Published in final edited form as:

Curr Opin Oncol. 2017 May ; 29(3): 201–209. doi:10.1097/CCO.0000000000000364.

Renal Cell Carcinoma: Molecular Characterization and Evolving Treatment Paradigms

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Abstract

Purpose of review—The treatment landscape of advanced renal cell carcinoma (RCC) continues to shift as both new targeted therapies and immunotherapies show efficacy in treating the disease. Contemporary insights into the molecular characterization of RCC are likely to fuel the development of additional therapies. This review summarizes recent advancements in the biologic characterization of RCC and discusses newly approved therapies and ongoing studies in the treatment of advanced RCC.

Recent findings—The Cancer Genome Atlas has now completed comprehensive molecular characterization of clear cell, papillary and chromophobe RCC, providing insights into the biology of these entities. Two new ‘targeted’ therapies, cabozantinib and lenvatinib, as well as a novel immune checkpoint inhibitor, the PD-1 inhibitor nivolumab, have recently been approved for the treatment of metastatic RCC. Although some of these newer therapies are associated with prolongation of survival, there are few long-term responders and the quest for more durable treatment strategies continues.

Summary—The addition of several new agents effective in metastatic renal cell carcinoma has resulted in improvements in overall survival; however, there are few avenues to durable responses or cure. Ongoing studies as well advances in our understanding of the molecular alterations underlying distinct forms of RCC promise further therapeutic advances and have the potential to alter the current treatment paradigm.

Keywords

renal cell carcinoma; targeted therapy; immunotherapy

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Conflicts of interest: None

Introduction

Renal cell carcinoma (RCC) is the eighth most common malignancy in the United States, with an estimated 62,700 new cases and 14,240 estimated deaths in 2016 [1]. At presentation, one third of patients have metastatic disease, and upwards of 30% of patients with localized disease will develop distant metastases after nephrectomy [2, 3]. The high burden of advanced disease highlights the need for systemic therapies. In this review, we highlight new insights into the biology of RCC along with recent advances in targeted therapy and immunotherapy.

Molecular Characterization of Renal Cell Carcinoma

RCC is an umbrella term for several cancers arising in the kidney that are genetically and morphologically distinct [4]. Currently, the World Health Organization recognizes 16 subtypes of RCC [5], and up to 12 hereditary conditions have been identified with increased lifetime risk of developing renal tumors [6]. The biology of the three most common histologic subtypes has recently been profiled by The Cancer Genome Atlas: clear cell [7], papillary [8] and chromophobe RCC [9].

Clear cell RCC (ccRCC) is the most common histologic subtype, accounting for approximately 75% of cases. Inactivation of *VHL* either by mutation or epigenetic silencing occurs in over 90% cases of sporadic ccRCC. Additionally, TCGA analysis has demonstrated recurrent mutations in several chromatin remodeling genes, including *PBRM1* (32.9%), *SETD2* (11.5%), and *BAP1* (10.1%) [7]. Moreover, aggressive high stage, high grade RCC demonstrated a metabolic shift away from the Krebs cycle and towards the pentose phosphate pathway and fatty acid synthesis, a phenotype consistent with the Warburg effect.

Papillary RCC (pRCC) is the second most common RCC subtype accounting for 10–15% of cases. An integrative TCGA analysis of 161 pRCC tumors was performed using whole-exome sequencing, RNA expression, copy number, methylation and proteomic analysis. The study affirmed differences in type 1 and type 2 pRCC, and found 4 distinct molecular subgroups with progressively worse survival (C1, C2a, C2b, and C2c). C1 consisted of mostly type 1 pRCC tumors, characterized by gain of chromosome 7 and 17, as well as alterations in *MET*. In contrast to the hereditary form of pRCC, Hereditary Papillary Renal Cancer (HPRC) which is characterized by germline *MET* mutations [10], somatic alterations of *MET* in non-hereditary pRCC was less common, occurring in ~15% of cases.

Type 2 pRCC could be further classified into subgroups C2a, C2b and C2c. C2a consisted of early stage tumors, while C2b consisted of later stage tumors and was characterized by mutations in *SETD2*. C2c had the poorest survival and was associated with a CpG island methylator phenotype. Other alterations in type 2 pRCC included loss of *CDKN2a*, activation of the NRF2 oxidative stress pathway, mutations of *FH*, gene fusions involving the MiTF gene family members TFE3 and TFEB, and mutations in chromatin remodeling genes.

