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PD-1/PD-L1 Blockade in Renal Cell Cancer

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Abstract

Introduction—Immunotherapy using checkpoint inhibitors is providing significant benefit to patients with renal cell carcinoma (RCC), both in overall survival and tolerability of treatment. Given the recent approval of the first checkpoint inhibitor in RCC, this review discusses the background and clinical data for checkpoint inhibition in RCC.

Areas covered—This review introduces and discusses the basic biologic mechanisms of checkpoint inhibitor function and focuses on the current evidence in clinical trials for the use of immunotherapy in RCC.

Expert commentary—Immunotherapy has been a mainstay of therapy in RCC but the recent approval of nivolumab with ORR of 25% and durable responses has provided a transformative new therapeutic option.

Keywords

Renal cell; PD-1; PD-L1; nivolumab; atezolizumab; pembrolizumab

1 Introduction

1.1 Epidemiology

Renal cell carcinoma (RCC) is a unique tumor due to its often slow progression of disease, inherent resistance to cytotoxic chemotherapy, and responsiveness to immunotherapy. In 2015, an estimated 61,560 people were diagnosed and 14,080 died from RCC. Overall survival has doubled in the last 50 years, with a current 5-year overall survival (OS) of nearly 75%. Approximately 65% of patients at initial diagnosis are found to have localized disease for which surgical resection is frequently curative. However, 30% of patients originally diagnosed with localized disease will recur and another 20% of people are diagnosed with synchronous metastatic disease. Risk factors for the development of RCC include cigarette smoking [1], hypertension, obesity [2], acquired cystic kidney disease,

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ingestion or exposure to agents causing kidney injury such as analgesics, and a number of well-defined genetic syndromes, such as VHL, familial papillary, and tuberous sclerosis [3].

1.2 Biology and Targeted Therapy for RCC

RCC is composed of several histologic subtypes including clear cell type which comprises 85% of RCC and the remaining subtypes include papillary, chromophobe, and oncocytic type, in order of decreasing frequency [4]. It is controversial whether the histology among these main subtypes predicts prognosis, although several more rare subtypes including renal medullary and collecting duct carcinoma are associated with a poorer overall survival [5,6]. Additional histologic features including nuclear grade, as defined by Fuhrman, is one of the most significant prognostic features in RCC [7]. In addition to categorization of this disease by pathologic subtype, RCC may be classified by biologic subtypes. Large scale sequencing efforts, including The Cancer Genome Research Atlas (TCGA), have identified dysregulated signaling networks in clear cell RCC (ccRCC), including novel changes in the PI3K/AKT pathways and the previously well-characterized loss of the tumor suppressor von Hippel-Lindau (VHL) [8] [9]. Autosomal dominant inheritance of the mutant VHL gene predisposes persons to the development of pheochromocytomas, hemangioblastomas, and, through family linkage studies, was connected to frequent loss of chromosome 3p in ccRCC [10]. The function of the VHL protein has been well characterized to act as an E3 ubiquitin ligase targeting the hypoxia inducible factor alpha family (HIF1a and HIF2a) for degradation in the presence of normal oxygen tension [11]. The HIFa family of proteins act as transcriptional regulators for thousands of genes by binding to hypoxia response elements throughout the genome. Therefore, loss of VHL in ccRCC allows for constitutive activity of HIF2a to upregulate pathways involved in angiogenesis through vascular endothelial growth factor (VEGF) [12]. Another commonly altered pathway includes the mammalian target of rapamycin (mTOR) which is involved in cell growth and metabolism and is activated in 60–80% of ccRCC. [13]. Lastly, a majority of the >400 ccRCC tumors in the TCGA showed epigenetic changes of hypomethylation associated with a mutation in the SET domain containing 2 (SETD2) gene [14]. Characterizing these basic biologic pathways has led to the development of VEGF and mTOR inhibitors, a radical shift in RCC treatment strategies. These agents have improved the median OS for patients with metastatic disease from less than a year to 24 months [15].

