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GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Current Status and Future Directions of Immunotherapy in Renal Cell Carcinoma

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Abstract

Purpose of Review Renal cell carcinoma (RCC) was recognized as an immunologically sensitive cancer over 30 years ago. The first therapies to affect the course of RCC were cytokines (interferon alfa-2B and interleukin-2). Subsequently, drugs that inhibit HIF (hypoxia-inducible factor)/VEGF (vascular endothelial growth factor) signaling demonstrated overall survival advantages (tyrosine kinase inhibitors and mTor inhibitors).

Recent Findings In the last 3 years, the immune checkpoint inhibitors (ICIs) have become the standard of care treatments in the first and second lines for RCC. Emerging data show that combinations of ICI, HIF signaling inhibitors, and cytokines are potentially powerful regimens.

Summary How to combine and sequence these types of therapies and how to integrate new approaches into the management of RCC are now the key questions for the field. Treatment of RCC is likely to change dramatically in the next few years.

Keywords Renal cell carcinoma · Immune checkpoint inhibitor · Interleukin-2 · mTor inhibitor · Hypoxia-inducible factor · VEGF receptor · CTLA-4 · PD-1 · PD-L1 · Cytoreductive nephrectomy

Introduction

In the USA in 2018, an estimated 65,340 people will be diagnosed with and 14,970 people will die of cancer of the kidney and renal pelvis [1]. The majority of patients with kidney cancer (> 80%) have renal cell carcinoma (RCC) with clear cell being the most common histologic subtype and papillary types 1 and 2 and chromophobe comprising the majority of the rest [2].

RCC is known to have a variable natural history with reports of spontaneous remission without systemic therapy [3], suggesting that endogenous systems exist to fight RCC, presumably via immune mechanisms. In the 1980s and 1990s, cytokine therapies demonstrated objective responses leading to the use of interferon alfa-2B (IFNα) and interleukin-2 (aldesleukin, IL-2) in patients. The discovery of the role of vascular endothelial growth factor (VEGF) and the mTOR signaling pathways in RCC led to multiple FDA approvals in the past 15 years for a VEGF-binding monoclonal antibody (bevacizumab), tyrosine kinase inhibitors of VEGF (TKI), and mTOR pathway inhibitors [4, 5]. Immune therapies in RCC had a resurgence with the discovery of the immune checkpoint inhibitors (ICI), which block PD-1, PD-L1, and CTLA-4. Despite these advances in the treatment of metastatic RCC, the majority of patients will die from their disease, stressing the need for novel therapeutic agents.

Biology of RCC

The histologic subtypes and molecular profiles of RCC are diverse but no therapies are approved currently that target molecular defects in subtypes other than clear cell carcinoma. Clear cell RCC is characterized by high levels of angiogenesis, largely because of the activation of two molecular pathways, the Von Hippel-Lindau (VHL) and the mammalian target of rapamycin (mTOR) pathways [6] (Fig. 1a). Most patients with clear cell RCC have inactivating mutations in the VHL gene. The VHL protein complex targets hypoxia-

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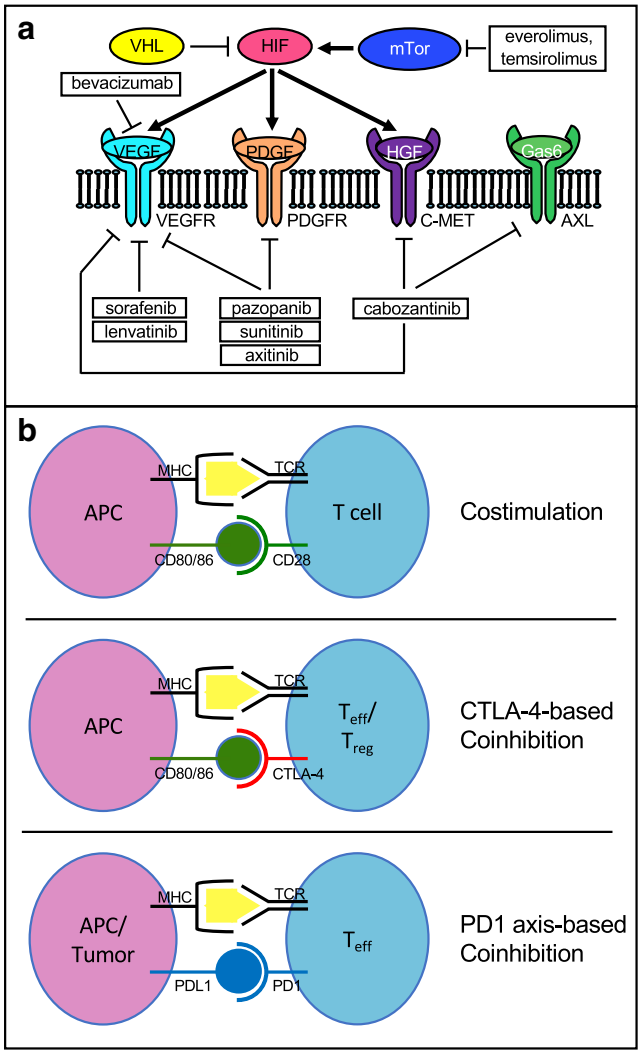