Chromophobe RCC (chRCC) accounts for around 5% of RCC cases. In comparison to ccRCC and pRCC, it usually exhibits relatively indolent behavior with 90% 10-year survival [11]; however, locally invasive and metastatic disease can occur [12]. The analysis from TCGA demonstrated that chRCC exhibit alterations in mitochondrial DNA and that 10% of cases had rearrangement in the *TERT* promoter. The majority of cases (86%) exhibited loss of most or all of chromosomes 1, 2, 6, 10, 13, and 17. Furthermore, *TP53* was mutated in 32% of cases, and mTOR pathway changes occurred in 23% of cases.

Together, the three TCGA reports highlight the genetic diversity of RCC. A better understanding of the molecular pathways driving these diseases may lead to the development of additional targeted therapies.

The state of treatment for clear cell RCC

Targeted Therapy

Understanding the biologic basis of clear cell RCC has led to the development of multiple therapies targeted against downstream consequences of VHL inactivation. In total, there are 11 FDA approved agents for RCC, with 3 main therapeutic approaches: VEGF pathway inhibition, mTOR pathway inhibition and immunotherapy (Table 1). Prior to 2016, there were five approved therapies targeting downstream mediators of the HIF activation pathway (sunitinib [15], sorafenib [14], bevacizumab [18, 26], pazopanib [20], and axitinib [21]), two drugs that target the mTOR pathway (temsirolimus [16] and everolimus [17]), and a cytokine-based immunotherapy (interleukin-2 [13]). Over the last 18 months, 3 new agents have been approved: cabozantinib, lenvatinib, and nivolumab.

Cabozantinib is an oral tyrosine kinase inhibitor that targets the VEGF, MET, and AXL pathways. Both the MET and AXL pathways are implicated in the development and metastasis of ccRCC through the VHL-HIF axis [27]. AXL is activated by HIF-1 and HIF-2, and inactivation of AXL decreases lung metastases in mice xenograft models of RCC. A phase III randomized study compared cabozantinib and everolimus in 658 patients with mRCC who had progressed after VEGF-targeted therapy [23]. Patients were randomly assigned (1:1) to receive cabozantinib (60 mg daily) or everolimus (10 mg daily); the primary end point of the study was progression-free survival (PFS), while overall survival (OS) and objective response rate (ORR) were secondary endpoints. Based on the primary endpoint analysis, the study concluded that cabozantinib was superior to everolimus in this setting (median PFS 7.4 vs 3.8 months; HR 0.51; $p < 0.0001$). Additionally, both the ORR (17% vs 3%, $p < 0.0001$) and OS (21.4 vs 16.5 months, HR 0.66, $p=0.00026$) were superior in patients receiving cabozantinib. Both agents were well tolerated, with adverse events (AEs) managed by dose reduction (60% for cabozantinib and 25% for everolimus). On the basis of these data, cabozantinib was approved as a second-line agent in April 2016.

Following publication of these data, the efficacy of cabozantinib in the front line setting is being explored (Table 2). In a randomized phase II trial comparing cabozantinib and sunitinib in the first-line setting (CABOSUN) in 157 patients with intermediate or poor-risk mRCC [28], cabozantinib was associated with increased median PFS (8.2 v 5.6 months; HR 0.66; 95% CI, 0.46–0.95; one-sided $p = .012$), OS (30.3 vs 21.8 months; HR 0.8; 95% CI

0.5–1.26) and ORR (46%; 95% CI, 34–57 versus 18%; 95% CI, 10–28) with a similar incidence of grade 3–4 AEs (67% for cabozantinib and 68% for sunitinib). The comparative efficacy of cabozantinib in the first-line setting among favorable risk patients remains to be demonstrated.

