapies.

Hence, nivolumab (anti-PD-1 monoclonal antibody) and ipilimumab (anti-CTLA-4 monoclonal antibody) combined with nivolumab were allowed to be used for the treatment of RCC in 2015 and 2018, respectively after clinical trials and research [15,16]. More recently, the combination of immunotherapeutic agents with antiangiogenic agents has proven to be a promising therapeutic strategy [17].

Table 1
Therapeutic methods and targets of renal cell carcinoma.

Therapeutic drugs	Target	Approval time
Targeted therapy		
TKIs		
Sorafenib	VEGFR-1,2,3	2005
Sunitinib	VEGFR-1,2,3	2006
Pazopanib	VEGFR-1,2,3	2009
Axitinib	VEGFR-1,2,3	2012
Cabozantinib	VEGFR-1,2,3	2016
Lenvatinib	VEGFR-1,2,3	2016
Tivozanib	VEGFR-1,2,3	2021
Anti-VEGF mab		
Bevacizumab	VEGF	2009
mTOR inhibitors		
Temsirolimus	mTOR	2007
Everolimus	mTOR	2009
ICIs		
Atezolizumab	PD-L1	–
Avelumab	PD-L1	–
Ipilimumab	CTLA-4	–
Nivolumab	PD-1	2015
Pembrolizumab	PD-1	–
Combined therapy		
Dual ICIs		
Nivolumab + Ipilimumab	PD-1 + CTLA-4	2018
TKIs + ICIs		
Axitinib + Avelumab	VEGFR + PD-L1	2019
Axitinib + Pembrolizumab	VEGFR + PD-1	2019
Cabozantinib + Nivolumab	VEGFR + PD-1	2021
Lenvatinib + Pembrolizumab	VEGFR + PD-1	2021
Cabozantinib + Atezolizumab	VEGFR + PD-L1	Under test
Axitinib + Toripalimab	VEGFR + PD-1	Under test
Anti-VEGF mab + ICI		
Bevacizumab + Atezolizumab	VEGF + PD-L1	2019

VEGF, vascular endothelial growth factor; VEGF, vascular endothelial growth factor; TKIs, tyrosine kinase inhibitors; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1 receptor; PD-L1, programmed death receptor ligand 1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; mTOR, mammalian target of rapamycin.

In this article, we review the application of ICI and targeted therapy in RCC. We outline the preclinical theoretical basis and mechanism of action of ICI and targeted therapy for kidney cancer. We also summarize the clinical development and evidence of efficacy of available agents. On the basis of nearly 20 years of research on cell signalling pathways and immune targets, we focus on observing the results of trials of targeted therapeutic agents combined with ICIs applied in the last 6 years. We discuss the current controversies in the use of targeted combination ICI strategies, including a comparison of various regimens currently available and those in clinical trials, and summarize the advances in combined therapy. Table 1 and Fig. 1 demonstrate the targets and progression of pharmacological treatments for renal cell carcinoma.

2. Molecular basis of targeted therapy and ICI therapy

2.1. Targeted therapy

The leading type of RCC is ccRCC, and most trials have clustered around this type; thus this review also focuses on ccRCC which is the most sporadic type of kidney cancer [18].

Deletion, promoter methylation and mutation of chromosome 3 lead to the functional inactivation of the Von Hippel–Lindau (VHL) gene that is a major characteristic of highly sporadic ccRCC and causes abnormal accumulation of Hypoxia-inducible factor (HIFs) [19,20]. VHL can encode a specific VHL protein (pVHL). pVHL is the substrate recognition subunit of ubiquitin ligase complex that also contains elongin B, elongin C, Cul2, and Rbx1 [21,22]. The main functions of this complex are polyubiquitination targeting of HIFs and degradation of proteasome [23]; when hypoxia occurs, degradation is inhibited, which may be due to the failure of key targeted modification in the HIF-α oxygen-dependent-degradation (ODD) domain. Moreover, the formation of VHL complex is restrained by cobaltous ions and desferrioxamine; thus, the interplay between HIF-1α and pVHL is iron-dependent [24]. The stimulation of the HIF pathway can result from the inactivation of the VHL gene, which is the main reason for early onset of VHL-mutant RCC.

In addition, the expression of genes related to cellular hypoxic response is regulated by series transcription factors of HIF. HIF is a heterodimer consisting of α subunit and β subunit, in which HIF-1α is involved in the preferential expression of glycolysis pathway and HIF-2α participates in promoting growth and angiogenesis [23]. When $Fe2^{+}$ and α-ketoglutarate (α-KG) exist and oxygen is sufficient, HIFs are hydroxylated by the prolyl hydroxylase domain (PHD) protein and then bind to VHL, where they are ubiquitinated and degraded in proteasome [20,23]. Under normoxic conditions, pVHL continuously represses protein levels and activity. Oppositely, HIF continues to accumulate and HIF-1α and HIF-1β further bond to form a heterodimer. The above process is caused by hypoxia or lack of functional pVHL [23–25]. Numerous studies have demonstrated that the accumulation of HIFs further stimulates the expression of genes such as VEGF, insulin-like growth factor-2 (IGF-2), platelet-derived growth factor (PDGF), erythropoietin (EPO), transforming growth factor-α (TGF-α), erythropoietin and hepatocyte growth factor receptor. These factors have important roles in RCC [26,27]. The mechanism of tumor cell genesis induced by hypoxia HIF is shown in Fig. 2.

What attracts the most interest among numerous proteins upregulated by HIFs is VEGF which is closely relevant to angiogenesis

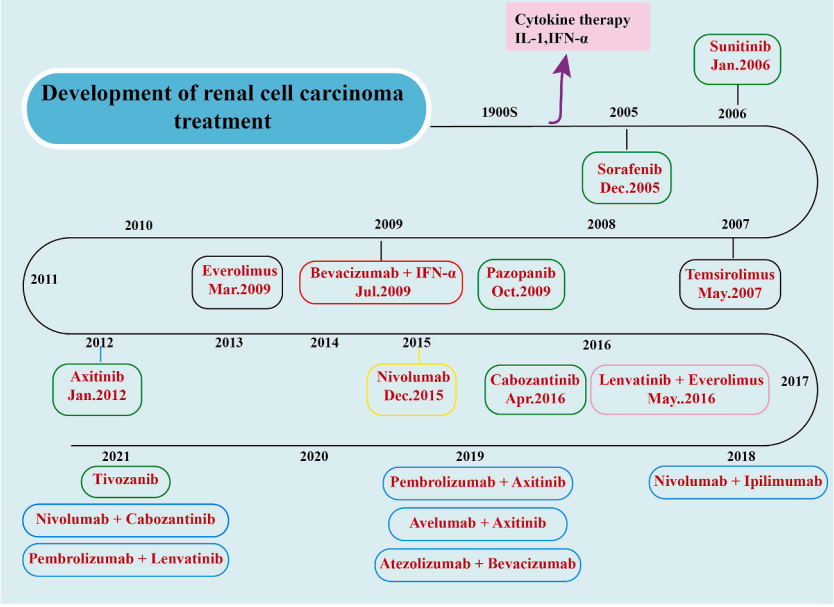

Fig. 1. Progress in treatment of renal cell carcinoma. In the last century, cytokine therapy was the main treatment for renal cell carcinoma. Since 2005, a variety of molecular targeted drugs for renal cell carcinoma have been approved to be listed. Nivolumab monotherapy, an immune checkpoint inhibitor, was approved in 2015. Since then, combined therapy has been gradually extended to clinical practice, creating a new era of renal cell carcinoma treatment.

and plays a momentous part in the progression of malignant tumors. Apart from this, it was found that VEGF has great research value in ccRCC because of the rich blood vessels in clinical practices [28]. However, as described above, mutations in VHL (a tumor suppressor) can be found in 60%–90% of patients with sporadic ccRCC. These mutations can lead to the activation of genes responsible for angiogenesis, particularly VEGF.

Current researches not only provide more profound comprehension of VHL mutation and its relationship with angiogenesis, but also demonstrate that VEGF and its VEGF receptor (VEGFR) related pathways make a difference in the development of RCC. As a result, a number of therapeutic targets, including VEGF ligands and their receptors such as VEGFR-1, VEGFR-2 and VEGFR-3, have been identified and are now the main targets of antiangiogenic therapy for patients with aRCC [21].

In addition to VEGF/VEGFR pathway inhibition, mTOR pathway inhibition is another crucial RCC targeting pathway. Similarly, sustained activation of HIFs stimulates the mTOR signaling pathway, which boosts several key tumorigenic processes, including vascular stimulation through enhanced production of VEGF [29]. In addition, mTOR is a resultful regulator of PI3K-AKT signaling, which has been shown to promote a variety of cellular functions, such as cell growth, reproduction, migration and survival [30]. It is often observed in all kinds of solid tumors that the modification of mTOR causes alterations or stimulation to PI3K signal pathway components, which further generates pathological changes of mechanism of organism and gives rise to the progress of cancer cell infiltration [31,32]. Therefore, mTOR is also an important therapeutic target(As shown in Fig. 3).