Fig. 1 Therapeutic targets in RCC. **a** HIF is a transcriptional activator that increases expression of ligands for the receptor tyrosine kinases VEGFR, PDGFR (platelet-derived growth factor receptor), and c-Met (hepatocyte growth factor (HGF) is its ligand); these receptors (primarily VEGFR2) drive RCC. RCC often has loss of VHL function, which normally inhibits HIF. The mTor pathway promotes HIF as well. Drugs that target the various aspects of these pathways are shown in the figure. Cabozantinib also inhibits Axl, a driver of innate immunity. **b** Costimulation through is required for T cell activation via CD80/86, CD28 interactions (top panel). CTLA4 competes with CD28 causing inhibition of costimulatory signaling (middle panel) and suppresses T_{eff} function but activates T_{reg} function; this interaction is inhibited by anti-CTLA4 monoclonal antibodies. A separate coinhibitory signaling pathway is the PD-1/PDL1 axis shown in the bottom panel, which primarily acts on T_{eff} cells. PDL1 can be expressed on professional antigen-presenting cells as well as tumor cells; this interaction is inhibited by monoclonal antibodies that block either PD-1 or PDL1

inducible factor alpha (HIFα) for ubiquitin-mediated proteasomal degradation. HIFα dimerizes with its partner HIFβ and activates transcription of a large number of genes, including VEGF. Thus, inactivating mutations in VHL lead to an increase in HIF activity and angiogenesis [7, 8]. mTOR expression promotes angiogenesis by increasing the levels of HIF independent of the VHL pathway and possibly through other pathways [9, 10]. Notably, loss-of-function mutations of PTEN (phosphatase and TENsin homolog), a negative regulator of mTOR, are found in 5% of patients with RCC [11]. Identification of these mediators of angiogenesis led to the use of VEGF and mTOR inhibitors for the treatment of metastatic renal cell carcinoma (Fig. 1a).

The Immune System and RCC

Immunogenicity of tumors is correlated with both a larger number of mutations in the tumor and the presence of an immune cell infiltrate. While RCC does not have a large mutational burden [12], it has a prominent and complex immune cell infiltrate [13, 14•].

For the immune system to attack tumor cells, it needs to see the tumor as foreign. Tumor cells make mutant proteins then partially degrade them and present their fragments (called tumor neoantigens) in MHC complexes on tumor cell surfaces. When tumor cells die, they are engulfed by professional antigen-presenting cells (mostly dendritic cells), which also present tumor neoantigens via their MHC complexes (Fig. 1b). A key second signal is required for neoantigens to activate T cells to attack tumors. This costimulatory signal is mediated by CD80/86 on the APC and CD28 on the T cell. Costimulation leads to T cell activation and IFNγ production, which expands tumor-specific CD8+ cytotoxic T cells (also called effector T cells or T_{eff}) that destroy tumor cells [15, 16]. In the absence of costimulation, T cell recognition of neoantigens can lead to downregulation of immune responses. Furthermore, systems in place to suppress inappropriate immune responses are hijacked by the tumor and prevent immune-mediated tumor killing. CTLA-4 on tumor cells competes with CD80/86 for binding with CD28, resulting in the inhibition of the costimulatory signal [17]. Another coinhibitory signaling system involves PD-1 on T cells interacting with PDL1 on the APC or tumor [18]. Thus, antibodies that block CTLA-4, PD-1, and PDL1 activate T cells to kill tumor cells (Fig. 1b).

There is evidence that the immune infiltrate is important for tumor control in RCC. For example, increased infiltration by mature dendritic cells predicts improved response to cytokine-based therapies [19]. NK cells, an MHC-independent immune cell population, are often identified in RCC and a higher percentage of NK cells predict improved survival while a low number of intratumoral mature NK cells are markers of poor survival [20–22]. A role for NK cells is consistent with the fact that RCC can evade immune attack by decreasing the expression of MHC I on tumor cells, thus becoming NK cell targets [16].