Lenvatinib is a tyrosine kinase inhibitor that targets VEGFR, FGFR1-4, PDGFR, RET and KIT. A phase II study assigned patients (1:1:1) to lenvatinib (24 mg daily) single-agent, everolimus (10 mg daily) single-agent or combination lenvatinib plus everolimus (18 mg daily and 5 mg daily, respectively) in the second-line setting in 153 patients with metastatic ccRCC who had progressed after previous VEGFR targeted tyrosine kinase inhibitor (TKI) therapy [24]. The combination of lenvatinib plus everolimus was associated with improved median PFS (14.6 vs 5.5 months; HR 0.40, 95% CI 0.24–0.68; $p = 0.0005$), improved median OS (25.5 vs 15.4 months, HR 0.51, 95% CI 0.30–0.88, $p = 0.024$), and ORR (43% vs 6%, $p < 0.0001$) compared to everolimus alone. These data led the FDA to approve the combination of lenvatinib plus everolimus for post-front line therapy for patients with mRCC in May 2016.

Other approaches to target more proximal consequences of VHL inactivation in clear cell RCC are the subject of active preclinical evaluation. Two recent studies have evaluated direct inhibition of HIF-2 α with a small-molecular inhibitor, PT2300 in clear cell RCC models. Cho and colleagues showed that PT2300 inhibits growth of VHL-deficient ccRCC cell lines in vitro and in mouse xenografts [31]. In a separate study, Chen and colleagues assessed the efficacy of PT2300 in a patient-derived mouse xenograft model, demonstrating decreased cell growth in 10/18 (56%) animals treated [32]. Taken together, these studies demonstrated the ability to induce antitumor effects by directly targeting HIF-2 α . This approach is currently being evaluated in patients with the oral HIF-2 α inhibitor, PT2385 (NCT02293980). Further exploration of this strategy in clinical trials will define the role of this class of therapy for patients with VHL-deficient RCC.

Immunotherapy

Owing to a lack of durable complete responses to targeted therapies, there has been a resurgence of interest in immunotherapy to treat RCC. Historically, the role of immune modulation in RCC was suggested by observations that metastatic lesions could spontaneously regress after radical nephrectomy to remove the primary tumor [33]. Together with evidence that tumor infiltrating lymphocytes [34, 35], circulating cytokines [36] and chemokines [37] are elevated in patients with RCC, there seems to be a complex interaction between tumor and host immune response in patients with RCC. Early phase results of several emerging immunotherapies have been reviewed recently [38]. This review will focus on the evidence for checkpoint blockade.

Programed death 1 (PD-1) is a cell-surface protein in the B7-CD28 family. PD-1 is expressed on T cells and a ligand, PD-L1, is expressed both on tumor cells and tumor-infiltrating lymphocytes and myeloid lineage cells. PD-1 is a negative regulator of T cell activation, and engagement by its ligand(s) results in inhibition of cytokine production, proliferation, and cytotoxic activity of T-cells [39]. Expression of PD-L1 on tumor cells might allow tumors to escape immune surveillance and is associated with poorer survival in

at least one study [40]. Many tumors, including RCC, can upregulate these cell-surface immune checkpoint proteins that block T cell function in response to inflammation in a process known as adaptive immune resistance [41].

A phase III trial in the second and third-line setting showed that PD-1 blockade using the monoclonal antibody nivolumab resulted in improved OS as compared to everolimus [22]. A total of 821 patients with advanced RCC with a clear-cell component who had progressed on treatment with one or two antiangiogenic agents were randomized to receive either 3mg/kg of nivolumab every 2 weeks or 10 mg of everolimus daily. OS was the primary end point but ORR and safety were also assessed. The most common prior therapy was sunitinib (59%), followed by pazopanib (30%). Most patients were intermediate risk (49%), and the majority of patients had a prior nephrectomy (88%). The median OS was 25 months (95% CI 21.8–not estimable) for nivolumab and 19.6 months (95% CI 17.6–23.1) for everolimus (HR 0.73; 98.5% CI 0.57–0.93; $p=0.002$). This improvement in OS met the pre-specified threshold for superiority outlined in the trial design ($p=0.0148$). Nivolumab was also associated with a better ORR than everolimus (25% vs. 5%; odds ratio 5.98, $p<0.001$), but did not lead to an improved PFS; median PFS was 4.6 months (95% CI 3.7–5.4) for nivolumab and 4.4 months (95% CI 3.7–5.5) with everolimus (HR 0.88; 95% CI 0.75–1.03; $p=0.11$). The FDA approved nivolumab for use in the second-line setting in 2015.