2.2. ICI therapy

2.2.1. Tumor microenvironment in RCC

Tumor microenvironment (TME) is internal environment for tumor occurrence production and growth, which composed of various

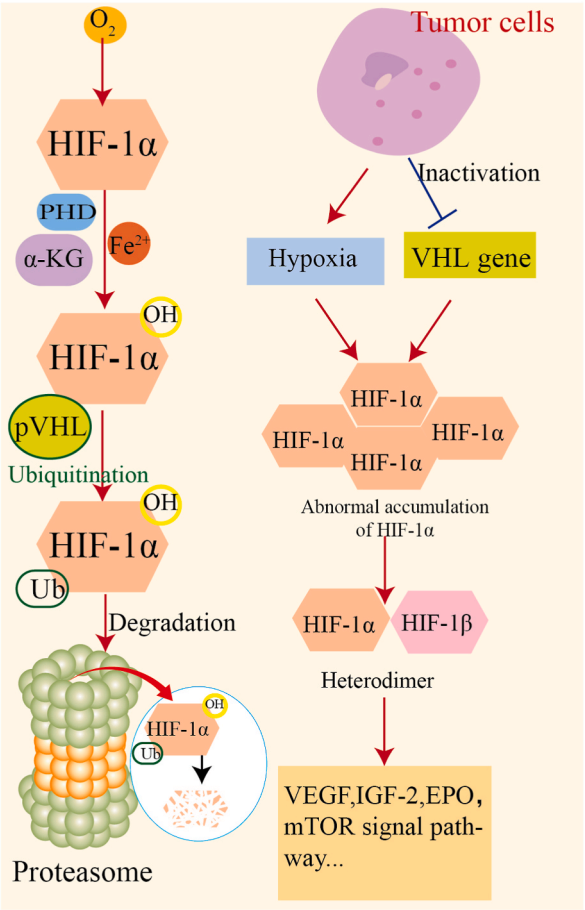

Fig. 2. The mechanism of tumor cell genesis induced by hypoxia inducible factor (HIF). When oxygen is sufficient and Fe2+ and α-keto-glutarate (α-KG) are existing, hypoxia-inducible factors (HIF) are hydroxylated by prolyl hydroxylase domain (PHD) protein and then bind to pVHL, where they are ubiquitinated and degraded in the proteasome. The inactivation of VHL gene and hypoxic microenvironment in renal cancer cells induce the accumulation of HIF-1α in large amounts, and HIF-1α and HIF-1β combine to form heterodimer, which further stimulates the activation of signal transduction pathways of vascular endothelial growth factor (VEGF), insulin-like growth factor-2 (IGF-2), erythropoietin (EPO) and rapamycin (mTOR) and promoted the further development of tumor.

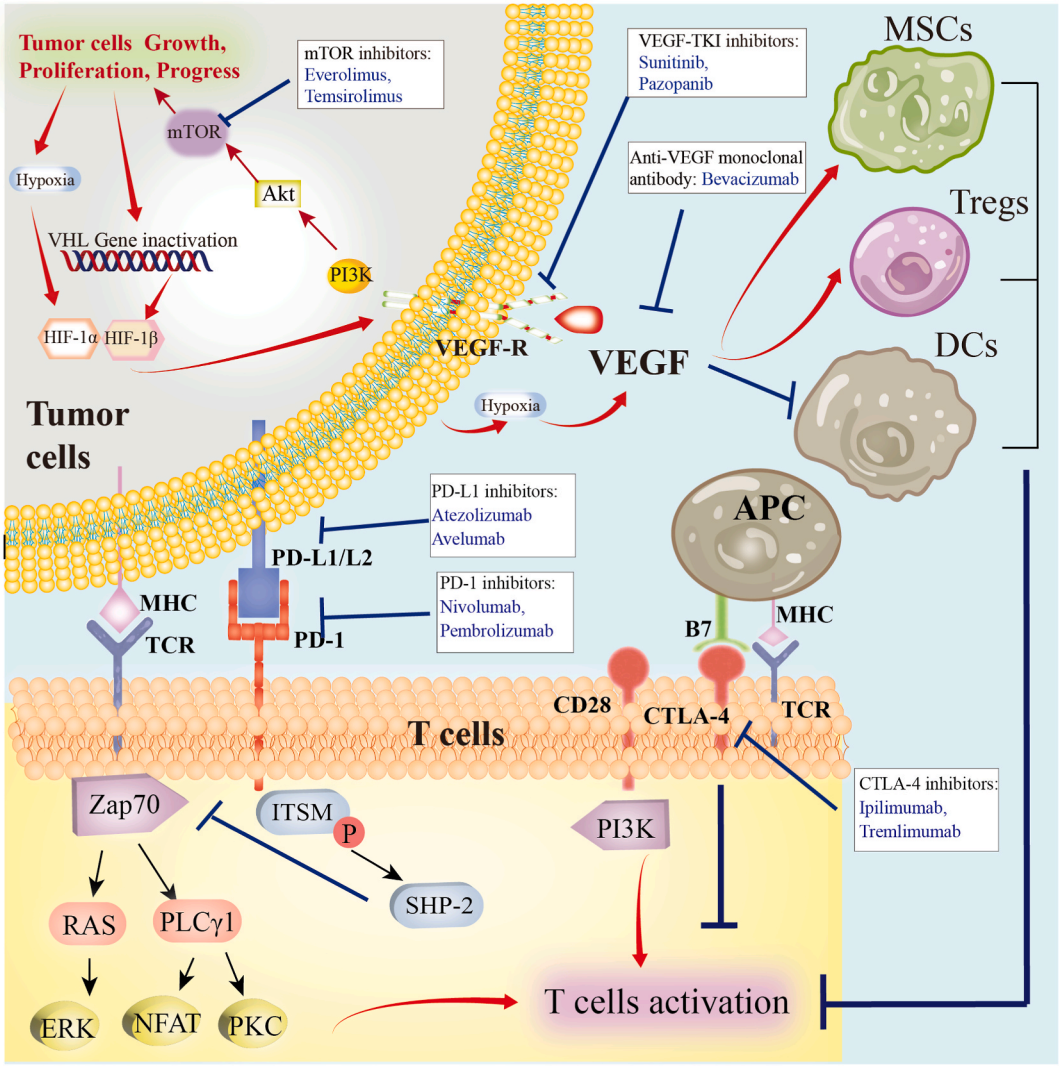

Fig. 3. The mechanism of action of targeted agents and immune checkpoint inhibitors and the synergistic effect of their combined treatment. The combination of VEGF and VEGFR activates PI3K-AKT-mTOR signaling pathway, which further promotes the progress of tumor cells. The hypoxia environment of tumor cells and the inactivation of VHL gene lead to the increase of HIF-1α and HIF-1β heterodimers, which further activates the signal transduction pathway. The presence of VEGF enhances the function of Tregs and MDSCs and inhibits the maturation of DCs, ultimately leading to suppression of T-cell activation.Targeted therapeutic drugs can effectively inhibit VEGF and its signalling pathways and exert an anti-tumour effect. CTLA-4 and CD28 on T cells can compete with B7 ligands (CD80 and CD86) expressed on APC. However, the affinity of CTLA-4 to B7 ligands is significantly higher than that of CD28, which can induce downstream inhibition signals and inhibit T cell activation. Tumor cells can use the interaction of PD-1 and PD-L1/L2 to release inhibitory signals to escape antigen-specific T cell immune response. Immune checkpoint inhibitors against CTLA-4 and PD-1/PD-L1 can restore effective anti-tumor immunity. It is clear from the above that the use of target agents enhances the anti-tumour activity of the immune system, thereby increasing the efficacy of immune checkpoint inhibitors, and therefore they have a synergistic effect.

biochemical components such as tumor cells, non-tumor cells, cytokines, etc. Its characteristics including complex and highly dynamic may affect the curative effect of targeted therapy and even immunotherapy in long-term research [33,34]. Tumors can affect their microenvironment by releasing cell signaling molecules that promote tumor angiogenesis and induce immunologic tolerance [35]. In turn, immune cells can inhibit the development of tumor cell infiltration by interacting with one another. In summary, the interpaly between tumor and its microenvironment is mutual. Key immune cells involved in constituting the TME of RCC include T cells, regulatory T cells (Tregs), tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs) and cancer-associated fibroblasts (CAFs) [36,37]. A growing body of evidence suggests that RCC has a unique immune microenvironment compared with other solid tumors. A large number of infiltrated immune cells, CAFs, abnormal vascular endothelial cells, some soluble factors of non-cellular components and extracellular matrix (ECM) appear in TME of RCC [38].

On the basis of the immunotherapeutic response, T-cell activation is recognized as a central element in the prognosis of ccRCC, as

well as being linked to positive clinical outcomes and immunotherapy responses [39]. Two main types of T cells, including CD 4^+ T cells and CD 8^+ T cells, have multifarious anti-tumor abilities, of which the former has the ability to harmonize the elaborate immune interactions and the latter can identify the superficial peptides on cells and assault antigen expression cells [40,41]. $CD8^+$ T-cell infiltration prospectively predicts disease prognosis; unlike other tumors, elevated $CD8^+$ T-cell level is associated with poor prognosis in ccRCC [42]. Meanwhile, another immune cell type of $CD4^+$ T cells, as a cell subset, playing a momentous role in the TME and keeping strong immunosuppressive traits called Tregs ($CD25^+$ cells). Tregs can indirectly promote angiogenesis by inhibiting the maturation of antigen-presenting cells (APCs), thereby regulating tumor development and immune escape [43,44].