However, not all immune cells produce immune responses against the tumor. In fact, these immune cells are dysfunctional in many cases, causing immunosuppression, rather than activation [23]. For example, within the tumor

microenvironment, tumor-associated macrophages (TAMs) produce immunosuppressive cytokines (IL-10 and TGFβ) which promote regulatory T cell (T_{reg}) development and decrease inflammation (through shifts of macrophages to M2 from M1 types and CD4+ helpers from T_h1 to T_h2 subtypes) [13, 24]. In addition, TAMs produce VEGF, which drives RCC proliferation in multiple ways [24, 25]. Myeloid-derived suppressor cells (MDSC), which promote T_{reg} and suppress Teff populations, are also found in the immune infiltrate. Increased T_{reg}s in the tumor microenvironment is associated with higher grade, stage and shortened overall survival (OS) [25].

Cytokine Therapy

Two decades ago, 2-year survival of metastatic renal cell carcinoma was approximately 20%. Traditional chemotherapy is ineffective and most patients were treated with supportive care or hormonal therapy with medroxyprogesterone acetate (MRCC 1999) [26]. The role of the immune system in RCC was first investigated using the immunomodulatory agents interferon alpha (IFNα), interferon gamma (IFNγ), and interleukin-2 (IL-2). Interferons are produced by activated T cells and facilitate cell-mediated cytotoxic and antiproliferative effects on tumor cells [27]. Several non-randomized trials of IFNγ demonstrated overall response rates of 15–30% [28–33]. A phase III study randomized subjects to subcutaneous weekly IFNγ (60 μg/m^2) or placebo. There was no statistically significant difference in overall response rates (ORR) (4% in the IFNγ and 6.6% in the placebo group) or overall survival (OS) (12.2 vs 15.7 months) [34]. Given these disappointing results, IFNγ was not pursued further.

IFNα has also been studied extensively with multiple phase 2 studies and eventually a randomized study comparing IFNα with medroxyprogesterone acetate in 350 subjects. That study found ORR, median OS, and 1-year OS in favor of IFNα (14% vs 2%, 8.5 months vs 6.0 months, and 43% vs 31%, respectively) [35, 36]. The hazard ratio for median OS was 0.72 (CI 0.55–0.94, $p = 0.017$). Based on the small but statistically significant benefit with IFNα, it became a standard treatment for this disease. Subsequently, it was combined with bevacizumab and the combination demonstrated a significantly improved PFS over IFNα alone though the combination was no better than IFNα alone for OS [37–39].

IL-2 is produced by activated T cells, and when bound to the IL-2 receptor (IL-2R), it promotes the clonal expansion of antigen-specific T cells and enhances cytotoxicity [40]. The FDA approved IL-2 in 1992 for patients with metastatic RCC based on several early phase trials. These trials used high-dose IL-2 with either 600,000 IU/kg or 720, 000 IU/kg as an intravenous bolus every 8 h for 5 days. The objective response rate was 14% [41]. There is significant toxicity of high-dose IL-2 with > 50% of patients in these studies requiring vasopressor support and a 4% treatment-related death rate. Given this toxicity, studies of low-dose IL-2 were done as well as studies comparing the combinations of low-dose IL-2, high-dose IL-2, and IFNα. While there was no overall survival advantage of high-dose IL-2 compared with other regimens and toxicity was greater with high dose, the durability of responses was better with high-dose IL-2, including some probable cures [42–46].

Guidelines have been developed to help manage toxicities associated with HD IL-2 and this regimen has been used safely and effectively at experienced centers [47]. From 2006 to 2017, 944 patients were treated with high-dose (HD) IL-2 on the PROCLAIM registry. They found complete responses in 5.4% and partial responses in 17.9% of patients [48]. After HD IL-2, patients received either targeted therapy, immune checkpoint blockade, the combination of both, or neither treatment; 3-year survival rates were 50%, 79%, 80%, and 65%, respectively [49••]. The sequence of targeted therapy with HD IL-2 was investigated in 352 patients; in those who received prior targeted therapy, the overall response rate to HD IL-2 was 19% with median overall survival of 22.1 months. In patients who received targeted therapy after HD IL-2, the median overall survival was 35.5 months. Though these data are retrospective, they suggest that the order of therapies might make a difference to the effectiveness [26]. In the era of targeted therapy and immune checkpoint inhibitors for RCC, the role of HD IL-2 is somewhat unclear though in appropriately selected patients, there are durable responses and these patients only need treatment for a very limited time.