There is significant interest in combining PD1/PDL-1 inhibitors with other agents, including other checkpoint inhibitors, VEGF inhibitors, HDAC inhibitors, and vaccines (Table 3). Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) is another checkpoint inhibitor that is expressed on suppressive, regulatory T cells (Tregs) and activated T cells. Ipilimumab, a CTLA-4 inhibitor, is FDA-approved in melanoma, and the combination of PD-1/CTLA-4 blockade appears to be synergistic in the treatment of metastatic melanoma [42]. Phase I data on the combination of ipilimumab and nivolumab in patients with mRCC were recently presented by Hammers et al [43]. Objective responses were seen in up to 43% of patients, with a median duration of response of 53.9 weeks. However, treatment related adverse events (AEs) occurred in 88% of patients, with grade 3–4 AEs in 34–64% of patients. Based on the preliminary efficacy of this approach, the combination of PD-1 blockade and CTLA-4 blockade is currently being evaluated in the first line setting in RCC. Checkmate 214 (NCT02231749) is a phase III trial comparing nivolumab combined with ipilimumab versus sunitinib in previously untreated patients with metastatic clear cell RCC; the trial has completed accrual and results are awaited [44].

Given that the majority of FDA-approved therapies for RCC are VEGF inhibitors, the utility of combining these agents with immune checkpoint blockade is under investigation. Indeed, VEGF-pathway inhibitors seem to have an immunomodulatory effect. Sunitinib has been associated with decreasing regulatory T cell numbers, thereby enhancing an anti-tumor immune response [45]. Furthermore, both sunitinib and sorafenib down-regulate the function of suppressive tumor-associated macrophages [46, 47]. Preliminary data from a phase I trial of nivolumab (2 mg/kg IV) and sunitinib (50 mg, 4 weeks on, 2 weeks off) or pazopanib (800 mg daily) in previously treated metastatic RCC demonstrated notable anti-tumor activity with an ORR of 52% in the sunitinib arm and 45% in the pazopanib arm [48]; however, the combination was also associated with increased toxicity, with grade 3–4 AEs

occurring in 73% and 60% of patients in the sunitinib and pazopanib arms, respectively, and with heightened concern for hepatotoxicity with the latter regimen. Ongoing studies attempt to mitigate the potential risk of combination therapy by utilizing newer, more specific VEGF pathway antagonists. Preliminary results from a phase 1 study of axitinib plus pembrolizumab in treatment-naïve mRCC demonstrated a 67.3% ORR, with 2 complete responses [49]. Grade 3–4 AEs occurred in 52% of patients. Additional studies, including axitinib in combination with avelumab in the first line setting (NCT02493751), and pembrolizumab plus axitinib in the second line setting (NCT02133742), are ongoing (Table 3).

Additionally, the combination of an anti-VEGF antibody with immunotherapy has shown efficacy in a pre-clinical study [50], which may be mediated by the ability of anti-VEGF antibodies to normalize the tumor vasculature and permit emigration of activated anti-tumor T cells. A phase IB study of atezolizumab, an anti-PD-L1 antibody, combined with bevacizumab demonstrated an ORR of 40% with no grade 3–4 AEs [51]. Similarly, Dudek et al designed a phase Ib/II trial of bevacizumab plus pembrolizumab in subjects with metastatic ccRCC. The phase Ib portion of the trial recently reported that the combination was well tolerated with no dose-limiting toxicity or serious adverse events and no grade 3 or 4 drug-related toxicities. This established a 200 mg fixed dose of pembrolizumab and 15 mg/kg dose of bevacizumab, both given every 3 weeks, as the regimen to be evaluated in the on-going phase II portion of the study (NCT02348008) [52]. While preliminary, these data suggest that the combination of anti-VEGF antibodies with PD-1 blockade may be more tolerable than VEGF TKI/checkpoint blockade combination therapies. A phase 2 study of atezolizumab in combination with bevacizumab or sunitinib in the first-line setting is also currently underway (NCT01984242) (Table 3).