Conversely, there is a growing body of research highlighting the important role of myeloid cells in tumor biology and therapy, including TAMs and MDSCs. MDSCs derive from myeloid progenitor cells and have been found to be associated with the process of angiogenesis by promoting angiogenesis, enhancing cancer cell viability and migration and achieving tumor metastasis [45]. In patients with tumors, the degree of infiltration of MDSCs in TME correlates with poor prognosis. MDSC transfer leads to a decrease in tumor cell apoptosis and necrosis in tumor-bearing mice, indicating that MDSCs provide survival signals to tumor cells [46]. MDSCs that accumulate in TME produce MMP9 to support tumor growth and angiogenesis [46,47]. What's more, a monocyte called TAM, as an inflammatory mediator, plays a significant part in TME. Similar to MDSC, TAMs promote neovascularization and tumor progression. Moreover, they involve in tumor immune escape and remodeling-related enzymes that induce tumor metastasis [36,48]. First, TAMs create a mutation-prone microenvironment by secreting pro-inflammatory mediators, such as TNF-α and ROS. They are prone to tumor initiation [49,50]. Second, a study in colorectal cancer mice found that TAMs can secrete C–C motif chemokine ligand 20 (CCL20) to recruit Tregs for tumor infiltration [51]. In RCC-bearing mice, pro-angiogenic factors such as VEGF are stimulated by TAMs, suggesting that TAMs exert VEGF-dependent pro-angiogenic effects [52]. Finally, a complementary type of cell is CAFs. CAF, a matrix component in tumor microenvironment, is common in solid tumors, which originate from the differentiation of intrinsic tissue fibroblasts or other resistant stromal cells and can regulate a variety of cells such as immune cells to control TME so that it is conducive to the malignant progress of tumors [53,54]. Overexpression of HIF-1α has been proved to be an important inducer of ccRCC, and some studies have found that CAFs is related to the progress of ccRCC through HIF-1α [55]. In addition, certain cytokines that promote angiogenesis and tumor growth, such as VEGF, TGF-β and fibroblast growth factor (FGF), are believed to be produced by the stimulation of CAFs [56].

In TME, the interaction between PD-L1 expressed on tumor cells and PD-1 on lymphocytes reduces the activity of effector T cells and allows tumors to escape the immune response [57]. These immune checkpoints will be discussed in detail below.

2.2.2. *T cell activation*

Immunotherapy refers to the generation of antigen-specific immune memory through memory T cells or antibodies to induce a durable anti-cancer response. First, APCs (mainly dendritic cells) come into contact with and react to the neoantigens produced by carcinoma. Then, the ultimate goal of the process that the major histocompatibility complexes I and II (MHC I and MHC II) molecules receive the signals generated by neoantigens transmitted by dendritic cells is to activate T cells which work on tumors so that they eventually lead to a series of events leading to tumor cell death [58].

The core of immune response is T cell activation, which needs double stimulation signals. The first signal comes from T cell receptor (TCR) recognizing MHC/antigen peptide complex and transmitting antigen-specific recognition signal, and the second signal comes from the interaction between pairs of costimulatory molecules on APC surface and corresponding receptors on T cells. CD3 is an important marker on the surface of T cells and it can combine with TCR to form a non-covalent TCR-CD3 complex. The complex can allow the activation signal generated by the binding of TCR to the antigen transmit to the inside of cells and induce T cell activation. In contrast to the first signal, the second signal is a nonspecific costimulatory signal (CD28, CTLA-4 and CD80, CD86, CD40 and CD40L, and PD-1 and PD-L1). CD28 molecules bind non-covalently to ligands B7 (CD80 and CD86) on the APC to form B7-CD28 complex, which ultimately stimulates T cell proliferation and initiates tumor immunity [10,59,60]. Reaction magnitude, duration and quality are triggered with antigen recognition by TCR, followed by ligand–receptor interactions [61]. An important part of this process is regulated by the balance between costimulatory and inhibitory signals, collectively referred to as immune checkpoints [62].

Reactive oxygen species (ROS) as important highly reactive molecules exert a major influence on the whole life activities of cells. In cancer cells, the number of ROS will increase due to hypoxia, gene mutation and other reasons [63,64]. In TME, ROS induce CAF to become active CAF by targeting the upregulation of HIF-α expression, which promotes tumor development, proliferation and invasiveness [65]. In addition, hydrogen peroxide(a kind of ROS) derivatized from CAF can induce normal fibroblasts to obtain oxidized CAF-like state. Increased CAF in tumor cells exhibited elevated ROS level and higher glucose uptake, raising the metabolic level of tumor [66]. The lower glucose content in TME and the higher competitiveness of tumor cells lead to the decrease of glycolytic ability and activity of T cells, which accelerates the progress of tumor. Therefore, by blocking immune checkpoints on tumor cells, it is possible to inhibit mTOR activity and reduce the expression of glycolytic enzymes. This reduces glucose consumption by the tumor and restores T-cell activity [67,68].

2.2.3. *Immune checkpoints*

Immune checkpoints for patients with RCC in current conventional clinical application are CTLA-4, PD-1, and PD-L1, which play a role in influencing the activation state of T cells and are highly expressed in ccRCC. In addition, ccRCC obtained a high immune infiltration scores in pan cancer analysis. As a highly inflammatory tumor type, ccRCC has a high response rate to PD-1 and/or CTLA-4 axis inhibition combinations [25,69].

At an early stage of T cell activation, CTLA-4, the first targeted immune checkpoint receptor to be used in clinic in T cells, is recruited to the plasma membrane to act in conjunction as a co-stimulatory receptor with CD28 [70]. Both CTLA-4 and CD28 can

compete with B7 ligands (CD80 and CD86) expressed on APCs for binding. As mentioned above, T cells are activated because that the combination of CD28 to B7 ligands and co-stimulatory signals are generated. However, the affinity of CTLA-4 for B7 ligand is significantly higher than that of CD28, thereby creating a complex that induces downstream inhibitory signals that suppress T-cell activation. Ultimately this process leads to diminished T-cell activation and a diminished $CD8^+$ cytotoxic T-cell response [25,71].

Unlike CTLA-4 which inhibits T cell function, CD28 binds to B7 ligands (CD80 and CD86) in an opposite function. As a result of the interplay of p85 subunit of Phosphatidylinositol3-kinase (PI3K), the Src family kinase Lck, interleukin-2 (IL-2) and inducible family kinase Itk, costimulatory signals are generated at the cytoplasmic tail of CD28, which further stimulates transcription factors including NF-κB and activator protein-1 (AP-1) that make a difference in IL-2 production and T cell survival [71]. From this, it can be seen that CTLA-4 has two functions: inhibiting CD28 which is a T cell costimulatory receptor and inhibiting T cell activation [59,70]. Ipilimumab and tremelimumab are two typical CTLA-4 immunosuppressants that bind to CTLA-4, allowing immune recognition and T-cell activation of tumor cells by antagonizing the binding of CTLA-4 to CD80/CD86.

PD-1 and its two ligands PD-L1 and PD-L2 are the second most widely used immune checkpoints in clinical practice. A 50–55 kDa type I transmembrane glycoprotein called PD-1 is composed of IgV domain and belongs to CD28 superfamily, which delivers negative signals by mediating the interaction of its ligands, PD-L1 or PD-L2, which are composed of type I transmembrane glycoprotein composed of IgC and IgV domains [72]. Immunoreceptor tyrosine motifs (ITSMs) in the cytoplasmic region of PD-1 are important for the inhibitory function of PD-1 whose phosphorylation enhances binding with SH2-domain containing tyrosine phosphatase 2 (SHP-2), which dephosphorylates TCR signal proximal signal molecule Zeta-chain-associated protein kinase 70 (Zap70), thereby weakening the activation of downstream signals such as Ras and phospholipase Cγ1 (PLCγ1). Extracellular regulated protein kinases (ERK), Nuclear factor of activated T cells (NFAT) and Protein kinase C (PKC) were also inhibited.(As shown in Fig. 3) [72–74].

The expression of PD-1 and its ligand is more extensive compared with other CD28 family members and plays a significant part in tumor progression such regulating the activation of T cells. What is analogous to CTLA-4 is that the expression of PD-1 occurs in activated effector T cells rather than resting T cells [73]. Moreover, PD-1 also expressed in other basic immune cells such as B cells, monocytes, dendritic cells (DCs), Tregs and natural killer T cells (NKTs). PD-L1 as ligands of PD-1 is not only expressed in T cells, B cells, macrophages, and some non-immune cells, but also widely expressed in tumor cells, of whose expression solid tumors and hemangioma tumor cells are up-regulated. The binding of PD-L1 on tumor cells to PD-1 on T cells can cause T cell dysfunction, depletion and neutralization [74,75]. What is different from PD-L1 is that the expression is finite for PD-L2 that majorly appears in macrophages and DC [76]. Tumor cells are able to use the expression and interplay of PD-1 and its two ligands to release inhibitory signals to evade antigen-specific T cell immune responses. Blocking PD-1/PD-L1-mediated signaling by PD-1 inhibitors may restore the immune response and effective anti-tumor immunity.

3. Biological rationale for combined ICIs and targeted therapy

ICIs are of higher remission rate and safety as neotype cancer immunotherapies which heighten the anti-cancer reaction and postpone tumor response by blocking the superficial immune receptors of T lymphocytes than targeted therapy among the competitions of RCC first-line treatment schemes [70,77,78]. However, many patients will achieve resistance during later treatment, though ICIs have lasting effects [58,79]. Despite some success, most patients with aRCC treated with VEGF-targeted therapy still demonstrate drug resistance [58,80].