Cytoreductive Nephrectomy

Cytoreductive nephrectomy refers to the removal of the primary tumor in the setting of metastatic renal cell carcinoma. The potential benefits of cytoreductive nephrectomy include removing tumorigenic growth factors, immunosuppression caused by the primary tumor, and palliation by decreasing pain and bleeding risk [50•]. In 2001, two phase III trials demonstrated an OS advantage with nephrectomy plus IFNα vs IFNα alone. Flanigan et al. randomized 120 patients to receive surgery followed by IFNα or IFNα alone. Median OS was 11.1 months on the surgery arm compared with 8.1 months on the arm that received IFNα alone ($p = 0.05$) [51]. In a similar study, 85 subjects were randomized to surgery followed by IFNα or IFNα alone; time to progression was 5 months vs 3 months (HR = 0.6, 0.36–0.97; $p = 0.04$) and median OS was 17 months vs 7 months (HR = 0.54, 0.31–0.94; $p = 0.03$), respectively [52]. A retrospective analysis of 89 patients treated with IL-2 after undergoing nephrectomy demonstrated a median survival of 16.7 months [53].

These studies established the role of cytoreductive nephrectomy in the cytokine therapy era.

Similar randomized studies were not done in the cytokine era until the recently published CARMENA trial, a prospective intention-to-treat non-inferiority study of sunitinib with or without nephrectomy in 450 patients with intermediate to poor risk metastatic clear cell RCC. Median OS was 13.9 months in the nephrectomy-sunitinib group vs 18.4 months in the sunitinib-alone group, demonstrating non-inferiority for the sunitinib-only group [54••]. The majority of patients (57%) had intermediate-risk disease, the remainder having poor-risk disease. In the nephrectomy-sunitinib group, 17.7% of patients did not receive sunitinib vs only 4.9% of patients in the sunitinib-alone group, the imbalance possibly suggesting that with more stringent patient selection, the outcomes in the surgery group could have been better [50•, 55]. The high proportion of poor-risk disease patients in this study also might explain why the nephrectomy arm of the study did poorly since the benefit might only accrue to healthier subjects. An approach that limits surgery to patients with intermediate risk may provide the population that would benefit the most from cytoreduction.

At this time, it is unclear whether cytoreductive nephrectomy provides benefit only in combination with cytokine-based systemic therapies or whether with a different patient population it could also benefit patients treated with TKIs. In addition, given the increased use of immune checkpoint therapies, further studies will need to be done to ascertain its future role.

Immune Checkpoint Inhibitors

Monoclonal antibodies that target immune checkpoints (PD-1, PD-L1, CTLA-4) have provided an overall survival benefit for multiple types of cancer. Ipilimumab, a monoclonal antibody that blocks CTLA-4, was used in a phase II study of patients with metastatic RCC. They received ipilimumab 3 mg/kg followed by 1 mg/kg or 3 mg/kg every 3 weeks. Five of the 40 patients who received 3 mg/kg had a partial response, including patients who had not previously responded to IL-2 therapy. Autoimmune adverse events were common and correlated with treatment response [56].

In a phase I trial of the anti-PD-1 antibody nivolumab, 34 patients with advanced renal cell carcinoma received nivolumab at 1 or 10 mg/kg every 2 weeks. Four of 17 patients treated with 1 mg/kg and 5 of 16 patients with 10 mg/kg had responses [57]. In the phase II setting, patients received either 0.3, 2, or 10 mg/kg every 3 weeks with overall response rates between 20 and 22% with the highest median overall survival of 25.5 months in the 2 mg/kg [58]. In a phase III study (CheckMate 025), 821 patients who had received at least one prior antiangiogenic therapy were randomized to receive either nivolumab 3 mg/kg every 2 weeks or everolimus 10 mg daily. The objective response rate for nivolumab vs everolimus was 25% to 5% (odds ratio 5.98, 95% CI 3.68–9.72; $p < 0.001$) and median OS was 25 months compared with 19.6 months (HR 0.73, 98.5% CI 0.57–0.93; $p = 0.002$) [59••]. Notably, PD-L1 status was prognostic for improved outcomes but not predictive (i.e., subjects with PD-L1+ tumors did better in both study arms; there was no added benefit to nivolumab in the PD-L1+ patients). Grade 3 or 4 adverse events were more common with everolimus; the most common adverse event with nivolumab was fatigue. This study led to FDA approval for nivolumab for patients with advanced renal cell carcinoma who had received prior antiangiogenic therapy.

The anti-PDL1 antibody atezolizumab was investigated in a phase I study in 70 patients with metastatic renal cell carcinoma. Atezolizumab was given every 3 weeks for 16 cycles or 1 year. The median progression-free survival was 5.6 months, with overall survival of 28.9 months [60]. This study led to both phase II and phase III trials with atezolizumab in combination with VEGF inhibitors (NCT01984242).