With so many therapies now available, there is a plethora of agents to choose from in both the front-line and subsequent lines of therapy. However, there is a dearth of evidence for the optimum initial selection and subsequent sequencing of agents [25, 53]. Based on current data, VEGF-pathway antagonists remain the best choice for front-line therapy in most patients with advanced ccRCC, although high-dose IL-2 is a reasonable consideration in selected patients. However, newer agents, including cabozantinib and nivolumab, have supplanted single agent everolimus as optimal initial choices for patients who have progressed on VEGF-pathway antagonists. Ongoing combination studies, as well as novel targeted approaches, are likely to further alter the optimal treatment choices and maximize oncologic outcomes.

The state of treatment for non-clear cell RCC

While there are no FDA approved therapies for non-ccRCC, emerging data are beginning to shed some light on the utility of current therapies for patients with non-ccRCC (Table 4). Within this arena, most of the data is for pRCC [54]. The SUPAP trial was a phase II study that evaluated the efficacy of sunitinib for locally advanced or metastatic pRCC [55]. Efficacy was demonstrated for both type 1 pRCC (median PFS 6.6 months, OS 17.8 months) and type II pRCC (median PFS 5.5 months, OS 12.4 months). The RAPTOR study evaluated the efficacy of everolimus in pRCC in 92 patients, and demonstrated efficacy in

both type 1 pRCC (OS 28 mo) and type 2 (OS 20 mo) pRCC. Two comparative phase 2 trials recently evaluated VEGF inhibition vs mTOR blockade in patients with metastatic non clear cell RCC. The ESPN trial (Everolimus versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma) compared sunitinib vs everolimus in the first-line setting [56]. The patient population included all subtypes of non-clear cell RCC, as well as clear cell patients with 20% sarcomatoid component, with a primary endpoint of PFS in the first-line setting in an effort to demonstrate superiority of everolimus. There was no statistical difference between the treatments, and the trial was stopped and accrual halted at the time of interim analysis. A second randomized phase 2 study, ASPEN (Phase II Study of Afinitor Vs. Sutent in Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma), in 108 patients with treatment-naïve metastatic pRCC, chRCC or unclassified non-ccRCC subtypes [57] demonstrated that Sunitinib was associated with an improved PFS (8.3 vs 5.6 mo; HR 1.4; $p=0.16$) compared to everolimus.

Though there is a lack of trial data to support the use of checkpoint inhibitors in non-ccRCC, there is some biologic rationale for their use. Many non-ccRCC express PD-L1, including 5.6% of chRCC, 10% of pRCC, 30% of Xp11.2 translocation RCC, and 20% of collecting duct carcinomas [58]. Trials of checkpoint inhibitors in non-ccRCC are needed to test whether this biologic rationale translates to clinical efficacy.

Other ongoing trials in pRCC include phase 2 studies of selective Met inhibitors, including INC280 and AZD6094, and the combination of the EGFR inhibitor erlotinib with bevacizumab [59], as summarized in Table 4.

Adjuvant/Neoadjuvant Therapy

With the advent of agents active in metastatic disease, there is growing enthusiasm for utilizing systemic therapy in the adjuvant or neoadjuvant setting in an attempt to alter the natural history of advanced RCC. Several large adjuvant studies of VEGF- and mTOR-pathway directed agents were undertaken soon after the approval of these agents in the metastatic setting; results from the earliest of these studies are now becoming available. Data from one such study, the ASSURE trial (Adjuvant Sorafenib and Sunitinib for Unfavorable Renal Carcinoma) were reported recently [15]. This phase III trial of 1943 patients with high-grade T1b or higher non-metastatic RCC randomized to receive 54 weeks of sunitinib, sorafenib or placebo demonstrated no improvement in outcome with adjuvant VEGFR TKIs (median PFS 5.8 years; HR 1.02; $p=0.8$ for sunitinib vs 6.1 years; HR 0.97; $p=0.7$ for sorafenib vs 6.6 years for placebo). There was a high rate of treatment-related discontinuation (44 and 45%) in the sunitinib and sorafenib arms, potentially attenuating any biologic effect in the intention to treat analysis.