3.1. Resistance to ICIs

Drug resistance caused by anoxic microenvironment and dysfunction of tumors and other reasons makes the treatment of RCC still an incurable disease even though some progress has been made in the past few decades. Cell dysfunction and the reduction of drug treatment effect may be caused by an important feature of malignant solid tumor called hypoxia, which leads to cell damage and even death in severe cases [81,82]. The cancer immunity cycle consists of seven steps from the release of tumor antigen to the lysis of tumor cells which requires the participation of immune system [83]. Most importantly, ICIs such as PD-1/PD-L1 and CTLA-4 inhibitors play a central role in the treatment of mRCC [84,85]. Immune evasion can occur at the steps of antigen presentation and activation, transportation of T cells and tumor infiltration and cytotoxic activity of T cells in TME; it can lead to primary or adaptive resistance in patients receiving immunotherapy [86,87].

As the most common RCC, ccRCC has very universal inactivation of VHL tumor suppressor, which further makes HIF that participated in angiogenesis, tumor cell survival, metastasis and invasion generate unusual accumulation [29,84,88–90]. At present, three HIF genes that encode different proteins have been identified. HIF-1α and HIF-2α are transcription factors that activate and encode erythropoietin, transferrin, VEGF, IGF-2 and so on. HIF-3α is an inhibitor of hypoxic transcriptional response. Therefore, HIF induces the production of a number of gene products and controls energetic metabolism and pH in cells, which can affect TME [91,92]. TME features are associated with resistance to ICI therapy in some studies [93–95]. For example, during atezolizumab monotherapy, myeloid inflammation may be a cause of drug resistance in patients with mRCC [96]. Moreover, long-term ICI-mediated anti-angiogenic therapy will inhibit angiogenic factor and lead to hypoxia. The expression of HIF gene is up-regulated under the stimulation of tissue hypoxia, which will make tumor cells adapt to hypoxic microenvironment. It is this adaptation that makes tumor cells resistant to drugs [97]. Thus, the microenvironment of ccRCC has a certain influence on the reaction of ICIs.

In the therapy of ICIs, the downregulation of cellular immune responses in TME is able to be held back by the interaction between PD-1 on T cells and its ligand (PD-L1) on tumor cells [98]. For instance, there is a humanized monoclonal antibody named atezolizumab, which has capability to enhance anti-cancer immunity by inhibiting the interplay between PD-L1 and its receptors PD-1 and

B7-1 as a blocker of programmed cell death-ligand (PD-L1) [99]. But the therapeutic effect of atezolizumab can be reduced by the high expression of myeloid inflammatory genes. Moreover, adaptive T cells with anti-tumor effects are in the position to be restrained by the microenvironment of myeloid inflammatory tumors [12,90,100]. In a previous study, the clinical therapeutic effect of the combined treatment of atezolizumab + bevacizumab was found to improve and show better safety when compared with atezolizumab monotherapy, indicating that adding bevacizumab to atezolizumab may avoid the inflammation-mediated resistance of the tumor itself [96]. Besides activation of myeloid cells, drug resistance also occurs in other changes in the microenvironment, such as angiogenic gene expression and T cell infiltration. High intra-tumoral heterogeneity (ITH) shows depletion of putative neoantigens, increased myeloid activation, decreased T cell diversity, and a wealth of genomic characteristics (SETD2 and PBRM1 mutations, loss of HLA heterozygosity, and loss of CDKN2A/B), all of which are generally related to evasion of the antitumor immune response [101].

The signal transduction pathways that are associated with malignant potential such as VEGF and mTOR will be activated because of the abnormal downstream gene expression of HIF stimulated by the deletion of VHL gene [84,102]. Molecular targeted drugs VEGF-TKIs have been developed such as axitinib, cabozantinib, sorafenib, and sunitinib, which inhibit angiogenesis and tumor growth by inhibiting VEGF receptor, whereas everolimus and temsirolimus can block the activity of mTOR [102,103].

3.2. Feasibility of combined medication

Fortunately, there is evidence that VEGFR-TKIs can enhance the effect of immunotherapy with ICIs via reversing the cancer microenvironment of immunosuppressive effects [58,104,105].

Sunitinib, as VEGF-TKI, not only has anti-angiogenesis function but also has the effect of immune regulation, including the enhancement of T cell infiltration and other immune cell functions when it is used for targeted therapy. The combination between the glycoprotein PD-1and the cognate ligand PD-L1 on APCs and tumor cells will repress the function of T cells and other immune cells. PD-1 ICI antibodies have been developed, such as nivolumab, which can block the combination of PD-L1 and PD-1 on the tumors and induce the functional enhancement of T cell to strengthen anticancer immunity [106,107]. Besides, a study suggests lenvatinib enhanced the anti-tumor activity of anti-PD-1 antibody by reducing tumor-associated macrophages and increasing IFN-γ positive $CD8^+$ T cells [108]. Therefore, the combination of targeted therapy and immune therapy may have certain synergistic efficacy in patients with RCC [106].

The immune checkpoint pathway, Tregs and MDSC have inhibitory effects to T cells [109,110], and VEGF may be able to alter TME to enhance the suppressive effects of these factors and may also suppress the maturation of DCs to reduce T-cell activation [111,112].

Studies have shown that sunitinib treatment increases the expression of PD-L1 in RCC tumors [104]. VEGF-A is an angiogenic molecule produced in TME that increases the expression of inhibitory checkpoints involved in $CD8^+$ T-cell exhaustion, and the expression of PD -L1 was significantly upregulated in M2 macrophages under the influence of autocrine VEGF signal. These processes can be recovered by targeting VEGF pathway antiangiogenic agents [113,114]. MDSCs are one of the reasons for inducing T cell inhibition [110,115]. The number of MDSCs in patients with RCC can be reduced by sunitinib, which reverses MDSC-mediated tumor-induced immunosuppression and plays a role in regulating antitumor immunity. Therefore, the function of combined therapy called targeted VEGF-TKI and immunotherapy that synchronously resist VEGF and PD-1 is synergistic [115]. Fig. 3 shows the mechanism of action of targeted agents and immune checkpoint inhibitors and the synergistic effect of their combined treatment.

The treatment for patients with mRCC has changed from monotherapy to combination therapy in clinical practice. Compared with monotherapy, combination therapy with higher survival rate and safety strengthens the antitumor immunity of patients [116,117].

3.3. Side effects

3.3.1. Targeted drugs

Sunitinib, pazopanib, and bevacizumab are anti-VEGF drugs that result in endothelial cell injury and podocyte lesions due to their antiangiogenic effect, and they subsequently cause proteinuria, hypertension and other renal injuries [118]. It also affects the turnover of endothelial cells during trauma, leading to hypercoagulability and thromboembolism [119]. For example, bevacizumab can directly beget cells and induce thrombotic microangiopathy (TMA) [120]. Besides, TKI will have side effects such as rash, discoloration of skin and hair, cardiac dysfunction, bone marrow suppression and hypothyroidism by affecting different signal pathways [121]. mTOR inhibitors can cause metabolic dysfunction, such as hypertriglyceridemia, hypercholesterolemia and hyperglycemia [122]. Similarly, patients treated with mTOR inhibitors also suffered from renal function damage such as proteinuria and nephrotic syndrome. Treatment with temsirolimus also caused changes in serum creatinine in patients (57%) [123].

An eight-year observational study described that the different degrees of renal function damage including proteinuria (100%; $\leq$1 g/day, 31%), hypertension (74%), microscopic hematuria (70%), and renal failure occurred after patients received anti-vascular treatment (6.87 $\pm$ 7.18 months).Besides, the main types of renal injury found by renal biopsy were renal TMA and minimal change disease and/or collapsing-like focal segmental glomerulosclerosis (MCN/cFSGS). After stopping the usage of anti-VEGF drugs and taking antihypertension drugs, symptoms of hypertension and proteinuria disappeared [124].

In short, targeted drugs triggered apparent nephrotoxicity. Therefore, it is necessary to monitor blood pressure and renal function of patients with RCC and other vital signs during targeted treatment including antiangiogenic therapy and mTOR inhibitors. In case of renal dysfunction, patients should terminate it in time. Plasmapheresis can ameliorate patients who develop focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis [123,124].

3.3.2. ICIs and immune-related AEs

Despite a few strengths, side effects called immune-related adverse events (irAEs) are caused by ICI therapy, which may endanger life in serious cases, creating new challenges in clinical management. The use of anti-CTLA4 and anti-PD-1/PD-L1 resulted in the continuous activation of T cells, increased production of cytokines and enhanced immune response. Many organs such as skin, gastrointestinal tract and endocrine organs can be affected by irAEs caused by excessive activation of the immune system of what appear most often are hypophysitis, colitis, hepatitis, pneumonia and rash. Besides, patients also exhibit arthritis, nephritis, myositis and polymyalgia-like syndromes that resemble autoimmune diseases [118,125–127].

The mechanism by which ICIs cause irAEs depends on the immune checkpoint targeted for treatment. CTLA-4 inhibitors can induce many cell changes, such as activation and proliferation of T cells, impaired survival of Treg. In addition, it can induce cross-reaction between anti-tumor T cells and antigens on healthy cells and produce autoantibodies. PD-1 and PD-L1 inhibitors can reduce survival rate and inhibitory function of Treg, and increase the production of cytokines. The above causes serious adverse reactions to important organs such as heart, skin, endocrine glands, gastrointestinal tract, liver and blood [128].