1.3 Cytokines in the Treatment of RCC

Renal cell carcinoma was considered to be an immune-responsive tumor based on several intriguing observations. First, spontaneous regression of metastatic lung lesions were noted in a handful of patients following nephrectomy for the primary tumor [16]. In several case reports, this regression occurred simultaneously with an autoimmune flair (e.g. psoriasis) [17,18]. Subsequent studies have suggested that cytoreductive surgery of the primary tumor prior to cytokine therapy is associated with superior outcomes. A phase III trial comparing interferon- α (IFN α) alone to nephrectomy with IFN α showed improvement in median overall survival (OS) from 8.1 to 11.1 months, respectively [19,20]. Second, immunotherapy with immunostimulatory cytokines, such as Interleukin-2 (IL-2) and IFN, has demonstrated activity in RCC. Due to the limited efficacy of cytotoxic chemotherapy in RCC, immunotherapy was the primary systemic treatment modality for RCC prior to the advent of

targeted therapy with multi-targeted kinase and mTOR inhibitors, as discussed above. High dose IL-2 treatment demonstrated a 10–19% overall objective response rate with durable remission in 5–8% of patients, which lead to its FDA approval in 1992. The therapeutic use of IL-2 is limited to a select group of healthy patients due to toxic side effects that include systemic inflammatory response syndrome with hepatic and renal toxicities [21]. The activity of these classic immune therapies combined with our subsequent enhanced understanding of the role of immune suppression and adaptive immune resistance in cancer has made the use of checkpoint inhibitors an attractive therapeutic strategy for patients with metastatic RCC.

2 Checkpoint Inhibition

2.2 Immune Regulatory Signaling in RCC

The human immune system has both an innate and adaptive component. The adaptive component is composed of B and T cells which are responsible for the recognition and elimination of foreign pathogens including tumor cells [22]. Many regulatory signaling cascades exist to both stimulate and inhibit T cells in order to modulate their activity as needed. The T cell receptor (TCR) recognizes antigens on the surface of antigen-presenting cells (APC) through the APC's ability to present processed peptides in conjunction with the major histocompatibility complex (MHC), signal 1 [23] (Figure 1). After recognition and binding of the TCR-MHC complex, a second signal, known as the co-stimulatory signal, must occur for T cell activation and effector cytokine function [24] (signal 2). These co-stimulatory surface molecules enhance T cell activation and are countered by negative feedback mechanisms, to prevent unrestrained T cell activity and autoimmune reactions. The T cell in turn has cell surface receptors which bind these ligands and either produce a co-stimulatory signal (e.g. CD28) or an inhibitory signal (e.g. cytotoxic T-lymphocyte-associated protein 4 (CTLA4) on CD4 and PD-1 on CD8 cells). CTLA4 is found on the surface of recently activated CD4 T cells in lymphoid tissue where it outcompetes CD28 for binding of ligand on the surface of the APC, B7.1 and B7.2 (CD80 and CD86), thus limiting specifically the initial activation threshold of T cells [25] (Figure 1). As an inhibitory cell surface molecule, CTLA4 was theorized to be a suitable therapeutic target using a monoclonal antibody for reactivation of T cell response in RCC and other cancers.

Programmed Cell Death 1 protein (PD-1) is expressed on many immune cells including T cells, B cells, natural killer cells, macrophages, and dendritic cells. On T cells, it is present at the cell surface after activation of TCR, and is commonly viewed as a marker of chronic stimulation [26]. PD-1 is activated after interaction with its ligands, PD-L1 or PD-L2, which are expressed by tumor cells, stromal cells and tumor infiltrating lymphocytes. PD-1 binding to its ligand inhibits TCR induction of the AKT pathway, thus blocking the glucose uptake necessary for T cell activation [27]. Inhibitory signaling through the PD-1 receptor will limit T cell effector function in the tumor microenvironment, making it an attractive target for checkpoint inhibition.

PD-L1 is expressed on endothelial, monocytic, dendritic, and epithelial cells, including cancer cells [28]. Though many attempts have been made to correlate PD-L1 expression with prognostic implications, these results have been variable. High expression of PD-L1 in

some tumors clearly correlates with poor survival but in other malignancies this relationship is either not present or even correlates with better outcome. In RCC, clinical studies have demonstrated that PD-L1 expression is a negative prognostic indicator in unselected patient populations [29]. Interestingly, PD-L1 expression in ccRCC appears to be promoted by HIF2a activation following VHL deficiency [30,31]. Investigation of PD-L1 expression was also evaluated in a recent analysis from the COMPARZ trial in 453 patients where formalin fixed paraffin tissue was available from patients who received VEGF inhibitor treatment with either pazopanib or sunitinib. The tissue was evaluated for PD-L1 expression on tumor cells, ruling out the PD-L1 expressing macrophages with a concomitant CD68 stain. Only 36% of patients had any degree of PD-L1 tumor expressing cells; the subset of patients with high PD-L1 expression (~13%, n=59) had a significantly shorter overall survival with a median OS of 15.1 vs 35.6 months and 15.3 vs 27.8 months for patients treated with pazopanib or sunitinib, respectively.

