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Genitourinary Cancer

The Current and Evolving Landscape of First-Line Treatments for Advanced Renal Cell Carcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Renal cell carcinoma • Tyrosine kinase inhibitors • Targeted therapy • Immunotherapy • Immune checkpoint inhibitors

Abstract

Agents targeting the vascular endothelial growth factor (VEGF) and its receptors (VEGFRs), as well as the mammalian target of rapamycin (mTOR) and immune checkpoint receptor programmed death 1 (PD-1) signaling pathway have improved clinical outcomes for patients with advanced renal cell carcinoma (RCC). The VEGFR tyrosine kinase inhibitors (TKIs) pazopanib and sunitinib are FDA-approved first-line treatment options for advanced RCC; however, other treatment options in this setting are available, including the recently approved combination of nivolumab (anti-PD-1) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein-4 [CTLA-4]) for patients with intermediate or poor risk. Unfortunately, treatment guideline recommendations provide little guidance to aid first-line treatment choice. In addition, several ongoing randomized phase III trials of investigational first-line regimens may complicate the RCC treatment paradigm if these agents gain approval. This article reviews clinical trial and real-world evidence for currently approved and investigational first-line treatment regimens for advanced RCC and provides clinical evidence to aid first-line treatment selection. ***The Oncologist*** 2019;24:338–348

Implications for Practice: Vascular endothelial growth factor receptor tyrosine kinase inhibitors are approved by the U.S. Food and Drug Administration as first-line treatment options for advanced renal cell carcinoma; however, the treatment paradigm is rapidly evolving. The combination of nivolumab plus ipilimumab was recently approved for intermediate- and poor-risk patients, and other combination strategies and novel first-line agents will likely be introduced soon.

Introduction

Kidney cancer accounts for approximately 338,000 new cancer cases per year and 2.4% of all malignancies worldwide and is responsible for an estimated ~140,000 deaths yearly [1]. The most common kidney cancer is renal cell carcinoma (RCC), which is often diagnosed after the patient has metastatic disease [2]. In the past, the only treatments for advanced RCC (aRCC) were interleukin-2 and/or interferon-α (IFN-α), although these are associated with substantial toxicity and benefit only a small subset of patients [3]. Since 2005, the introduction of agents that target the vascular endothelial growth factor (VEGF) and its receptors (VEGFRs), as well as the mammalian target of rapamycin (mTOR) and the immune checkpoint receptor programmed death 1 (PD-1), has led to improvements in outcomes for patients with RCC [4, 5]. Improved understanding of the molecular mechanisms of RCC has led to the approval of new treatments over the past few years, with expectations that other agents will soon likely increase the therapeutic options available for patients with RCC [6–8].

The management of RCC has greatly improved over the past few decades, and future advances in diagnosis, local management, and systemic therapy are expected to lead to even greater improvements in long-term survival [3]. Indeed, new treatments in the first-line setting have the greatest impact for patients with aRCC, and results from

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recent first-line trials are expected to rapidly transform the RCC treatment landscape. Treatment choice will be highly dependent on patients' risk status per International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, as recent first-line agents have been approved for specific IMDC risk groups [6, 8]. IMDC criteria utilize six independent clinical/laboratory risk factors to predict whether a patient will have favorable (0 risk factors), intermediate (1–2 risk factors), or poor (3–6 risk factors) prognosis [9]. This risk classification system will be increasingly relevant for clinicians who are faced with multiple treatment choices for their patients with aRCC.

This review provides an overview of efficacy and safety of currently available and investigational agents in the first-line setting for aRCC.

VEGF-Targeted Agents

Tyrosine kinase inhibitors (TKIs) targeting VEGFRs remain the cornerstone of therapy for patients with aRCC [4, 5, 10]. Because VEGFR-TKIs inhibit multiple targets of angiogenesis and tumor cell proliferation in this highly vascular tumor type, they are effective treatments for RCC [3]. In addition to VEGFR inhibition, TKIs used for aRCC inhibit a spectrum of other tyrosine kinases with varying selectivity [11, 12], which leads to on- and off-target effects that may result in differences in the efficacy and/or safety profiles observed between TKIs. The efficacy and safety data from pivotal trials of first-line agents carrying the highest level of recommendation in treatment guidelines, or agents with new data that are expected to transform treatment guidelines soon, are shown in Table 1.