It was found in a systematic review that irAEs of grade III are more likely to appear ICI treatment for CTLA-4 rather than PD-1 (31% vs. 10%; OR = 4.0, 95% CI, 3.5–4.6). Moreover, all grades of colitis (OR 8.7, 95% CI 5.8–12.9) and hypophysitis (OR = 6.5, 95% CI 3.0–14.3) were easier to appear in CTLA-4 ICI, whereas pneumonitis (OR = 6.4, 95% CI 3.2–12.7) and hypothyroidism (OR = 4.3, 95% CI 2.9–6.3) more often occurred in anti-PD-1 therapies [129]. These results were similar to those description in another study. They showed that 39.7% of patients treated with ipilimumab reported gastrointestinal irAEs, mainly colitis (34.2%), of which 5.1% led to life-threatening intestinal perforation. Moreover, nivolumab caused severe autoimmune thyroid disease [126]. The combination of ICI (nivolumab plus ipilimumab) may further increase the risk of irAEs [130].

With the application of ICI treatment, the incidence of renal drug-related AEs is also rising, such as acute interstitial nephritis (AIN), which may resemble kidney transplant rejection. The frequency of renal irAEs is lower than that of other irAEs, whereas the mortality of patients is higher [131]. Compared with anti-CTLA-4 immunotherapy, more common renal AEs (reporting odds ratio [ROR] = 1.75; 95% CI, 1.52–2.01) are reported in the treatments of anti-PD-1/PD-L1. More than this, compared with monotherapy of nivolumab or ipilimumab, combination therapy of nivolumab plus ipilimumab group generated frequently acute renal injuries and level 3 or higher treatment-related AEs [132]. Therefore, clinicians should continue to be vigilant against long-term chronic complications and irAEs that may occur in late stage or treatment withdrawal, so as to intervene and treat in time and improve patients' conditions [133].

4. Emerging drugs for the treatment of RCC

4.1. Targeted inhibitors

The inactivation of VHL gene in ccRCC will block the ubiquitination degradation of HIF in proteasome, which leads to the accumulation of HIF and enhances the expression of VEGF. The germination of tumors is expedited by the formation of blood vessels and the proliferation of endothelial cells [134]. Therefore, the basis of antiangiogenic therapy is the inhibition of the targeted VEGF pathway [135,136].

4.1.1. Sunitinib and pazopanib

TKIs have become an effective treatment for patients with aRCC [137]. Compared with IFN-α (a cytokine), the overall survival (OS; 26.4 months vs. 21.8 months; hazard ratio [HR] = 0.821; 95% CI, 0.673–1.001), progression-free survival (PFS; 11 months vs. 5 months; $P < 0.001$), and objective response rate (ORR) (47% vs. 12%) of patients receiving sunitinib has improved [138]. The 25 patients were treated with targeted therapies again (including sunitinib) after they were diagnosed with recurrence of RCC, of which 24 showed progress in treatment. The PFS was 12 months (95% CI, 5.78–18.2), the median OS was 29.1 months (95% CI, 16.4–41.8), and the ORR was 20.5% [139].

Pazopanib is an oral targeted TKI that can restrain angiogenesis and cell proliferation in tumors [140,141]. Studies suggested that pazopanib treatment shows significant PFS benefits compared with placebo (9.2 months vs. 4.2 months; HR = 0.46; 95% CI, 0.34–0.62) [141]. Pazopanib was found to reduce patient mortality (HR = 0.504; 95% CI, 0.315–0.762). However, OS was not different between groups of pazopanib and placebo (22.9 months vs. 20.5 months; HR = 0.91; 95% CI, 0.71–1.16), which may be due to the high crossover rate. Post-hoc analyses adjusting for crossover showed that pazopanib treatment is beneficial to OS for patients with mRCC [142].

4.1.2. Bevacizumab

Bevacizumab is a specific anti-VEGF monoclonal antibody. A previous study confirmed that the time to progression of patients receiving high-dose bevacizumab treatment is significantly longer than that of the placebo group (HR, 2.55; $P < 0.001$), and the tumor of most patients receiving bevacizumab treatment would shrink [143,144].

Moreover, the combination of bevacizumab and IFN-α has shown remarkable clinical effects in the treatment of mRCC [143]. Researchers from two randomized phase III trials (AVOREN and CALGB 90206) divided patients with mRCC into experimental group (bevacizumab plus IFN-α) and control group (placebo plus IFN-α). Then they found that the PFS of the experimental group ameliorated in both phase III trials (10.2 months vs. 5.4 months; 8.5 months vs. 5.2 months) [145,146]. However, patients in the experimental groups are prone to more severe level 3 and above toxicity (79% vs. 61%, $P < 0.0001$) [146]. AVOREN and CALGB90206 showed that the OS of patients with mRCC treated with bevacizumab plus interferon was longer than that of patients treated with interferon plus placebo [147,148].

4.1.3. Everolimus

As mentioned above, abnormal regulation of the mTOR signaling pathway is closely related to tumorigenesis [149]. Everolimus and temsirolimus are mTOR inhibitors. They reduce the growth of cancer cells by curbing the activity of mTOR [118].

In the first-line treatment, everolimus failed to certify non-inferiority compared with sunitinib (7.4 months vs. 10.7 months; HR = 1.4; 95% CI, 1.2–1.8) [150]. A phase II trial revealed that bevacizumab plus everolimus is an active program after the failure of sunitinib or sorafenib, and was well tolerated by the majority of patients [151,152]. Bevacizumab plus everolimus held the 6-month PFS rate of 8%, median PFS of 13.7 months (95% CI, 10.8–16.4 months), ORR of 35%, and median OS of 33.9 months (95% CI, 23.3–71.9) in another phase II trial for papillary variant RCC [153].

4.2. ICIs

CTLA-4, PD-1, PD-L1 are immune checkpoints that are applied in routine clinical practice [25,77].

B7–H1 is also known as PD-L1. A retrospective study described that the risk of death in patients expressing with tumor PD-L1 was nearly four times that of PD-L1-negative patients (risk ratio [RR], 3.92; 95% CI, 2.61–5.88). In addition, the patients with PD-L1-negative showed a higher 5-year cancer-specific survival rate (82.9% vs. 41.9%). These results suggested that the harm of renal cancers could be alleviated by blocked interplay between PD-L1 and PD-1 [154].

4.2.1. Nivolumab

Nivolumab acts on human PD-1 protein, which induces the increase in T cell function to enhance anticancer immunity. A phase III study called CheckMate 025 indicated that the median OS rate was 25 and 19.6 months in nivolumab group and everolimus group, respectively. Although the PFS in the two groups was similar (4.6 months vs. 4.4 months; HR = 0.88; 95% CI, 0.75–1.03), the ORR of the nivolumab group was obviously higher than that of everolimus group (25% vs. 5%; odds ratio = 5.98; 95% CI, 3.68–9.72). Patients treated with nivolumab had lower level 3 or 4 treatment-related AEs (19% vs. 37%) [155].

Table 2
Antitumor Activity among Combined therapies in phase III trials.

phase III trials		Arms	ORR (95% CI), %	Median PFS (95% CI), months	Median OS (95% CI), months
CheckMate 214 [159]		Nivolumab + Ipilimumab	42 (37–47)	11.6 (8.7–15.5)	NR (28.2 - NE)
		Sunitinib	27 (22–31)	8.4 (7.0–10.8)	26.0 (22.1 - NE)
KEYNOTE-426 [165]		Pembrolizumab + Axitinib	59.3 (54.5–63.9)	15.1 (12.6–17.7)	–
		Sunitinib	35.7 (31.1–40.4)	11.1 (8.7–12.5)	–
CLEAR [166]		Pembrolizumab + Lenvatinib	71.0 (66.3–75.7)	23.9 (20.8–27.7)	NR
		Everolimus + Lenvatinib	53.5 (48.3–58.7)	14.7 (11.1–16.7)	NR
		Sunitinib	36.1 (31.2–41.1)	9.2 (6.0–11.0)	NR
JAVELIN Renal 101 [167]	Patients with PD-L1–Positive	Avelumab + Axitinib	55.2 (49.0–61.2)	13.8 (11.1 - NE)	–
		Sunitinib	25.5 (20.6–30.9)	7.2 (5.7–9.7)	–
	Overall Population	Avelumab + Axitinib	51.4 (46.6–56.1)	13.8 (11.1 - NE)	–
		Sunitinib	25.7 (21.7–30.0)	8.4 (6.9–11.1)	–
CheckMate 9 ER [168]		Nivolumab + Cabozantinib	55.7 (50.1–61.2)	16.6 (12.5–24.9)	NR
		Sunitinib	27.1 (22.4–32.3)	8.3 (7.0–9.7)	NR
RENOTORCH [169]		Toripalimab + Axitinib	56.7 (49.7–63.5)	18.0 (15.0 - NE)	NR
		Sunitinib	30.8 (24.6–37.5)	9.8 (8.3–13.8)	26.8
CONTACT-03 [170]		Atezolizumab + Cabozantinib	41 (35–47)	10.6 (9.8–12.3)	25.7 (21.5 - NE)
		Cabozantinib	41 (35–47)	10.8 (10.0–12.5)	NE (21.1 - NE)
IMmotion 151 [171]	intention-to-treat population	Atezolizumab + Bevacizumab	37 (32–41)	11.2	–
		Sunitinib	33 (29–38)	8.4	–
	Patients with PD-L1–Positive	Atezolizumab + Bevacizumab	43 (35–50)	11.2	–
		Sunitinib	35 (28–42)	7.7	–

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; NR, not reached; NE, not estimated.