3 Preclinical

The six hallmarks defined to characterize the development of cancer include evasion of apoptosis, self-sufficiency of growth signals, decreased sensitivity to anti-growth signals, ability to invade and metastasize, promotion of angiogenesis, and limitless replication potential [32]. Two additional traits necessary for tumor formation were added to this list: reprogramming energy metabolism and immune evasion [33]. Immune evasion occurs through various mechanisms, including reduced immune recognition by downregulation of MHC presentation, increased resistance to apoptosis, development of an immunosuppressive tumor environment through expression of negative regulatory markers (such as PD-1/PD-L1, TIM-3, or CTLA4), and recruitment of immune regulatory cells such as Tregs [34]. Several particular immune features in the microenvironment suggest an ongoing tumor-directed immune response is limited by PD-1/PD-L1 interaction, thus providing a potential therapeutic target.

In RCC, the features of an exhausted immune response, with expression of many checkpoint inhibitory molecules, are variably present. An inflamed tumor microenvironment and T cell infiltration are common in RCC, as is PD-L1 expression. In RCC, the clonal tumor infiltrating T cells express substantially more PD-1 and LAG3, another inhibitory T cell marker, compared with their corresponding peripheral blood clonal T cells, suggesting the tumor infiltrating lymphocytes (TILs) are more chronically stimulated and suppressed [35]. Additional evidence suggestive of exhausted immune response is that the overall number of clonal T cells assessed in RCC is markedly lower than that found in other immunogenic cancers such as melanoma [36]. Mouse models have shown that recruitment of additional immune suppressive components may be relevant in RCC. In one model, Devaud et al. showed that depletion of regulatory T cells induced regression of subcutaneous tumors but not intra-renal RCC tumors by using a spontaneously derived renal adenocarcinoma mouse cell line (RENCA) and comparing intra-renal injected RCC to a subcutaneous orthotopic model of RCC. This suggests that another immunosuppressive component may contribute in the kidney specific tumor environment, such as myeloid-derived suppressor cells or regulatory macrophages (M2) [37]. Preclinical evidence continues to enhance our

understanding of the mechanisms underlying checkpoint inhibitor therapy and to identify potential combination strategies.

Direct investigation of preclinical work for anti-PD-1 in RCC is not abundant. Data from work in mice show that PD-1 is important for peripheral self-tolerance because PD-1 knockout mice show development of autoimmune-like diseases such as lupus [38]. A knockout model of the PD-1 ligand, PD-L1 null mouse, demonstrated an inability of T cells to properly undergo apoptosis during the contraction phase of T cell development, and these PD-L1 knockout mice were more prone to induced autoimmune diseases [39]. Further knowledge for understanding the role of PD-1/PD-L1 in cancer came after mechanistic understanding of the pathway including discovery that IFN gamma signaling causes increased expression of the cell surface receptors PD-L1 to downregulate T cell activity a process identified as “adaptive resistance” [40].

4 Therapeutics

Ipilimumab, a monoclonal antibody to CTLA4 was the first checkpoint inhibitor used in RCC. In a phase II study, two cohorts of patients were treated with ipilimumab at either 1 mg/kg or 3 mg/kg every three weeks. One of 21 patients in the low-dose cohort and 5 of 40 in the high dose group (12.5%, 95% CI 4 – 27%) had a response. Notably, approximately 30% ORR was observed in patients experiencing grade 3 or 4 immune-related adverse events (irAE) such as enteritis, dermatitis, hepatitis or endocrinopathies [41]. While ipilimumab is not approved in RCC as a single-agent, it is now approved in advanced melanoma, and is being developed in combination with other agents in RCC (see below). The overall experience with ipilimumab in RCC and other cancer types, demonstrated the clinical potential for immune checkpoint inhibition in solid tumors.