Sunitinib

Sunitinib is a multitargeted TKI that inhibits VEGFR-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)-α and -β, stem cell factor receptor (c-Kit), fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type 1, and the glial cell line derived neurotrophic factor receptor (RET) [12–16]. Approval of sunitinib for patients with aRCC was granted in 2006 by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [14, 15]. The efficacy and safety of sunitinib in treatment-naive patients with advanced clear cell RCC was demonstrated in the pivotal phase III trial, in which sunitinib significantly prolonged median progression-free survival (mPFS) but not overall survival (OS) versus IFN-α [17, 18] (Table 1). Several real-world studies confirm the effectiveness of first-line sunitinib in patients with aRCC [19–30]. Most large (n > 150) real-world studies are retrospective, multicenter analyses with a wide range in mPFS (7.0–20.0 months) and median OS (mOS; 18.7–45.1 months) reported across studies [19–30]. In one of the larger real-world sunitinib studies that provided information about the effectiveness in patient subgroups often excluded from clinical trials, an expanded-access trial in 4,543 patients with metastatic RCC demonstrated that the objective response rate (ORR) was 16% and mPFS and mOS were 9.4 and 18.7 months, respectively [21]. Despite the established efficacy of sunitinib in aRCC, two recent first-line trials have demonstrated superiority of newer agents (cabozantinib and nivolumab plus ipilimumab) over sunitinib in patients with intermediate- or poor-risk status (Table 1) [31, 32].

Unlike other oral TKIs that are dosed daily to treat aRCC, the approved schedule for sunitinib is continuous daily dosing for 4 weeks (50 mg per day) followed by 2 weeks off treatment (4/2 schedule) [14, 15]. The 4/2 schedule was initially chosen based on a request from health authorities to allow patients to recover from potential bone marrow and adrenal toxicity that was observed in preclinical studies [33]. Even with the 4/2 schedule, aRCC patients treated with sunitinib in phase III trials frequently underwent dose reductions (32%–51%) and dose interruptions (39%–49%) [17, 34].

To improve tolerability, several clinical trials and real-world studies investigated alternative, off-label sunitinib dose schedules, most notably continuous 37.5 mg per day dosing and 50 mg per day for 2 weeks followed by 1 week off treatment (2/1 dosing) [35–40]. Although results suggest that 2/1 dosing might improve the safety of sunitinib, studies have not been robustly designed to assess efficacy [35–37, 39, 40]. Patients should be initiated on the approved 50 mg per day 4/2 schedule, with dose modifications and/or dose interruptions as required based on patient safety and tolerability, as approved by regulatory authorities [14, 15].

Pazopanib

Pazopanib is a multitargeted TKI that inhibits VEGFR-1, -2, and -3, PDGFR-α and -β, and c-Kit, with modest activity against other tyrosine kinases such as fibroblast growth factor receptor (FGFR)-1 and -3 and c-fms receptor tyrosine kinases [41–43]. Pazopanib was approved by the FDA in 2009 for the treatment of aRCC and by the EMA in 2010 for the first-line treatment of aRCC in patients who received prior cytokine therapy for advanced disease [42, 43]. The pivotal randomized, double-blind, phase III VEG105192 study of pazopanib versus placebo was conducted in 435 treatment-naive or cytokine-pretreated patients with advanced/metastatic RCC and predominant clear cell histology [44, 45]. The primary endpoint of PFS was significantly better with pazopanib versus placebo in the overall study population (Table 1) and in the subpopulation of treatment-naive patients and cytokine-pretreated patients [44]. Although no OS benefit was observed with pazopanib versus placebo, this was confounded by the early and high rate of crossover from placebo to pazopanib [44, 45]. Real-world studies confirm the effectiveness and safety of first-line pazopanib in patients with aRCC, [28–30, 46–50], but these have generally been conducted in older patients with similar survival results when compared with younger patient populations in clinical trials (median age: ≥65 vs. 59–61 years [34, 44]). Most completed real-world studies of first-line pazopanib are retrospective, multicenter analyses (n > 80), with a mPFS range of 8.3–13.7 months and mOS range of 19–29.1 months across studies [28–30, 42–46], consistent with results from phase III trials [34, 44, 45, 51]. The retrospective, observational Spanish SPAZO study in 278 patients with metastatic RCC, which was one of the largest reported real-world studies of first-line pazopanib (mPFS and mOS were 11.1 and 22.2 months,