In the 5-year long-term follow-up of CheckMate 025, the total incidence of related AEs in nivolumab group was still lower than that in everolimus (80.5% vs. 88.9%). Compared with the baseline, the health-related quality of life (HRQOL) of nivolumab group was improved, but it was not changed or even deteriorated in everolimus group [156].

4.2.2. Atezolizumab

Atezolizumab is a blocking agent of PD-L1. A phase I study proved the safety and clinical activity of atezolizumab in the treatment of RCC; the median OS and PFS of 63 patients with ccRCC could be raised to 28.9 and 5.6 months via atezolizumab therapy, respectively, of which 62 patients had an ORR of 15% (95% CI, 7%–26%) because of the lack of follow-up data of one patient [157].

4.2.3. Nivolumab + ipilimumab

In addition to monotherapy, ICI combination therapy has been approved [158]. In the phase III trial CheckMate 214, compared with sunitinib, substantial improvement of the 18-month OS rate (75% vs. 60%), ORR (42% vs. 27%), and median PFS happened in nivolumab plus ipilimumab group. The probability of occurrence of level 3 or level 4 AEs in the two groups was 45.7% and 62.6% [159].

In the subsequent long-term follow-up, the OS (median not reached, NR [95% CI 35.6–not estimable,NE] vs. 26.6 months [22.1–33.4]) and proportion of patients who achieved objective response (42% vs. 29%) were better than those in the sunitinib group [160]. Compared with sunitinib, nivolumab plus ipilimumab had long-term benefits for patients with aRCC who had not been treated before. It also improved HRQOL and reduced the burden of symptoms [160,161].

In addition, the latest research suggests that some patients failed to respond to Nivolumab monotherapy can benefit from the

Table 3
Occurrence of adverse events and common adverse events in phase 3 trial.

phase III trials	Arms	Adverse events of any grade (%)	The most common all grades AEs (%)	3 or higher AEs(%)	The most common grade 3 or higher AEs (%)
CheckMate 214 [159]	Nivolumab plus Ipilimumab	93.1	Fatigue(36.9)，pruritus(28.2)，diarrhea(26.5)	45.7	Increased lipase (10.2), fatigue(4.2), diarrhea(3.9)
KEYNOTE-426 [165]	Pembrolizumab + Axitinib	98.4	Diarrhea(54.3)， Hypertension(44.5) Fatigue(38.5)，hypothyroidism（35.4）	75.8	Hypertension(22.1), alanine aminotransferase increased(13.3), diarrhea(9.1)
	Sunitinib	99.5	Diarrhea(44.9),hypertension(45.4), fatigue(37.9)	70.6	Hypertension(19.3), fatigue(6.6), diarrhea(4.7)
CLEAR [166]	Pembrolizumab + Lenvatinib	99.7	Diarrhea(61.4),hypertension(55.4), hypothyroidism(47.2)	82.4	Hypertension(27.6), diarrhea(9.7), weight decrease(8), proteinuria(7.7)
	Everolimus + Lenvatinib	99.7	Diarrhea (66.5), stomatitis(47.6), hypertension(45.6), fatigue(42)	83.1	Hypertension(22.5), diarrhea(11.5), proteinuria(8.2)
	Sunitinib	98.5	Diarrhea(49.4), hypertension (41.5), stomatitis(38.5)	71.8	Hypertension(18.8), fatigue(4.4), diarrhea(5.3)
JAVELIN Renal 101 [167]	Avelumab + Axitinib	99.5	Diarrhea(62.2), hypertension(49.5), fatigue(41.5), nausea(34.1)	71.2	Diarrhea(47.6), fatigue(40.1), nausea (39.2), palmar-plantar erythrodysesthesia(33.7)
	Sunitinib	99.3	Hypertension(25.6), diarrhea(6.7), alanine aminotransferase increased (6%)	71.5	Hypertension(17.1), anemia(8.2), neutropenia(8.0), thrombocytopenia (6.2)
CheckMate 9 ER [168]	Nivolumab + Cabozantinib	99.7	Diarrhea(63.8), palmar–plantar erythrodysesthesia(40.0), hypertension(34.7)	75.3	Hypertension(12.5), palmar–plantar erythrodysesthesia(7.5), diarrhea (47.2), hyponatremia(9.4)
	Sunitinib	99.1	Diarrhea(47.2), palmar–plantar erythrodysesthesia(40.6), hypertension(37.2)	70.6	Hypertension(13.1), palmar–plantar erythrodysesthesia(7.5), diarrhea(4.4)
RENOTORCH [169]	Toripalimab + Axitinib	99.5	Proteinuria(41.8), ddrrhea(40.4), hypertension(40.4), hypothyroidism (40.4)	71.2	Hypertension(15.4), proteinuria (11.1), alanine aminotransferase(7.2)
	Sunitinib	99.5	Platelet count decreased(60.5), anemia(58.1), white blood cell count decreased(57.6)	67.1	Platelet count decreased(15.2), hypertension(15.2), anemia(11.0)
CONTACT-03 [170]	Atezolizumab + Cabozantinib	100	Diarrhea(65), Palmar–plantar erythrodysesthesia syndrome(39), decreased appetite(38)	68	–
	Cabozantinib	99	Diarrhea(71), Palmar–plantar erythrodysesthesia syndrome(41), decreased appetite(38)	62	–
IMmotion 151 [171]	Atezolizumab + Bevacizumab	99.1	Hypertension, fatigue, proteinuria, diarrhea, asthenia	40.4	Hypertension(14), proteinuria, asthenia
	Sunitinib	96.2	Diarrhea, palmar-plantar erythrodysesthesia, hypertension	53.8	Hypertension(17), palmar-plantar erythrodysesthesia(9)

AEs, Adverse events.

combination of nivolumab and ipilimumab. These provides guidance for second-line treatment [162,163].

4.3. ICIs combined with targeted therapies

The combined treatment of ICIs and VEGF-TKIs has shown significant efficacy in the treatment of mRCC, and it has gradually become the nursing standard of first-line treatment [117,164]. Table 2 describes the anti-tumor activity of the combination therapy in several phase III trials. Table 3, on the other hand, demonstrates the incidence of adverse events (AEs) in phase 3 trials.

4.3.1. ICIs combined with TKIs

4.3.1.1. Pembrolizumab + axitinib. Pembrolizumab is a monoclonal antibody targeting PD-1, and axitinib is a selective inhibitor of VEGF receptors. A phase 1b trial indicated that untreated patients with mRCC experienced varying degrees of tumor shrinkage following the combination of pembrolizumab and axitinib [172]. Meanwhile, the combination therapy also showed long-term clinical benefits at the follow-up visit [173].

A phase III trial called KEYNOTE-426 showed that after a median follow-up of 12.8 months, the survival rate (89.9% vs. 78.3%), median PFS (15.1 months vs. 11.1 months), and ORR (59.3% vs. 35.7%) of patients with advanced ccRCC in the axitinib plus pembrolizumab group were superior to those in sunitinib group. The incidence of grade 3 and above AEs in the two groups was 75.8% and 70.6% [165]. As the first-line treatment combination with the longest follow-up time, axitinib plus pembrolizumab treatment group with 43-month follow-up was in OS (HR = 0.73), PFS(HR = 0.68) and ORR (60% vs. 40%) is still higher than that of sunitinib group. Long-term curative effect and higher safety continue to support this combination as the first-line treatment of aRCC [174].

4.3.1.2. Pembrolizumab/everolimus + lenvatinib. In a phase 3 trial, compared with sunitinib, lenvatinib plus pembrolizumab had a PFS advantage (median PFS: 23.9 months vs. 9.2 months) and longer OS (HR for death = 0.66). Similarly, the median PFS of lenvatinib plus evolutionus was higher than that of sunitinib (14.7 months vs. 9.2 months), but its OS was lower than that of sunitinib. During treatment, 82.4%, 83.1%, and 71.8% of patients in three groups had grade 3 or higher AEs [166]. The HRQOL analyses of CLEAR (study 307/KEYNOTE-581) suggested that the scores of lenvatinib plus pembrolizumab were favorable in terms of the final deterioration time compared with sunitinib [175].

Moreover, an extended phase 3 follow-up experiment supported that combination of lenvatinib + pembrolizumab which kept higher overall survival rate of patients (HR = 0.72, 95% CI: 0.55–0.93) and more durable curative effect as a first-line therapy [176]. Even when RCC patients present with metastatic lesions, the therapeutic effect of combination is still better than that of sunitinib [177]. The benefits in first-line treatment are also demonstrated by the higher rate of tumor shrinkage after treatment [178].

4.3.1.3. Avelumab + axitinib. Avelumab is a monoclonal antibody against PD-L1 and axitinib is a second-generation TKI [179]. In phase III trial JAVELIN renal 101, the median PFS of avelumab plus axitinib showed advantages in the overall population (13.8 months vs. 8.4 months). The ORR of combined group and sunitinib group was 51.4% and 25.7%, respectively, and the stratified odds ratio was 3.10 (95% CI, 2.30–4.15). Moreover, among patients with PD-L1-positive tumor (63.2%), the median PFS was 13.8 and 7.2 months, respectively (HR for disease progression or death, 0.61), the ORR was 55.2% and 25.5%, and the stratified odds ratio was 3.73 (95% CI, 2.53–5.37). The two groups had similar incidences of treatment-related AEs [167].