After years of preclinical work, a phase I study was conducted to determine the safety and dosage of the PD-1 inhibitor, Nivolumab (MDX-1106, BMS-936558, Opdivo™). Nivolumab is a genetically engineered, fully human monoclonal IgG4 antibody specific for PD-1. Efficacy was assessed in patients with advanced cancer including melanoma, non-small cell lung cancer (NSCLC), RCC, castrate-resistant prostate cancer, and colorectal cancer. A total of 54 patients were enrolled and received a single dose infusion in escalating cohorts from 0.3 to 10 mg/kg. This trial demonstrated patient tolerability to the maximum 10 mg/kg dosage. One patient with metastatic RCC had a partial response which was durable for 18 months [42]. A subsequent multi-dose trial enrolled 296 patients with advanced cancers including NSCLC, melanoma, RCC, as well as a small cohort that included prostate cancer and colorectal cancer (Table 1). These patients underwent dose escalation from 0.1 to 10 mg/kg using nivolumab without any dose limiting toxicity [43]. In this trial, 34 patients with metastatic RCC were enrolled and received nivolumab every 2 weeks with a treatment maximum of up to 96 weeks (12- 8 week courses). Of these, approximately 25% experienced an objective response (4/17 patients at 1 mg/kg and 4/16 at 10 mg/kg.). At the time of the initial analysis, 5 patients had a response lasting longer than a year while an additional 27% of patients experienced stable disease for at least 6 months. Across the entire trial of 296 patients, 14% had a grade 3–4 adverse event, the most common being fatigue, but also included classic irAEs such as dermatitis, hepatitis, colitis/diarrhea, and

pneumonitis. Importantly, the side effect profile and tolerability was distinct from ipilimumab, where ipilimumab induced grade 3 or 4 irAEs in up to 23% of treated patients including largely colitis, hepatitis, dermatitis, and endocrinopathies. Nivolumab was only rarely associated with colitis, but did produce immune mediated pneumonitis in a low percentage of patients (~1%) [43,44]. Subsequent longer-term follow-up for the RCC patients treated on this study showed that 29% achieved an objective response by RECIST criteria with a median duration of response of 12.9 months. Median overall survival was 22.4 months, with 3-year OS of 44% and median progression free survival (PFS) of 7.3 months [45].

In this large phase I clinical trial, nivolumab appeared to have an excellent safety profile in patients with metastatic RCC. Thus, a phase II study including only patients with RCC was conducted to better assess the tumor response, dose- response relationship, and further explore side effects and tolerability. A total of 168 patients who had previously progressed after treatment with a VEGF inhibitor were randomized to nivolumab at 0.3, 2, or 10 mg/kg IV every three weeks. No statistically significant dose-response was identified by the respective PFS of 2.7, 4.0, and 4.2 months; the ORR of 20%, 22% and 20%; or the median OS which was 18.2, 25.5, and 24.7 months for each dose, respectively. Again, the most common side effect was fatigue and 7% of patients discontinued treatment for adverse events [46]. Thus, this first phase II trial in RCC corroborated the safety and anti-tumor efficacy observed in the phase I trials.

These trials led to a randomized phase III trial for patients with advanced RCC [47]. The study enrolled patients with advanced clear cell RCC who had previously received treatment with one or two anti-angiogenic therapies. Patients were stratified based on the geographic region of enrollment, Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score, and number of prior therapies. They were randomized to either nivolumab 3 mg/kg every two weeks or everolimus 10 mg daily. Everolimus, an oral inhibitor of mTOR, was chosen as a comparator arm, as it is approved in the second line setting for patients with advanced RCC who have failed treatment after VEGF tyrosine kinase inhibitor (TKI) therapy. The primary endpoint of this study was overall survival with secondary endpoints predefined as ORR, PFS, correlation of survival with PD-L1 expression, and the incidence of adverse events. This trial was conducted from October 2012 to November 2014, enrolled 821 patients, and had a minimum follow-up of fourteen months at the time of reporting. Nivolumab demonstrated an improved overall survival compared with everolimus (median 25.0 months vs. 19.6 months, HR = 0.73, p = .002). The objective response rate was also higher in the nivolumab group (25% vs 5%). Of the patients in the nivolumab arm who responded, 31% had a treatment response lasting at least 12 months. PD-L1 expression was not predictive of outcome or overall survival in this study in contrast to anti-PD-1 studies in other tumors. The side effect profile in this study recapitulated the prior experience where 79% of patients treated with nivolumab had a treatment-related adverse event of any grade and the majority of these were fatigue, nausea, and pruritus. Only 19% of patients had a grade 3 or 4 reportable event with nivolumab treatment, most commonly fatigue (2%), but also included pneumonitis (1%), anemia (2%), and diarrhea (1%). These trials collectively provided indelible evidence that a subset of patients with advanced RCC respond to PD-1 inhibition and many of these are durable responses. Based on the benefit in overall survival,

nivolumab received approval for the treatment of advanced RCC in patients who have received prior anti-angiogenic therapy.