Table 1. Efficacy and safety data from pivotal trials of first-line agents with category 1 evidence in treatment guideline recommendations, and first-line agents anticipated to be added to treatment guidelines soon

			Efficacy			Safety		
Study	**Agent**	**Comparator arm**	**Median PFS, months**	**Median OS, months**	**ORR, %**	**Grade 3/4 AEs or laboratory abnormalities in ≥5% pts with experimental agent**	**Dose reduction, %**	**Treatment discontinuation due to AEs, %**
Phase III RCT [17, 18]	Sunitinib	IFN-α	11 vs. 5 ($p < .001$)	26.4 vs. 21.8 ($p = 051$)[a]	31% vs. 6% ($p < .001$)	Diarrhea, fatigue, hypertension, hand-foot syndrome, increased lipase, increased uric acid, lymphopenia, neutropenia, leukopenia	32% vs. 21%	8% vs. 13%
Phase III RCT (VEG105192) [44, 45]	Pazopanib	Placebo	9.2 vs. 4.2 ($p < .0001$)	22.9 vs. 20.5 ($p = .224$)[b]	30% vs. 3% ($p < .001$)	Increased ALT, increased AST, hyponatremia	NR	14% vs. 3%
Phase III RCT (AVOREN) [58, 60]	Bevacizumab + IFN-α	Placebo + IFN-α	10.2 vs. 5.4 ($p = .0001$)	23.3 vs. 21.3 ($p = .336$)[a]	31% vs. 13% ($p = .0001$)	Fatigue, asthenia, proteinuria	Not permitted for bevacizumab	28% vs. 12%
Phase III RCT(CALGB 90206) [59, 61]	Bevacizumab + IFN-α	IFN-α	8.5 vs. 5.2 ($p < .0001$)	18.3 vs. 17.4 ($p = .097$)[a]	26% vs. 13% ($p < .0001$)	Fatigue, anorexia, proteinuria, hypertension, low neutrophils/ granulocytes, nausea, dyspnea[c]	Not permitted for bevacizumab	24% vs. 19%
Phase II RCT (CABOSUN) [31] [68] (int/poor-risk pts only)	Cabozantinib	Sunitinib	8.2 vs. 5.6 ($p = .012$)	26.6 vs. 21.2 ($p = .27$)[d]	46% vs. 18%	Hypertension, diarrhea, fatigue, hand-foot syndrome, ALT increase, anorexia, oral mucositis	58% vs. 49%	20% vs. 21%
Phase III RCT (TIVO-1) [71]	Tivozanib	Sorafenib	11.9 vs. 9.1 ($p = .042$)	29.3 vs. 28.8 ($p = .105$)	33% vs. 23% ($p = .014$)	Hypertension, fatigue, increased lipase	14% vs. 43%	7% vs. 7%
Phase III RCT [81] (poor-risk pts only)	Temsirolimus	IFN-α vs. temsirolimus + INF-α	5.5 vs. 3.1 vs. 4.7 ($p < .001$ for temsirolimus vs. IFN-α)	10.9 vs. 7.3 vs. 8.4 ($p = .008$ for temsirolimus vs. IFN-α)	9% vs. 5% vs. 8%	Anemia, asthenia, hyperglycemia, dyspnea, pain, infection	23% vs. 39% vs. (combination arm: 48% IFN; 30% temsirolimus)	7% vs. 14% vs. 20%
Phase III RCT [32] (CheckMate-214) (int/poor-risk pts only)	Nivolumab + ipilimumab	Sunitinib	*Int/poor-risk:* 11.6 vs. 8.4 ($p = .03$) *Fav risk:* 15.3 vs. 25.1 ($p < .001$)	*Int/poor-risk:* NR vs. 26 ($p < .001$)[f] *Fav risk:* NR vs. 32.9	*Int/poor-risk:* 42% vs. 27% ($p < .001$) *Fav risk:* 29% vs. 52% ($p = .001$)	Increased lipase level[c]	Not allowed vs. 53%	22% vs. 12%[e]