Furthermore, in long-term experiments, compared with sunitinib, avelumab plus axitinib demonstrated favorable efficacy in both PFS and OS in all age groups (age <65, ≥65 to <75, and ≥75 years) of patients with aRCC [180]. In the latest third interim analysis, median OS is still better in combined group(NR vs. 37.8 months; HR = 0.79), as is median PFS (13.9 months vs. 8.5 months; HR = 0.67). Subsequent research on this first-line treatment is still in progress [181].

4.3.1.4. Nivolumab + cabozantinib. The nivolumab plus cabozantinib group showed longer median PFS than the sunitinib group (16.6 months vs. 8.3 months) in the phase III trial CheckMate 9 ER. The 12-month OS rate was 85.7% and 75.6%, respectively. An objective response occurred in 55.7% of the former and in 27.1% of the latter. Grade 3 or higher AEs occurred in 75.3% of patients treated with combination therapy, while sunitinib group was 70.6% [168]. In the subsequent long-term follow-up, the median OS (37.7 months vs. 34.3 months) and median PFS (16.6 months vs. 8.3 months) in the combined group suggested certain benefits [182].

With the advantage of a large patient sample (>650 patients) and high patient-reported outcome (PRO) completion rates (>75% across most time points), CheckMate 9 ER demonstrated that nivolumab plus cabozantinib in patients with aRCC is accompanied with maintenance or improvement in clinical benefit. Combined therapy had also favorable tolerance and fewer patients reported suffering from side effects of treatment [183]. Moreover, an observational study named CaboCombo is being conducted to further investigate the efficacy and tolerability of nivolumab plus cabozantinib in the real world [184].

4.3.1.5. Toripalimab + axitinib. Toripalimab, a new anti-PD-1 monoclonal antibody, has been demonstrated in previous studies to provide benefits for patients with aRCC when used in combination with axitinib as a second-line treatment after failure of a first-line VEGF TKI. The ORR of the combined therapy was 31.6%, and the median PFS was 11.7 months. The combination is also well tolerated with a low incidence of irAEs, improving patient safety [185].

Although the latest phase 3 trial, RENOTORCH, had a shorter follow-up period, its results showed that toripalimab plus axitinib prolonged median PFS (18.0 months vs 9.8 months) and OS (NR vs. 26.8 months) compared to the sunitinib group in the first-line

treatment of aRCC. The combination had a higher ORR (56.7% vs. 30.8%) but more grade ≥3 treatment-related AEs (61.5% vs. 58.6%) [169].

4.3.1.6. Atezolizumab + cabozantinib. The combination of atezolizumab and cabozantinib showed a encouraging efficacy. In a phase Ib study, patients with solid tumors were asked to be prescribed 40 mg of oral cabozantinib once daily or 60 mg once daily plus atezolizumab. In the 40 mg ccRCC group (n = 34), median follow-up was 25.8 months, ORR was 53%, and median PFS was 19.5 months. In the 60 mg ccRCC group (n = 36), median follow-up was 15.3 months, ORR was 58 % and median PFS was 15.1 months. In addition, the percentage of patients with ccRCC in the 40 mg group who reported grade 3 or 4 treatment-related AEs was 71%, and another was 67% [186].

However, the opposite was found in another phase 3 trial, CONTACT-03. The median PFS and OS of RCC patients who received the combination of atezolizumab and cabozantinib were 10.6 months (95% CI, 9.8–12.3) and 25.7 months (95% CI, 21.5-not evaluable), respectively. Cabozantinib monotherapy was 10.8 months (95% CI, 10.0–12.5) and not evaluable (95% CI, 21.1-not evaluable). Besdies, the risk of serious AEs in combination therapy is higher (48% vs. 33%) [170].

4.3.1.7. Sintilimab + pazopanib. Fudan University Shanghai Cancer Center enrolled A total of 17 patients with advanced ccRCC, who were treated with sunitinib as first-line therapy. After progression of the disease, pazopanib together with 6–8 cycles of sintilimab was administered, then single use of pazopanib was followed. For first-line use of sunitinib, median PFS was 10.2 months (95 % CI, 3.9–16.5 months), and median PFS (95% CI, 8.9–15.5 months) for second-line treatment with sintilimab in combination with pazopanib was 12.2 months. All AEs were manageable. Notably, this treatment modality could reduce patients' economic burden [187].

4.3.1.8. Nivolumab + tivozanib. In a phase Ib trial, the primary endpoints of combination of tivozanib + nivolumab were safety, tolerability, dose-limiting toxicity, maximum tolerated dose, and preliminary antitumor activity. With a mean treatment duration of 14.5 months, 80% of patients experienced one or more treatment-related grade 3/4 AEs. With a median follow-up of 19.0 months (range, 12.6–22.8), median PFS was 18.9 months (95% CI, 16.4-NR). For treatment-naïve patients, median PFS was 18.9 months (95% CI, 4.7-NR). For previously treated patients, median PFS had not been reached (95% CI, 11.0-NR) [188].

4.3.1.9. Nivolumab + sunitinib/pazopanib. Check Mate 016 (NCT01472081), a phase I study, aimed to evaluate the efficacy and safety of nivolumab plus sunitinib (N + S group) or nivolumab plus pazopanib (N + P group) in patients with aRCC or mRCC. The results showed that the confirmed ORR of the N + S group was 54.5%, median PFS was 12.7 months, and PFS rates at 6, 12, 18, and 24 months were 79.4%, 51.8%, 29.6%, and 29.6%, respectively. At a median follow-up of 50.0 months, the median OS was NR (95% CI, 36.8–NR). OS rates at 12, 18, and 24 months were 90.9%, 81.5%, and 81.5%, respectively. In the N + P group, the confirmed ORR was 45.0% (95% CI, 23.1–68.5), the median PFS was 7.2 months, and the 6-month PFS rate was 54.9%. At a median follow-up of 27.1 months, median OS was 27.9 months. OS rates at 12, 18, and 24 months were 84.4%, 73.9%, and 63.3%, respectively. Even though both groups showed good reactivity, the combination added sunitinib or pazopanib to nivolumab could not go further because of possible TKI-related AEs and high toxicity [189].

4.3.2. ICIs combined with anti-VEGF monoclonal antibody

4.3.2.1. Atezolizumab + bevacizumab. IMmotion151 was the first randomized phase 3 trial that combined anti-PD-L1–PD-1 antibody with anti-VEGF drugs to treat patients with mRCC. The median PFS (11.2 months vs. 7.7 months) and PFS at 12 months (49% vs. 38%) of PD-L1 positive patients in the atezolizumab plus bevacizumab group were better than those in sunitinib group. In the combination group, 43% patients achieved definite objective remission, 9% patients achieved complete remission, whereas those in sunitinib group were 35% and 4%, respectively. In the intention-to-treat population, the results showed that the median PFS benefit of atezolizumab plus bevacizumab group was also confirmed (11.2 months vs. 8.4 months). There were fewer patients with grade 3 or above AEs in atezolizumab plus bevacizumab group than in sunitinib group (40.4% vs. 53.8%) [171].

Subsequent PROs demonstrated that patients with atezolizumab plus bevacizumab treatment not only show milder symptoms and less treatment side effects and better HRQOL at most visits than those with sunitinib, but also have no significant increase in symptoms or treatment burden [190].

5. Future for aRCC therapy

The development of ICI combined with targeted therapy has contributed to improving the prognosis of aRCC, and several of the combinations discussed in the previous article have been approved for first-line clinical use. Nevertheless, some patients still develop drug resistance, and it is important to understand the mechanisms of resistance and to develop novel therapies [191].

5.1. Treatment after progress

Patients with metastatic renal cells were treated with second-line treatment after first-line TKI treatment failed in a real-world study. The results showed that the total ORR and disease control rate (DCR) of second-line treatment was 23.6% and 75.5%, respectively. Subsequent analysis indicated that the ORR and DCR of patients treated with ICIs plus TKIs were evidently higher than

those treated with alternative TKIs alone. Whether applying ICIs + TKIs in combination or alternative TKI alone, the incidence of all-grade and grade 3–4 AEs were analogous. (all-grade AEs: 90.4% vs. 84.5%; grade 3–4 AEs: 40.4% vs. 44.8%). These results suggested that ICIs plus TKIs had better efficacy and safety than TKI monotherapy in patients with mRCC who failed to receive first-line TKI treatment [192]. In addition, another recent real-world study also found that anti-PD-1 in combination with TKI therapy is a more effective and safer second-line treatment option after progression from first-line treatment in non-clear cell renal cell carcinoma (nccRCC) [193]. In a multicentre trial, patients with RCC treated with ICI discontinued treatment due to disease progression or associated toxicity. They were then reintroduced to nivolumab plus ipilimumab, and the results showed some benefit and security [194].

In summary, the combination of the above combined therapies has proved the first-line treatment standard beneficial to patients with RCC. At present, limited data are available regarding ICIs plus TKIs as second-line therapy in patients with RCC. Therefore, future research needs to further confirm therapeutic effect of ICIs plus TKIs on patients with mRCC who failed systematic first-line treatment in the past. Further studies should compare the first-line and second-line sequence of ICIs plus targeted therapy in the treatment of patients with RCC, so as to determine a more safe and effective treatment plan for patients.