As described above, PD-1 is a cell surface receptor commonly expressed by T cells that are chronically activated and functions as a negative feedback mechanism. PD-1 is bound by programmed death receptor ligand 1 or 2 (PD-L1/2) which are commonly expressed on endothelial cells, other T cells, macrophages, dendritic cells, stromal cells and of course tumor cells. In addition to targeting PD-1 inhibition, another therapeutic approach is to target its ligand, PD-L1 with a monoclonal antibody. A phase I study using 0.3–10 mg/kg of BMS-936559 was given every 2 weeks and enrolled 207 patients with NSCLC, melanoma, colorectal, ovarian, pancreatic, breast, gastric, and kidney cancer [48]. The safety profile was similar with PD-L1 inhibition compared to PD-1 where only 7% of patients had grade 3 or 4 adverse events, including infusion reactions seen with higher doses of the PD-L1 inhibitor and cases of adrenal insufficiency. In this trial, 17 patients were enrolled with RCC and 2 patients had an objective response at the 10 mg/kg dosage with duration lasting 4 and 17 months. An additional 41% of patients with RCC had stable disease for 6 months while on treatment.

Another fully humanized and modified IgG1 PD-L1 antibody, atezolizumab (MPDL3280A), was recently evaluated in a phase I study involving multiple tumor types including 70 patients with locally advanced or metastatic RCC [49]. At time of publication, this is the only anti-PD-1/PD-L1 study to enroll non-clear cell histology (comprising 10% of the study group). All patients received atezolizumab at dosages of 10, 15, or 20 mg/kg infusion every three weeks. Relatively similar to the PD-1 inhibitors, 17% of patients had a grade 3 adverse event which was most commonly fatigue and anemia; no dose limiting toxicity was observed. Of the 62 patients with clear cell histology, the ORR was 15%, with median duration of response of 17.4 months and 2 year OS of 58% [49]. Analysis of ccRCC subgroups suggested higher ORR (22%) in patients with Fuhrman grade 4 or having sarcomatoid features. Notably, none of the 7 patients with non-clear cell histology had an objective response as measured by RECIST criteria, although one responded based on immune related response criteria. This study also made important observations of biological markers of response by finding that a decrease in VEGFA and acute phase proteins following atezolizumab treatment correlated with response. Unlike in melanoma tumors, where CD8 infiltration and a cytotoxic T effector gene signature has been predictive of response to anti-PD-1 and anti-PD-L1 antibodies, in clear cell RCC these biomarkers were not predictive. However a higher ratio of cytotoxic T cells vs T regulatory cell gene expression, as measured by FOXP3 levels, was associated with response to atezolizumab [49].

5 Future of PD-1/PD-L1 inhibition in RCC

These trials represent the beginning of a new era for RCC therapy. Many seminal mechanistic questions remain unanswered. One priority is predicting which patients will respond to PD-1/PD-L1 inhibition. We eagerly anticipate the results of a recently closed phase I biomarker trial investigating functional and phenotypic characterization of peripheral immune cells as well as modulation of soluble factors following various dosages of

nivolumab treatment in patients with advanced RCC. Further studies are needed in RCC to understand the impact of clonally expanded T cells present in the tumor, effector T cell interferon gamma gene expression signatures, and PD-1/PD-L1 expression in the microenvironment. Studies like these may provide markers of treatment response and help refine which patients benefit most from nivolumab. Another priority going forward is determining the response of patients with non-clear cell RCC histology to checkpoint inhibition and whether the biological difference between histologies may explain response rate to immunotherapy.