In contrast, results from S-TRAC (Sunitinib as Adjuvant treatment for patients at high risk of recurrence of renal cell carcinoma following nephrectomy), a phase III trial that randomized 615 patients with T3 or greater RCC to sunitinib vs placebo for 1 year [30] suggest that sunitinib was associated with improved DFS compared to placebo (6.8 vs 5.8 years, $p = 0.03$). Treatment-related discontinuation on this study was lower than that seen in the ASSURE trial (28.1%). These conflicting data may be a reflection of the fact that S-

TRAC enrolled patients with more advanced disease and was restricted to ccRCC, compared to ASSURE. At the present time, the role of adjuvant treatment after nephrectomy remains unclear and further evaluation is necessary to clarify the clinical benefits of this strategy. Several ongoing trials (Table 2) are evaluating axitinib, everolimus and sorafenib vs placebo in the adjuvant setting. Trials using PD-1 inhibitors in the adjuvant space are now underway as well (Table 2).

In the neoadjuvant setting, existing trials have focused mainly on downsizing locally advanced tumors. Karam and colleagues demonstrated that the median reduction of primary renal tumor diameter was 28.3% in patients treated with neoadjuvant axitinib in a phase II study [61]. In a follow-up study, the feasibility of partial nephrectomy before and after neoadjuvant axitinib was assessed by querying urologists blinded to treatment status [62]. The feasibility of partial nephrectomy increased 22.8-fold after treatment with axitinib. Similarly, the use of neoadjuvant targeted therapy prior to IVC thrombectomy results in tumor shrinkage in 44% of patients, but only 1 of 25 patients had a change in surgical approach secondary to tumor shrinkage [63]. Ongoing neoadjuvant studies are evaluating the role of everolimus, sunitinib, pazopanib, and nivolumab as summarized in Table 2. The role of neoadjuvant therapy is currently unclear in the majority of patients and this approach is largely restricted to the clinical trial setting.

Several trials are evaluating the combination of systemic therapy and surgery for metastatic disease. A recent study evaluated the role of pre-operative pazopanib before cytoreductive nephrectomy in patients with metastatic RCC [64]. In 104 patients who received pazopanib, 61% went on to undergo nephrectomy. Median PFS was 7.1 mo, and OS 22.7 mo. Biomarker analysis demonstrated a decrease in CD8 lymphocytes, reduction in expression of VHL and C-Met, and increase expression of PD-L1; however, no biomarkers correlated with treatment. Finally, ECOG 2810 is a phase III trial currently open to accrual, comparing adjuvant pazopanib vs. placebo after metastasectomy (NCT01575548). While aggressive surgical intervention can often provide considerable benefit to patients with advanced RCC, careful patient selection and treatment by experienced surgical teams at high-volume centers should be considered.

Conclusion

Advances in targeted therapy and immunotherapy have led to approval of three new drugs for advanced RCC over the last 18 months. While VEGFR inhibitors remain the standard first-line treatment for the majority of patients, this paradigm is being challenged by ongoing studies. In the post-VEGFR therapy setting, everolimus has been supplanted by other therapies, including cabozantinib and nivolumab, but may still have a role in subsequent lines of therapy. The current landscape is notable for a dearth of therapies for non-ccRCC and for evidence regarding the optimal sequencing of agents for patients with progressive disease. The search for actionable diagnostic, therapeutic, and prognostic RCC biomarkers continues. Additional work is also needed to understand the role of neoadjuvant/adjuvant systemic therapy and combination therapies, and the impact such strategies will have on survival and quality of life measures.

Acknowledgments

None

Funding: This research was funded by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research, Bethesda, Maryland, USA, and by a grant from the National Cancer Institute (P30CA072720).

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* of special interest

** of outstanding interest

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Key points

1. Our understanding of the biology of RCC has been greatly improved with the recent molecular characterization of three kidney cancer subtypes: clear cell, papillary and chromophobe RCC.
2. The therapeutic landscape for advanced RCC continues to evolve with the addition of 3 new agents approved for use in the second line
3. The approval of nivolumab, an immune checkpoint inhibitor, marks the availability of a new class of therapies and will provide the basis of evaluation of novel combination strategies.
4. The role of adjuvant therapy for non-metastatic RCC remains unclear with conflicting data emerging from recent studies.