5.2. New treatment methods

5.2.1. Genome editing

Genome editing refers to the process of modifying a specific part of the genome of an organism by means of gene editing technology. For instance, the current CRISPR-Cas9 is a gene-editing technology that enhances anti-cancer activity by modifying the DNA of human T-cells [195]. Using CRISPR-Cas9 technology, the researchers eliminated two genes that encode the endogenous TCR chain, namely TCRα (TRAC) and TCRβ (TRBC), as well as a third gene that encodes PD-1 (PDCD1) from human T cells in a phase 1 trial. The engineered T cells were then used to treat refractory patients, and the results demonstrated that they appeared to be well tolerated, providing a direction for the future treatment of aRCC patients [196].

Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T) is a novel precise targeted therapy for tumor that combines chimeric antigen receptors (CAR) with T cells through genetic engineering, resulting in CAR-T cells that can efficiently recognize tumor cells [197]. However, side effects such as tumor toxicity and off-target effects have also been limiting factors. This was the case with the first generation of CAR-T cells that targeted carboxy-anhydrase-IX (CAIX, a highly expressed enzyme in RCC) [198]. CD70 is a promising target for its high expression in RCC and low expression in normal tissues. A study developed CAR T cells with anti-CD70 single chain fragment variable (scFv), which demonstrated potent anti-tumor activity without any apparent toxicity. This provides a basis for further research into other CAR T cell therapies [199,200].

5.3. Cytokine therapy

IL-2 is a cytokine that has been extensively studied for its immunostimulatory and immunosuppressive effects. However, its use in clinical practice has been limited due to its severe toxicity at high doses. It is found that Bempegaldesleukin (NKTR-214) formed by releasable polyethylene glycol (PEG) combined with IL-2 can consume Tregs and enhance T cell-mediated anti-cancer response [201].

Furthermore, the first-phase PIVOT-02 study suggests that the combination of bempegaldesleukin and nivolumab has a positive impact on advanced ccRCC [202]. But the treatment combination did not prove to be as effective in the phase 3 trial PIVOT-09 [203]. Recent research suggests that the killer immunoglobulin-like receptors(KIR) and its KIR ligand inherited by the study population may be responsible for the results observed in PIVOT-02. Further research is needed [204]. In addition to IL-2, clinical trials of therapies for other cytokines (such as IL-12,IL-15,IL-27, etc.) are under way [205].

5.3.1. HIF inhibitor

HIF-2α is a crucial factor in ccRCC development, and researchers are continuously investigating its inhibitors such as Belzutifan. Belzutifan demonstrated a favorable safety profile and promising anti-tumor activity in a Phase 1 trial. The sustained and safe therapeutic efficacy of Belzutifan in patients with advanced ccRCC was demonstrated in the latest long-term follow-up results of up to 41.2 months [206–208]. It was also the first HIF inhibitor to be approved for the treatment of VHL-associated RCC and other VHL-associated cancers based on satisfactory safety and efficacy. The latest results on Belzutifan and other novel HIF-2α inhibitors are currently awaiting further investigation in several phase 2 or 3 clinical trials [209].

5.3.2. Gut microbiome

Homeostasis is maintained by the complex composition of microorganisms in the gut and their internal interactions. Current studies suggest that the occurrence of ccRCC may be closely linked to changes in gut microbiota and its associated metabolites [210]. Patients with RCC have altered gut flora and increased levels of the tryptophan metabolite Kynurenine (Kyn). In vitro experiments showed that Kyn can activate aromatic hydrocarbon receptor (AhR) to suppress anti-tumor immune reactions and thereby mediate RCC metastasis. Therefore, it is possible that the Kyn metabolic pathway could become a target for treatment [211]. Fecal microflora transplantation (FMT) may be a promising adjuvant therapy for RCC. There is evidence that it may enhance the therapeutic effect of ICI in RCC and trials are underway [212].

6. Conclusion

Over the past few decades, the treatment of aRCC has evolved with the application of new techniques. Due to the complex composition of TME and the intricate internal mechanism of action affecting the therapeutic efficacy of RCC, combination therapy (dual ICIs or ICI plus targeted therapy) has also become the first-line treatment for aRCC, particularly advanced ccRCC, following the emergence of monotherapies of targeted therapy and immunotherapies. Of the approved first-line treatment regimens, nearly all combination regimens have improved overall patient survival and have a good track record of efficacy and safety. Nevertheless, RCC remains a difficult cancer to fully manage owing to the inevitable limitations of drug resistance and side effects, and less is known about second-line treatment after failure of first-line therapy at present, and the order in which drugs are given needs further research. Simultaneously, new therapeutic approaches are undergoing clinical trials. The emergence of new drug targets offers new therapeutic avenues to further improve the prognosis of patients with aRCC, which may be the key to the next update in therapeutic technology.

Data availability statement

This article is a review and all data generated or analyzed during this study are included in this published article.

Ethics declarations

Review and/or approval by an ethics committee and informed consent were not needed for this study because this airticle is a review and all the data and research results in this review come from existing articles.

CRediT authorship contribution statement

Siwei Yang: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Xianrui Yang:** Visualization, Validation, Data curation, Writing – review & editing. **Zekai Hou:** Visualization, Formal analysis, Data curation, Writing – original draft. **Liang Zhu:** Writing – original draft, Methodology, Conceptualization. **Zhili Yao:** Writing – original draft, Visualization, Conceptualization. **Yifei Zhang:** Writing – original draft, Conceptualization. **Yanzhuo Chen:** Data curation. **Jie Teng:** Data curation. **Cheng Fang:** Formal analysis. **Songmao Chen:** Formal analysis. **Mingfei Jia:** Visualization. **Zhifei Liu:** Supervision. **Shaosan Kang:** Supervision. **Yegang Chen:** Supervision. **Gang Li:** Supervision. **Yuanjie Niu:** Supervision. **Qiliang Cai:** Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by National Natural Science Foundation of China (72174144), Tianjin National Science Foundation for Distinguished Young Scholars (23JCJQJC00080), Tianjin Natural Science Foundation of China (2021JCYBJC01470), Scientific Research Project of Tianjin Educational Committee (2022ZD068), Tianjin Health High-level Talent Cultivation Project (TJSQNYXXR-D2-158), Talent Cultivation Project of Tianjin Institute of Urology (MYSRC202305), Tianjin Municipal Natural Science Foundation (21JCYBJC01690).

Abbrebations

AEs	adverse events
AhR	aromatic hydrocarbon receptor
AIN	acute interstitial nephritis
AP-1	activator protein-1
APCs	antigen-presenting cells
aRCC	advanced renal cell carcinoma
CAFs	cancer-associated fibroblasts
CAIX	carboxy-anhydrase-IX
CAR	chimeric antigen receptors
CAR-T	chimeric antigen receptor T-Cell immunotherapy
ccRCC|	cell renal cell carcinoma
CTLA-4	cytotoxic T lymphocyte-associated protein 4
DCR	disease control rate
DCs	dendritic cells
ECM	extracellular matrix

EPO	erythropoietin
ERK	Extracellular regulated protein kinases
FGF	fibroblast growth factor
FMT	fecal microflora transplantation
HIFs	Hypoxia-inducible factors
HRQOL	health-related quality of life
ICIs	immune checkpoint inhibitors
IFN-α	interferon-α
IGF-2	insulin-like growth factor-2
IL-2	interleukin-2
irAEs	immune-related adverse events
ITH	intra-tumoral heterogeneity
ITSM	Immunoreceptor tyrosine motifs
ITSMs	Immunoreceptor tyrosine motifs
KIR	killer immunoglobulin-like receptors
Kyn	Kynurenine
MCN/cFSGS	minimal change disease and/or collapsing-like focal segmental glomerulosclerosis
MDSCs	myeloid-derived suppressor cells
MHC	major histocompatibility complexes
mRCC	metastatic renal cell carcinoma
mTOR	mammalian target of rapamycin
nccRCC	non-clear cell renal cell carcinoma
NE	not estimated
NFAT	Nuclear factor of activated T cells
NR	not reached
NKTs	natural killer T cells
ODD	oxygen-dependent-degradation
ORR	objective response rate
PD-1	programmed cell death protein 1
PDGF	platelet-derived growth factor
PD-L1	programmed death receptor ligand 1
PEG	polyethylene glycol
PFS	progression-free survival
PHD	prolyl hydroxylase domain
PI3K	Phosphatidylinositol3-kinase
PKC	Protein kinase C
PLCγ1	phospholipase Cγ1
PRO	patient-reported outcome
RCC	renal cell carcinoma
ROS	Reactive oxygen species
scFv	chain fragment variable
SHP-2	SH2-domain containing tyrosine phosphatase 2
TAMs	tumor-associated macrophages
TCR	T cell receptor
TGF-α	transforming growth factor-α
TKIs	tyrosine kinase inhibitors
TKIs	tyrosine kinase inhibitors
TMA	thrombotic microangiopathy
TME	tumor microenvironment
TRAC	T cell receptor α
TRBC	T cell receptor β
Tregs	regulatory T cells
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	Von Hippel–Lindau
Zap70	Zeta-chain-associated protein kinase 70
α-KG	α-ketoglutarate

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