A second major objective is devising combinatorial regimens or treatment modifications to increase the approximately 20% current response rate. Numerous pre-clinical studies and clinical trials are ongoing to address these issues (Table 2). Based on results seen in advanced melanoma, combination trials of nivolumab with ipilimumab in advanced RCC are ongoing, with preliminary reports presented at ASCO 2014. This study had two arms including group A (nivolumab 3 mg/kg and ipilimumab 1 mg/kg) and group B (nivolumab 1 mg/kg and ipilimumab 3 mg/kg). Patients in group B experienced higher rates of grade 3 or 4 toxicities including transaminitis, elevated lipase or amylase, diarrhea, and colitis but no reported cases of pneumonitis. The secondary endpoint of tumor response at 35 weeks of treatment showed an ORR of 43% in group A and 48% in group B. Based on this trial the group A regimen was taken forward into a phase III trial in comparison to sunitinib in previously untreated advanced ccRCC patients which has completed accrual. Similar in concept, a phase I trial is recruiting patients with metastatic solid tumors to determine the safety of combination with durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Numerous positive and negative immune checkpoints are also being characterized, expanding the possible number of therapeutic targets. Combinations of anti-PD-1/PD-L1 plus agents targeting LAG-3, TIM-3, CD276 (B7-H3), CD-27 and more are all in phase I trials for patients with RCC (Figure 1, Table 2).

In addition to consideration of combination checkpoint inhibitors, many questions now arise regarding the timing of treatment with checkpoint inhibition in renal cell carcinoma. The current use of nivolumab is approved in the second line setting following TKI therapy in RCC. A retrospective review of 99 patients who were treated with PD-1/PD-L1 blockade in the first-line setting and went on to receive VEGFR or mTOR inhibition suggested that checkpoint inhibitor therapy did not compromise subsequent efficacy of these agents (median OS after progression 17.5 months) [50]. A presentation at the 2015 Genitourinary Cancer symposium showed early preliminary data from a phase II trial comparing atezolizumab alone, in combination with bevacizumab, or compared to sunitinib. Four of ten patients with RCC had objective responses (40%) by RECIST criteria with combined atezolizumab and bevacizumab which, when compared to historical data of atezolizumab or bevacizumab alone, showed a response rate of 15% and 10% respectively. A phase III trial is examining the use of atezolizumab in combination with bevacizumab in the treatment naïve patient population compared to sunitinib. Modulation of the tumor microenvironment with timing of VEGF inhibition or through alternative mechanisms could change the response to immunotherapy.

6 Expert Commentary

The use of immunotherapy in RCC has been a mainstay of treatment for many years, and the only promise of durable response in the past was treatment with IL-2. High-dose IL-2 produced durable responses in a small subset of patients, but the overall use of this treatment approach was severely limited by their toxicities and requirement for administration in specialized centers. More recently, the novel use of checkpoint inhibitors targeting negative regulatory receptors on T cells including PD-1 and PD-L1, have shown objective tumor responses of over 20% in patients with advanced RCC, which in many cases have been durable. This is an exciting time for patients and their physicians treating RCC with immunotherapy where many more questions than answers exist and the mechanistic understanding is being sought at the basic science level as well as in new clinical trials attempting to augment the percentage of patients obtaining response to immunotherapy treatments.

7 Five-year view

In the next five years, we will likely see the approval of novel checkpoint inhibitors including anti-PD-L1 in combination with bevacizumab and combination therapy targeting CTLA-4 and PD-1 or PD-L1 treatment. Due to the extensive search and early identification of promising biomarkers, there will likely be the discovery of biomarkers that will refine our ability to predict which patients will respond to single agent anti-PD-1/PD-L1, and who needs combination therapy (and possibly who will not respond to immune checkpoint inhibitors at all) [51]. It is likely that clinical trials will ultimately demonstrate a role for the use of checkpoint inhibitors in the upfront treatment of metastatic RCC. There will be many additional checkpoint inhibitors trials in patients with advanced solid tumors and, hopefully, with increasing research, use of biomarkers can be identified to help predict patients that will respond to these immune based therapies.

8 Key Bullet Points

- Advanced RCC has improved overall survival with current targeted therapy treatment to VEGF and mTOR inhibition, but progression remains universal and long-term survival is still very limiting.
- Clear cell RCC is a histologic subtype that commonly has loss of the VHL protein upregulating HIF activity and ultimately results in the biology associated with this tumor including angiogenesis.
- PD-1 inhibition in patients with RCC exhibits a relatively safe side effect profile, the most common symptoms being fatigue and the most worrisome adverse events being pneumonitis, diarrhea/colitis, hepatitis, or endocrinopathies.
- Over 20% of patients with RCC experience objective response to treatment with PD-1 inhibition and many of these responses are durable.
- Nivolumab, a PD-1 inhibitor, has been approved for use in the second-line treatment of advanced RCC

- We may see combined immunotherapy treatments, including ipilimumab and nivolumab, approved for use in the initial treatment of advanced RCC in the next five years