The combination of nivolumab and ipilimumab was studied in RCC in the phase I dose-finding CheckMate 016 trial. The objective response rate was 40.4% with a 2-year overall survival of 67.3% and 69.6%, respectively [61]. These promising results led to the CheckMate 214 phase III trial in the first-line setting with the combination of ipilimumab 1 mg/kg and nivolumab 3 mg/kg for four cycles followed by nivolumab 3 mg/kg every 2 weeks compared with the standard of care sunitinib (50 mg daily for 4 weeks of a 6-week cycle) [62••]. Five hundred fifty patients received combination immune therapy and 546 patients received sunitinib; patients were stratified by IMDC risk criteria and three quarters of them had intermediate or poor risk disease (defined as having at least one of the following: Hgb < normal, < 1 year from the diagnosis until treatment, corrected Ca++ > normal, platelets > normal, LDH > 1.5× normal, neutrophils > normal, Karnofsky < 80%) [63]. For the intermediate/poor-risk patients, for immunotherapy vs sunitinib, 18-month survival was 75% vs 60% and the median OS was not reached vs 26 months (HR 0.63; $p < 0.001$). For ipilimumab/nivolumab vs sunitinib, ORR was 42% vs 27% ($p < 0.001$) and complete response was 9% vs 1%. In patients with favorable risk disease by the IMDC criteria, median OS was not reached but appeared similar between the arms. However, a higher ORR and longer progression-free survival were seen with sunitinib. Whether there is a qualitative difference between good risk vs intermediate/poor risk disease that explains the difference is unknown though the percent of subjects with tumors that had ≥ 1% expression of PD-L1 in the tumor was 11.5% in the good-risk group vs 27.6% in the intermediate/poor-risk group, possibly making the good-risk group less sensitive to anti-PD-1 therapy. Grade 3 or 4 adverse events were seen in 46% of patients receiving ipilimumab plus nivolumab leading to

discontinuation in 22% of patients vs 63% of patients on sunitinib leading to discontinuation in 12% of patients. This study led to FDA approval for ipilimumab in combination with nivolumab in the first-line setting for patients with intermediate or poor-risk advanced renal cell carcinoma.

ICI/TKI Combinations

The combination of ICI and VEGF axis inhibitors (TKI or bevacizumab) may have an important role in the treatment of RCC. VEGF inhibition has been shown to normalize vasculature and increase the recruitment and infiltration of T cells into the tumors [64–66]. The combination of anti-PD-1 and anti-VEGFR2 treatment in a murine model led to decreased tumor neovascularization, upregulation of pro-inflammatory cytokines, and synergistic tumor growth inhibition [67]. A large number of trials are testing the combination of ICI and other molecules, most of which block VEGF signaling (Table 1).

In patients with metastatic RCC treated with the combination of atezolizumab and bevacizumab (anti-VEGF monoclonal antibody), intratumoral CD8+ T cells and unique T cell clones within the tumor increased following treatment. Of 10 patients treated, 4 patients had a partial response and another 4 patients had stable disease [68]. Results from a phase II trial that randomized subjects to receive atezolizumab and bevacizumab vs atezolizumab alone or sunitinib alone revealed encouraging antitumor activity [69•]. A phase III trial is underway of subjects randomized to atezolizumab and bevacizumab vs sunitinib; early results reveal the progression-free survival hazard ratio is 0.74 in PD-L1+ patients in favor of atezolizumab/bevacizumab [70•].

The combination of pembrolizumab (anti-PD-1 monoclonal antibody) and pazopanib (TKI) was studied in a phase I/II trial in which patients received pembrolizumab 2 mg/kg every 3 weeks with either pazopanib 600 mg or 800 mg. In both cohorts, 90% of patients experienced grade 3/4 adverse events with significant hepatotoxicity, which limited further investigation of this combination [71•]. Other combinations with pembrolizumab have had success in early phase trials including pembrolizumab in combination with axitinib and pembrolizumab with lenvatinib. In 52 patients, the combination of pembrolizumab and axitinib (TKI) led to an ORR of 73% with complete responses in 8% of subjects [72•]. The combination of lenvatinib (TKI) and pembrolizumab was investigated in 30 patients who had received ≥ 1 prior anticancer therapy; ORR was 66.7% with median progression-free survival of 17.7 months with the most common adverse events being diarrhea, fatigue, hypothyroidism, stomatitis, and nausea (Lee 2018) [73]. Both of these studies have led to phase III trials vs sunitinib. The KEYNOTE-426 study (NCT02853331) is an ongoing phase III randomized trial of treatment-naïve metastatic RCC in which patients receive pembrolizumab 200 mg every 3 weeks with either axitinib 5 mg twice daily or sunitinib 50 mg once daily for 4 weeks of a 6-week cycle. Another ongoing phase III study (NCT02811861) randomized patients to receive lenvatinib/pembrolizumab vs lenvatinib/everolimus vs sunitinib in the first-line setting.