[a]Based on unstratified log-rank test.
[b]Based on one-sided stratified log-rank test.
[c]Reported as treatment-related AEs.
[d]Study not powered to detect difference in OS.
[e]Discontinuation due to treatment-related AEs.
[f]Predefined threshold for statistical significance: $p = .009$.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; fav, favorable; IFN-α, interferon-α; int, intermediate; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pts, patients; RCT, randomized controlled trial.

respectively), validated the IMDC criteria widely used for assessing prognosis with first-line anti-VEGF therapy [46]. Two large, prospective, observational, multicenter studies of first-line pazopanib in aRCC were recently completed—the global PRINCIPAL study (ClinicalTrials.gov Identifier NCT01649778) and the PAZOREAL study conducted in 150 German sites [52]—and are expected to provide further evidence of the real-world effectiveness and safety of first-line pazopanib.

Notably, the prescribing information for pazopanib carries a black box warning for hepatotoxicity; however, a meta-analysis of clinical trial data showed that most transaminase elevations are asymptomatic, isolated events that resolve with time [43, 53]. In the meta-analysis of phase II/III clinical trials of pazopanib in patients with advanced cancer (n = 2,080, including 1,149 with RCC), alanine aminotransferase (ALT) and aspartate aminotransferase elevations >3× the upper limit of normal (ULN) occurred in 23% and 26% of RCC patients, respectively [53]. Most (91%) ALT elevations occurred within the first 18 weeks of treatment, and 89% of patients recovered to ALT <2.5× ULN in a median time of 30 days. Furthermore, only 0.4% of patients met the criteria for Hy's law. Serum liver tests are recommended before initiation of pazopanib and during treatment with pazopanib, and if ALT elevations >8× ULN occur, dose interruption is recommended until recovery to grade 1 or baseline [43]. Pazopanib should be permanently discontinued if ALT elevations >3× ULN occur concurrently with bilirubin elevations >2× ULN.