Table 1
Selected FDA-Approved Agents for Advanced Renal Cell Carcinoma with Pivotal Trial Parameters

Therapy	FDA-Approval	MOA	Treatment Line	Comparison Arm	Primary Endpoint	Route
Interleukin-2 [13]	May 1992	Cytokine Immunotherapy	First-line	Phase II - none	ORR	IV
Sorafenib [14]	December 2005	VEGFR, PDGFR, KIT inhibitor	Cytokine Failure	Placebo	OS	PO
Sunitinib [15]	January 2006	VEGFR, PDGFR inhibitor	First-line	IFN- α	PFS	PO
Temsirolimus [16]	May 2007	mTOR inhibitor	First-line	IFN- α	OS	IV
Everolimus [17]	March 2009	mTOR inhibitor	VEGFR Failure	Placebo	PFS	PO
Bevacizumab + IFN- α [18] [19]	July 2009	Anti-VEGF monoclonal antibody	First-line	IFN- α +/- Placebo	OS	IV + SC
Pazopanib [20]	October 2009	VEGFR, PDGFR, KIT inhibitor	First-line or Cytokine Failure	Placebo	PFS	PO
Axitinib [21]	January 2012	VEGFR inhibitor	Second-Line	Sorafenib	PFS	PO
Nivolumab [22]	November 2015	Anti-PD1 monoclonal antibody	Second-Line	Everolimus	OS	IV
Cabozantinib [23]	April 2016	VEGFR, MET, AXL inhibitor	Second-Line	Everolimus	PFS	PO
Levatinib + everolimus [24]	May 2016	VEGFR, EGFR, PDGFR, RET, KIT inhibitor + mTOR inhibitor	Second-Line	Everolimus or levatinib	PFS	PO

ORR: overall response rate; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor, mTOR: mammalian target of rapamycin

Based on [25]

Table 2

Recent and Ongoing Trials for the Treatment of Advanced RCC

Trial Name	Treatment	Phase	Trial
1st line Therapy			
CaboSun [28]	Cabozantinib vs sunitinib	II	NCT01835158
ADAPT	AGS003 + SOC vs SOC	III	NCT01582672
CheckMate 214	Nivolumab + ipilimumab vs sunitinib	III	NCT02231749
WO29074	Atezolizumab +/- bevacizumab vs sunitinib	II	NCT01984242
BTCRC-GU14-003	Pembrolizumab + bevacizumab	II	NCT02348008
Previously treated			
Meteor [23]	Cabozantinib vs everolimus	III	NCT01865747
CheckMate 025 [22]	Nivolumab vs everolimus	III	NCT01668784
Adjuvant			
ASSURE [29]	Sorafenib or sunitinib vs placebo	III	NCT00326898
ATLAS	Axitinib vs placebo	III	NCT01599754
EVEREST	Everolimus vs placebo	III	NCT01120249
PROTECT	Pazopanib vs placebo	III	NCT01235962
S-TRAC [30]	Sunitinib vs placebo	III	NCT00375674
SORCE	Sorafenib vs placebo	III	NCT00492258
ECOG 2810	Pazopanib vs placebo after metastatectomy	II	NCT01575548
PT2385 (HIF-2 α inhibitor)	PT2385 alone or PT2385 & nivolumab or PT2385 & cabozantinib	I	NCT02293980
Neoadjuvant			
ARTIC	Everolimus	II	NCT01715935
University of Toronto	Sunitinib	II	NCT00480935
University of North Carolina	Pazopanib	II	NCT01361113
Johns Hopkins	Nivolumab	I	NCT02575222
MD Anderson	Axitinib	II	NCT01263769
MD Anderson	Nivolumab vs Nivolumab + Bevacizumab vs Nivolumab + Ipilimumab	II	NCT02210117
Perioperative			
PROSPER RCC (EA8143)	Nivolumab neoadjuvant and adjuvant vs surgery alone	III	Pending
Trial Name	Treatment	Phase	Trial
1st line Therapy			
CaboSun [14]	Cabozantinib vs sunitinib	II	NCT01835158
ADAPT	AGS003 + SOC vs SOC	III	NCT01582672
CheckMate 214	Nivolumab + ipilimumab vs sunitinib	III	NCT02231749
WO29074	Atezolizumab +/- bevacizumab vs sunitinib	II	NCT01984242
BTCRC-GU14-003	Pembrolizumab + bevacizumab	II	NCT02348008
Previously treated			
Meteor [11]	Cabozantinib vs everolimus	III	NCT01865747