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Reference annotations:

*Of importance

**Of significant importance

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Figure 1. Interacting Antigen Presenting Tumor cell and the T cell

Abbreviations. CD70, cluster of differentiation 70; OX40L, OX40 ligand, CD252; GITR, glucocorticoid-induced tumor necrosis factor; GITRL, GITR ligand; MHC, major histocompatibility complex; LAG-3, lymphocyte activated gene 3; TCR, T cell receptor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; CD80, cluster of differentiation 80, B7.1; CD86, cluster of differentiation 86, B7.2; CTLA-4, cytotoxic T-lymphocyte associated protein 4; B7-H3, cluster of differentiation 276; TIM-3, T-cell immunoglobulin and mucin-domain containing 3.

Table 1

Summary of Clinical Trial data for checkpoint inhibition in RCC

Agent	Nivolumab	Nivolumab	Nivolumab	Nivolumab	Nivolumab	MDX1105-01	Atezolizumab
Study Design	Phase I	Phase I	Phase II	Phase III	Phase I	Phase I	Phase I
Number of RCC Patients	1	34	168	821	17	70	70
Brief Description	dose escalation	dose escalation, no MTD reached	dose-response & anti-tumor activity	2nd line PD-1 inhibition vs everolimus	dose escalation study	safety and toxicity	safety and toxicity
Primary Endpoint	safety	safety	PFS	OS	safety	safety	safety
ORR	obj response	29%	20–22%	25%	12% (RCC)	7–26%	7–26%
PFS (months)			2.7–4.2	4.6		3.9–8.2	3.9–8.2
OS (months)	n/a	22.4	18.2–25.5	25	n/a	28.9	28.9
Most common irAE	colitis	fatigue, rash, diarrhea	rash, diarrhea, pneumonitis	fatigue, anemia, diarrhea	rash, diarrhea, infusion reaction	fatigue, anemia, rash	fatigue, anemia, rash
Grade 3–4 irAE (%)	1/39 patients	14%	11%	19%	9%	17%	17%
Source	Brahmer et al., 2010	Topalian et al., 2012; McDermott et al., 2015	Motzer et al., 2015	Motzer et al., 2015	Brahmer et al., 2012	McDermott et al., 2016	McDermott et al., 2016

Abbreviations. RCC, renal cell carcinoma; ORR, objective response rate; PFS, progression free survival; OS, overall survival; irAE, immune related adverse events; obj, objective;

Table 2**Ongoing Checkpoint Inhibitor Clinical Trials in RCC**

Experimental Arm	Control Arm	Study Design	Patient Criteria	Clinical Trial
anti-CTLA4 (yervoy) + anti-PD-1 (nivolumab)	Sunitinib	phase III	untreated advanced RCC	NCT02231749
anti-PD-L1 (atezolizumab)+bevacizumab	Sunitinib	phase III	untreated advanced RCC	NCT02420821
anti-PD-1 (avelumab) +Axitinib	Sunitinib	phase III	untreated advanced RCC	NCT02684006
anti-PD-1 (pembrolizumab)	N/A	phase I	neoadjuvant RCC	NCT02212730
CXCR4 (X4P-001)	N/A	phase I/II	advanced RCC	NCT02667886
anti-GTTR (MK-4166) + anti-PD-1 (pembrolizumab)	N/A	phase I	advanced cancers	NCT02132754
anti-PD 1 (pembrolizumab) + IAK (INCB039110) or PI3K (INCB050465)	N/A	phase I	advanced cancers	NCT02646748
anti-TIM3 (MBG453) +/- anti-PD-1 (PDR001)	N/A	phase I/II	advanced cancers	NCT02608268
PD-L1 (atezolizumab) + CD27 (varlilumab)	N/A	phase I/II	advanced cancers	NCT02543645
LAG-3 (LAG525) + PD-1 (PDR001)	N/A	phase I/II	advanced cancers	NCT02460224
CTLA4 (ipilimumab) + B7-H3 (MGA217)	N/A	phase I	advanced cancers	NCT02381314
CTLA4 (tremelimumab) + PD-L1 (durvalumab)	N/A	phase I	advanced cancers	NCT01975831
recombinant Interleukin 10 (AM0010)	N/A	phase I	advanced cancers	NCT02009449
recombinant Interleukin 15 (interleukin 15)	N/A	phase I	advanced cancers	NCT01727076

Abbreviations. RCC, renal cell carcinoma.