Sunitinib versus Pazopanib

Two randomized, head-to-head phase III trials directly compared first-line sunitinib and pazopanib in patients with advanced/metastatic RCC. The noninferiority COMPARZ study of 1,110 patients with advanced/metastatic clear cell RCC demonstrated comparative efficacy of first-line pazopanib and sunitinib [34, 51]. The primary endpoint of noninferior PFS with pazopanib versus sunitinib was met (median, 8.3 vs. 9.5 months; hazard ratio [HR], 1.05; 95% confidence interval [CI], 0.90–1.22) [34], and subgroup analyses of PFS were consistent with the primary analysis regardless of sex, age (<65 or ≥65 years), geographic region (Asia, North American, or European Union), baseline Karnofsky performance status (90–100 or 70–80), or Memorial Sloan Kettering Cancer Center or Heng risk (favorable or intermediate risk) [34]. The comparative efficacy of pazopanib and sunitinib was confirmed by the secondary efficacy endpoints of ORR (31% vs. 25%, respectively; p = .03) and mOS (28.3 vs. 29.1 months, respectively; p = .24) [34, 51]. Furthermore, the proportion of patients with a long-term PFS response (≥18 months) was similar with pazopanib and sunitinib in a post hoc analysis (14.2% and 15.4%, respectively) [54]. This is also similar when compared with the percentage of metastatic RCC patients with a PFS duration ≥18 months (15.7%) with sunitinib across eight phase II or III clinical trials or the expanded access program [55]. One potential difference in efficacy between pazopanib and sunitinib is the time to response in patients who achieved a partial or complete response, which was numerically shorter for pazopanib versus sunitinib (11.9 vs. 17.4 weeks) in a post hoc analysis of COMPARZ [54]. The COMPARZ study also revealed differences in the safety and quality-of-life (QoL) profiles between pazopanib and sunitinib [34]. Symptomatic and hematologic adverse events (AEs) were more common with sunitinib, whereas asymptomatic AEs, mainly liver enzyme abnormalities, were more common with pazopanib and most (11 out of 14) QoL measures significantly favored pazopanib over sunitinib. Similar proportions of pazopanib- and sunitinib-treated patients in COMPARZ underwent dose reductions (44% and 51%, respectively) and dose interruptions lasting ≥7 days (44% and 48%, respectively) [56]. These dose modifications allowed longer median time on treatment and larger median cumulative doses, as well as numerically longer mPFS in both treatment arms, suggesting that dose modifications due to AEs do not compromise efficacy. The randomized, cross-over, double-blind, phase III PISCES study revealed differences in patient preference between first-line pazopanib and sunitinib in patients with metastatic RCC [57]. A significantly greater proportion of patients preferred pazopanib compared with sunitinib (70% vs. 22%; p < .001), with the most common reasons being better overall QoL and less fatigue.

Real-world analyses of large patient populations (n > 150 for each treatment arm) in the IMDC and the U.S. Oncology Network confirm the comparative effectiveness of first-line pazopanib and sunitinib in aRCC [28, 29].

Bevacizumab

Another first-line treatment option for patients with advanced clear cell RCC is the anti-VEGF monoclonal antibody bevacizumab administered in combination with IFN-α [4, 5, 10]. However, this combination regimen is used less commonly than pazopanib and sunitinib, which may be due in part to the less convenient intravenous administration of bevacizumab [5, 58]. Approval for bevacizumab plus IFN-α is supported by two randomized phase III studies. The AVOREN study demonstrated significantly prolonged PFS with bevacizumab plus IFN-α versus placebo plus IFN-α, and the CALGB 90206 study demonstrated significantly improved PFS with bevacizumab plus IFN-α versus IFN-α alone (Table 1) [58, 59]. Although absolute median OS values were longer for both treatment arms in AVOREN compared with CALGB 90206, neither study demonstrated significantly prolonged survival with bevacizumab plus IFN-α versus the control arm [60, 61].

Cabozantinib

The multitargeted TKI cabozantinib inhibits VEGFRs, MET, the GAS6 receptor (AXL), KIT, RET, FLT3, Tie-2, ROS1, TYRO3, MER, and tropomyosin receptor kinase B [62–64]. Cabozantinib was initially approved in Europe for treatment following VEGF-targeted therapy and in the U.S. following antiangiogenic therapy, and the FDA recently extended approval to the first-line treatment setting [63–65]. Accordingly, U.S. National Comprehensive Cancer Network (NCCN) treatment guidelines now recommend cabozantinib as a first-line option for patients with intermediate or poor risk per IMDC criteria after positive results from a randomized phase II study [4, 31]. Initial approval

for cabozantinib followed the randomized phase III METEOR study, in which cabozantinib significantly improved PFS, OS, and ORR compared with everolimus in VEGFR-TKI pretreated patients with aRCC [66, 67]. The subsequent randomized phase II CABOSUN study provided evidence of the benefit of cabozantinib versus sunitinib in previously untreated aRCC patients with intermediate or poor IMDC risk (n = 157) [31]. The primary endpoint of significantly improved PFS per investigator review with cabozantinib versus sunitinib was met, and an improvement in ORR with cabozantinib was also observed (Table 1) [31]. Subsequent analysis by an independent review committee confirmed the PFS advantage with cabozantinib over sunitinib (mPFS, 8.6 vs. 5.3 months; p = .0008) [68]. Cabozantinib did not significantly improve OS compared with sunitinib [68]; however, the study was not powered to detect a difference in survival [31]. Although the ORR with cabozantinib was higher when assessed by the investigator compared with independent review, the disease control rate with cabozantinib was similar by investigator and independent assessments, indicating a shift from confirmed partial response to stable disease in the independent review assessment. Grade 3/4 AEs were reported by a similar percentage of patients with cabozantinib and sunitinib (67% and 68%, respectively), and 58% and 49% of patients underwent dose reductions with cabozantinib and sunitinib, respectively [31].