Trial Name	Treatment	Phase	Trial
CheckMate 025 [10]	Nivolumab vs everolimus	III	NCT01668784
Adjuvant			
ASSURE [15]	Sorafenib or sunitinib vs placebo	III	NCT00326898
ATLAS	Axitinib vs placebo	III	NCT01599754
EVEREST	Everolimus vs placebo	III	NCT01120249
PROTECT	Pazopanib vs placebo	III	NCT01235962
S-TRAC [16]	Sunitinib vs placebo	III	NCT00375674
SORCE	Sorafenib vs placebo	III	NCT00492258
ECOG 2810	Pazopanib vs placebo after metastatectomy	II	NCT01575548
PT2385 (HIF-2 α inhibitor)	PT2385 alone or PT2385 & nivolumab or PT2385 & cabozantinib	I	NCT02293980
Neoadjuvant			
ARTIC	Everolimus	II	NCT01715935
University of Toronto	Sunitinib	II	NCT00480935
University of North Carolina	Pazopanib	II	NCT01361113
Johns Hopkins	Nivolumab	I	NCT02575222
MD Anderson	Axitinib	II	NCT01263769
MD Anderson	Nivolumab vs Nivolumab + Bevacizumab vs Nivolumab + Ipilimumab	II	NCT02210117
Perioperative			
PROSPER RCC (EA8143)	Nivolumab neoadjuvant and adjuvant vs surgery alone	III	Pending

Table 3

Phase I Combination Checkpoint Inhibitor Trials

Immunotherapy	Target	Second Agent (Mechanism)	Phase	Population	Trial ID
Nivolumab	PD-1	BMS-986016 (anti-LAG-3)	I	Advanced malignancies including mRCC	NCT01968109
Pembrolizumab	PD-1	Pazopanib	I	Treatment naïve advanced RCC	NCT02014636
		Axitinib	I	Previously untreated mRCC	NCT02133742
		Vorinostat (HDAC inhibitor)	I	Advanced Renal or Urothelial Cell Carcinoma	NCT02619253
		Ipilimumab (anti-CTLA4) or pegylated interferon-alpha	I/II	Advanced RCC or melanoma	NCT02089685
		Bevacizumab	Ib/II	Clear cell mRCC	NCT02348008
Atezolizumab (MPDL3280A)	PD-L1	Cobimetinib (MEK)	I	Advanced solid tumors including RCC	NCT01988896
		Ipilimumab (anti-CTLA4) or IFN-alpha	I	Advanced solid tumors including RCC	NCT02174172
Durvalumab (MED4736)	PD-L1	Tremelimumab (anti-CTLA4)	I	Advanced solid tumors including RCC	NCT01975831
		MEDI0680 (anti-PD-L1)	I	Advanced solid tumors including RCC	NCT02118337

Modified from Ball et al., 2016, with permission from Discovery Medicine [38]

Table 4**Recent and Ongoing Non-Clear Cell Renal Cell Carcinoma Trials**

Treatment (Trial Name)	Phase	Trial ID
Any Non-ccRCC		
Axitinib	II	NCT01798446
Everolimus and bevacizumab	II	NCT01399918
Sunitinib	II	NCT
Everolimus vs Sunitinib (ASPEN)	II	NCT01108445
Sunitinib	II	NCT01034878
Pazopanib	II	NCT01538238
Everolimus vs Sunitinib (ESPN)	II	NCT01185366
Papillary RCC		
Vandetanib and Metformin	I/II	NCT02495103
Cabozantinib, Crizotinib, Volitinib or Sunitinib	II	NCT02761057
Sunitinib (SUPAP)	II	NCT00541008
Everolimus (RAPTOR)	II	NCT00688753
INC280	II	NCT02019693
Axitinib	II	NCT02489695
AZD6094	II	NCT02127710
Erlotinib and Bevacizumab	II	NCT01130519
Pazopanib (PINCR)	II	NCT01767636
Crizotinib	II	NCT01524926

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