The JAVELIN Renal 100 trial investigated the anti-PD-L1 antibody avelumab in combination with axitinib in patients with advanced clear cell RCC and primary tumor resection in the first-line setting. All six of the patients in the dose-finding phase and 26 of the 49 patients in the dose-expansion phase experienced an objective response. Adverse events ≥ 3 were common (58%) with the most frequent being hypertension in 29% with one patient dying from autoimmune myocarditis [74•]. A phase III study (Javelin Renal 101, NCT02684006) is underway and will compare avelumab and axitinib vs sunitinib in the first-line setting.

Trials combining nivolumab and cabozantinib are underway (CheckMate 9ER) (NCT03141177 and NCT02496208). Cabozantinib is an interesting TKI because it not only inhibits VEGFR and c-Met signaling but Axl signaling as well. Axl is a MERTK member receptor tyrosine kinase, which is involved in innate immunity [75]. The inhibition of Axl might increase tumor microenvironment inflammation, which could synergize with PD-1 axis therapies.

While the response rates for these combinations are very impressive, whether response rates will translate into improvements in progression-free and overall survival is unknown. In addition, these response rates could be merely from additive effects of the drugs rather than synergy. It is also possible that using these medications one after the other might be as efficacious as the combination with fewer side effects. Lastly, given the results of the CheckMate 214 trial (ipilimumab/nivolumab vs sunitinib), the comparator arm for these phase III trials in intermediate/poor-risk disease should be ipilimumab/nivolumab.

Cytokine/Immune Checkpoint Combinations

High-dose IL-2 is probably too toxic to combine with PD-1 axis inhibition. However, a PEGylated IL-2 drug, NKTR-214, is given at doses that allow outpatient treatment. When IL-2 is given at a high dose, there is binding of both the IL2Rβγ responsible for the expansion of effector T cells and the IL2Rαβγ isoform, which expands both effector and regulatory T cells [40]. PEGylation appears to sterically inhibit binding to the IL2Rαβγ isoform, thus conferring on NKTR-214 the ability to preferentially activate effector T cells [76]. The PIVOT study is a phase I/II of NKTR-214 in combination with nivolumab in patients with advanced solid tumors. There were 24 patients with RCC who had not previously

Table 1 Currently open trials using immune agents in RCC

Identifier	Combinations	Phase	Disease
ICI/VEGF blockade			
NCT01472081	Nivolumab (BMS-936558; MDX-1106) in combination with sunitinib, pazopanib, or ipilimumab in subjects with metastatic renal cell carcinoma (RCC) (CheckMate 016)	I	mRCC
NCT02210117	Nivolumab with or without bevacizumab or ipilimumab before surgery in treating patients with metastatic kidney cancer that can be removed by surgery	I	mRCC
NCT02496208	Cabozantinib-s-malate and nivolumab with or without ipilimumab in treating patients with metastatic genitourinary tumors	I	Metastatic GU tumors
NCT03136627	Phase 1/2 study of tivozanib in combination with nivolumab in subjects with RCC	I/II	mRCC
NCT03141177	A study of nivolumab combined with cabozantinib compared with sunitinib in previously untreated advanced or metastatic renal cell carcinoma (CheckMate 9ER)	III	mRCC
NCT02133742	Dose-finding study to evaluate safety, drug interaction, tumor markers of axitinib in combination with MK-3475 in adult patients with previously untreated advanced renal cell cancer	I	aRCC
NCT03006887	Phase 1b trial of lenvatinib plus pembrolizumab in subjects with selected solid tumors	I	Solid tumors
NCT02348008	Phase Ib and phase II studies of anti-PD-1 antibody MK-3475 in combination with bevacizumab for the treatment of metastatic renal cell carcinoma: big 10 cancer research consortium GU14-003	Ib/II	mRCC
NCT02014636	Safety and efficacy study of pazopanib and MK 3475 in advanced renal cell carcinoma (RCC; KEYNOTE-018)	I/II	aRCC
NCT03149822	Study of pembrolizumab and cabozantinib in patients with metastatic renal cell carcinoma	I/II	mRCC
NCT02501096	Phase 1b/2 trial of lenvatinib (E7080) plus pembrolizumab in subjects with selected solid tumors	I/II	Solid tumors
NCT02853331	Study to evaluate the efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy in participants with renal cell Carcinoma (MK-3475-426/KEYNOTE-426)	III	aRCC
NCT02811861	Lenvatinib/everolimus or lenvatinib/pembrolizumab versus sunitinib alone as treatment of advanced renal cell carcinoma (CLEAR)	III	aRCC
NCT03170960	Study of cabozantinib in combination with atezolizumab to subjects with locally advanced or metastatic solid tumors	I/II	Advanced solid tumors
NCT02724878	Study of atezolizumab + bevacizumab in patients with advanced non-clear cell renal cell carcinoma	II	Advanced non-clear cell RCC
NCT02420821	A study of atezolizumab in combination with bevacizumab versus sunitinib in participants with untreated advanced renal cell carcinoma (RCC) (IMmotion151)	III	aRCC
NCT02493751	A study of avelumab in combination with axitinib in advanced renal cell cancer (JAVELIN Renal 100)	I	aRCC
NCT03200587	Cabometyx and avelumab in patients with metastatic renal cell carcinoma (mRCC)	I	mRCC
NCT02684006	A study of avelumab with axitinib versus sunitinib in advanced renal cell cancer (JAVELIN Renal 101)	III	aRCC
ICI/cytokines			
NCT02983045	A dose escalation and cohort expansion study of CD122-biased cytokine (NKTR-214) in combination with anti-PD-1 antibody (nivolumab) or in combination with nivolumab and anti-CTLA4 antibody (ipilimumab) in patients with select advanced or metastatic solid tumors (PIVOT-02)	I/II	Metastatic solid tumors
NCT02989714	Phase Ib/II trial of interleukin-2 and PD-1 checkpoint inhibitor, nivolumab in metastatic clear cell renal cell cancer	Ib/II	Clear cell mRCC
NCT02089685	Safety and tolerability of pembrolizumab (MK-3475) + PEGylated interferon alfa-2b and pembrolizumab+ ipilimumab in participants with advanced melanoma or renal cell carcinoma (MK-3475-029/KEYNOTE-29)	I	aRCC and melanoma