Following the positive results from the CABOSUN trial, NCCN treatment guideline recommendations added cabozantinib as a first-line treatment option for IMDC poor- and intermediate-risk patients (category 2A), albeit at a lower level of recommendation than the category 1 agents pazopanib, sunitinib, and bevacizumab plus IFN-α [4]. The European Society of Medical Oncology (ESMO) and European Association of Urology (EAU) guidelines have yet to add cabozantinib as a first-line treatment option, with ESMO requiring confirmatory data before assessing the role of cabozantinib in the first-line setting [5, 10].

Tivozanib

Tivozanib is a multitargeted TKI that inhibits VEGFR-1, -2, and -3, as well as PDGFR-α and -β, c-Kit Tie-2, and EphB2 [69]. In August 2017, the European Commission approved tivozanib in the European Union (EU), Norway, and Iceland for the first-line treatment of aRCC in patients who are VEGFR- and mTOR-pathway naive following disease progression after one prior cytokine treatment for aRCC [70]. Tivozanib has not been approved outside of the EU for the treatment of aRCC. The pivotal phase III TIVO-1 trial of tivozanib versus sorafenib was conducted in 571 patients with metastatic clear cell RCC who were treatment naive or had received one prior systemic therapy but could not have received prior VEGF- or mTOR-targeted therapy [71]. Tivozanib significantly prolonged the primary endpoint of PFS versus sorafenib per independent review in the overall study population (Table 1) and in the subpopulation of treatment-naive patients (mPFS, 12.7 vs. 9.1 months; p = .037) [71]. ORR per independent review was higher with tivozanib compared with sorafenib; however, the sorafenib arm had higher OS (Table 1) [71]. OS results were likely confounded by the imbalance between arms in patients who received subsequent targeted therapy (63% vs. 13% in the sorafenib arm and tivozanib arm, respectively), predominantly because of most (60%) patients in the sorafenib arm receiving subsequent tivozanib in an open-label extension study [71]. Tivozanib treatment was associated with fewer AE-related dose reductions and dose interruptions compared with sorafenib; AEs more common with tivozanib versus sorafenib included hypertension (44% vs. 34%) and dysphonia (21% vs. 5%), whereas diarrhea (23% vs. 33%) and hand-foot syndrome (14% vs. 54%) were more common with sorafenib [71]. FDA review concluded that the potential increased risk of death with tivozanib may have been due to poor trial design, more favorable efficacy of sorafenib, or greater delayed toxicity or toxicity not recognized with tivozanib [72]. Looking critically at the TIVO-1 trial design, it is plausible that the detrimental effect of tivozanib on patients' survival (derived by hazard ratio versus sorafenib) may be due to a design that allowed patients on the tivozanib arm to cross over to sorafenib but not vice versa. Furthermore, in countries that participated in the trial, there was a lack of active treatment options after the study [73]. This case represents a discrepancy between the U.S. FDA and the EMA. The FDA did not approve tivozanib because of uninterpretable OS results [72], whereas the EMA Committee for Medical Products for Human Use (CHMP) released a positive opinion for tivozanib in June 2017 after receiving an application for marketing authorization in February 2016 [74]. The EMA CHMP concluded that the increase in median PFS of 2.4 months for tivozanib versus the active comparator sorafenib was clinically relevant and supported by phase II data and ORR and duration of response, with a safety profile in line with that expected for a VEGF inhibitor [74]. The EMA CHMP considered that OS results could potentially have been confounded by the study design, which permitted only sorafenib patients to cross over. This difference in opinion between the U.S. FDA and the EMA may result in a discrepancy between the use of first-line tivozanib in the U.S. and the EU.