Table 1 (continued)

Identifier	Combinations	Phase	Disease
NCT02964078	Interleukin-2 and pembrolizumab for metastatic kidney cancer	II	mRCC
NCT03063762	Study to evaluate safety, pharmacokinetics and therapeutic activity of RO6874281[1] as a combination therapy in participants with unresectable advanced and/or metastatic renal cell carcinoma (RCC)	I/II	aRCC
NCT01984242	A study of atezolizumab (an engineered anti-programmed death-ligand 1 [PD-L1] antibody) as monotherapy or in combination with bevacizumab (Avastin®) compared with sunitinib (Sutent®) in participants with untreated advanced renal cell carcinoma (IMmotion150)	II	aRCC
ICI/immune modulator			
NCT03502330	APX005M[2] with nivolumab and cabiralizumab[3] in advanced melanoma, non-small cell lung cancer or renal cell carcinoma	I	aRCC, melanoma, NSCLC
NCT02646748	Pembrolizumab combined with itacitinib (INCB039110)[4] and/or pembrolizumab combined with INCB050465[5] in advanced solid tumors	I	Advanced solid tumors
NCT02655822	Phase 1/1b study to evaluate the safety and tolerability of CPI-444[6] alone and in combination with atezolizumab in advanced cancers	I	Advanced solid tumors
NCT03598816	Polyimmune (durvalumab (MEDI4736) and tremelimumab) and vaccine-orchestrated treatment for patients with advanced/metastatic renal cell carcinoma (PIVOT-RCC)	II	aRCC
NCT02643303	A phase 1/2 study of in situ vaccination with tremelimumab and iv durvalumab plus polyICLC[7] in subjects with advanced, measurable, biopsy-accessible cancers	I/II	Advanced solid tumors
NCT01975831	A phase 1 study to evaluate MEDI4736 in combination with tremelimumab	I	Advanced solid tumors
ICI/other			
NCT02619253	Phase I/Ib study of pembrolizumab with vorinostat[8] for patients with advanced renal or urothelial cell carcinoma	I	aRCC or TCC
NCT02178722	A phase 1/2 study exploring the safety, tolerability, and efficacy of pembrolizumab (MK-3475) in combination with epacadostat (INCB024360)[9] in subjects with selected cancers (INCB 24360-202 / MK-3475-037 / KEYNOTE-037/ ECHO-202)	I/II	Solid tumors
NCT03024437	Atezolizumab in combination with entinostat[10] and bevacizumab in patients with advanced renal cell carcinoma	I/II	aRCC
NCT03483883	Avelumab/gemcitabine in sarcomatoid RCC	I	Sarcomatoid RCC
NCT03308396	Study of durvalumab and guadecitabine[11] in advanced kidney cancer	Ib/II	aRCC
NCT02819596	MEDI4736 combinations in metastatic renal cell carcinoma (CALYPSO)[12]	II	mRCC
Cell therapies			
NCT02926053	T cell therapy for patients with metastatic renal cell carcinoma	I	mRCC
NCT02886897	A phase II study of combinations of dendritic cells and cytokine-induced killer cell (D-CIK) immunotherapy and anti-programmed death-1 in refractory solid tumors	II	Solid tumors
Cytokines			
NCT01038778	Phase I/II study of high-dose interleukin 2, aldesleukin, in combination with the histone deacetylase inhibitor entinostat in patients with metastatic renal cell carcinoma	I/II	mRCC

Table 1 (continued)

Identifier	Combinations	Phase	Disease
NCT01550367	Inhibiting the systemic autophagic syndrome—a phase I/II study of hydroxychloroquine and aldesleukin in renal cell carcinoma patients (RCC). A Cytokine Working Group (CWG) study	I/II	RCC

[1] FAP/IL-2
[2] APX005M IgG1 agonistic CD40
[3] Cabiralizumab—IgG4 antibody against CSF1R
[4] JAK1 inhibitor
[5] PI3K-delta inhibitor
[6] Adenosine-A2A receptor inhibitor
[7] TLR3 agonist
[8] HDAC inhibitor
[9] IDO-1 inhibitor
[10] HDAC inhibitor
[11] DNMT inhibitor
[12] Combinations are durvalumab monotherapy or with tremelimumab or with savolitinib or savolitinib monotherapy

been treated with an immune-oncology agent; in this group, the objective response rate was 54% [77].

IFN has also been PEGylated and was used in a trial of atezolizumab/PEG-IFN/bevacizumab (NCT02174172) and in combination with pembrolizumab (NCT02089685 MK-3475/029/KEYNOTE-29). Both trials have completed recruitment but neither has reported results.

Adoptive Cell Therapy

Adoptive cell therapy (ACT) begun over 30 years ago and is the process in which cells with antitumor reactivity are transferred into the tumor-bearing host [78]. The use of tumor-infiltrating lymphocytes (TIL) involves removing tumor from the patient, ex vivo expansion, and activation of immune cells followed by transfer of the cells back into the same patient. A partial response was seen in a patient with RCC who received TIL [79]. In a 1989 study, of 7 patients with RCC who received TIL in combination with IL-2, two patients experienced a partial response lasting 5 and 6 months [80]. In a phase III trial, 81 patients underwent nephrectomy followed by randomization to receive either TIL and IL-2 or IL-2 alone. There was no difference in response rates or OS between the two arms [81]. However, this study did not lymphodeplete patients before treatment, which is now considered a necessary step for TIL function.

Since these early studies, the process of ACT has been further refined in the metastatic melanoma population. Current TIL protocols include lymphodepletion, which removes a large number of T_{reg}s, decreases antiinflammatory cytokines, and opens up a niche for infused TIL [82–84]. With these methods, there have been reports of durable responses in patients with metastatic melanoma treated with TIL [83, 84] [85]. Despite the advances seen in melanoma TIL production, it has been challenging to reproducibly generate RCC TIL. In the trial by Figlin et al., the TIL production failure rate was 41% [81]. Now, using enzymatic or combined enzymatic/mechanical disaggregation of tumors, Baldan et al. have developed a protocol to consistently produce TIL from RCC biopsies [85]. In light of these new techniques in TIL expansion and the success seen in melanoma TIL trials with lymphodepleting regimens, adoptive cell therapy with TIL might be reassessed.

Conclusion

The role of the immune system in the pathogenesis of renal cell carcinoma was recognized nearly three decades ago and led to the first immune-based therapies. Much progress has been made; we now have cytokine as well as immune checkpoint inhibitor therapies and can occasionally cure patients

with metastatic disease. The combination of these therapies with each other and with TKI medications might result in much better control of disease. Lastly, the standard of care now in intermediate- and poor-risk RCC patients in the first-line setting is ipilimumab/nivolumab and nivolumab monotherapy is a standard of care second-line therapy.

That said, there are more unanswered questions now than ever. How the various therapies (ICI, cytokine, and anti-VEGF axis) can best be sequenced and combined is in the early stages (Table 1). How good vs intermediate/poor-risk disease and PDL1 expression levels impact therapy also are still unknown. Whether cell-based therapies will become viable is only just beginning to be studied.

It is a very exciting time to be treating RCC. The rapid development of combination immune-based therapies in renal cell carcinoma has the potential to increase efficacy, prolong survival, and potentially cure patients with this disease.

Compliance with Ethical Standards

Conflict of Interest Bryden Considine declares that he has no conflict of interest.

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- •• Of major importance

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