Axitinib

Axitinib is a TKI that inhibits VEGFRs 1–3 [75]. Although it is not approved as a first-line treatment, axitinib is included as a first-line treatment option in NCCN guidelines (category 2A) but not in ESMO or EAU guidelines [4, 5, 10]. Despite a lack of significant PFS improvement with first-line axitinib compared to first-line sorafenib by phase III analysis (10.1 vs. 6.5 months; HR, 0.77; 95% CI, 0.56–1.05; p = .038), NCCN guidelines conclude that axitinib demonstrated clinical activity and an acceptable safety profile in this setting [4, 76].

Sorafenib

Sorafenib is a multitargeted TKI that inhibits VEGFRs 1–3, PDGFR-β, KIT, FLT-3, RET, RET/PTC, c-CRAF, BRAF, and mutant BRAF [77]. Sorafenib is included as a first-line option in ESMO guidelines (level of evidence II, grade of recommendation B), but not NCCN or EAU guidelines [4, 5, 10]; however, recent results from the SWITCH-II trial

suggest that sorafenib is a less effective first-line agent than pazopanib [78]. In SWITCH-II, the primary endpoint of total mPFS was 8.6 months with the treatment sequence sorafenib followed by pazopanib, compared with 12.9 months with the sequence pazopanib-sorafenib (HR, 1.36; upper limit of one-sided 95% CI, 1.68), which did not meet the criterion for noninferiority; furthermore, first-line PFS significantly favored the pazopanib-sorafenib sequence [78]. This followed results from the SWITCH-I study, in which total PFS did not differ significantly between the treatment sorafenib-sunitinib and sunitinib-sorafenib sequences in treatment-naive patients with metastatic RCC (mPFS, 12.5 vs. 14.9 months; HR, 1.01; 90% CI, 0.81–1.27; p = .5 for superiority) [79].

mTOR inhibitors

The mTOR is a component of intracellular signaling pathways that regulates cell growth, proliferation, metabolism, and angiogenesis [80]. The mTOR inhibitors everolimus and temsirolimus are both effective agents for the treatment of aRCC, although only temsirolimus is recommended in the first-line setting, and only for patients with poor risk features [4, 5, 10]. Temsirolimus was approved after a randomized, three-arm, phase III trial of temsirolimus versus temsirolimus plus IFN-α versus IFN-α in patients with at least three of six risk factors for survival [81]. Temsirolimus alone significantly prolonged OS compared with IFN-α (Table 1), whereas combination temsirolimus plus IFN-α did not provide a significant survival benefit versus IFN-α monotherapy. Despite the positive phase III results, there is no clear evidence that temsirolimus is superior to commonly used TKIs in poor-risk patients [5], and temsirolimus is rarely used in this setting [82].

Immune Checkpoint Inhibitors

Combination therapy with the immune checkpoint inhibitor antibodies nivolumab and ipilimumab was recently shown to be effective in the first-line setting in the phase III CheckMate-214 study [32]. Nivolumab is a PD-1 inhibitor approved as monotherapy in the second-line setting in patients with aRCC [6, 83] and is now also approved in the U.S. as a combination regimen with ipilimumab, an inhibitor of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), in patients with treatment-naive aRCC with intermediate or poor risk [6]. PD-1 and CTLA-4 are involved in temporally, anatomically, and functionally different stages of the immune response [84], and combined inhibition of these pathways improved intratumoral infiltration of CD8+ T cells and antitumor efficacy in an animal model, and enhanced antitumor efficacy in patients with metastatic melanoma, when compared with either antibody alone [6, 85, 86]. Similar efficacy has been demonstrated in RCC. In the CheckMate-214 study, treatment-naive patients with advanced or metastatic clear cell RCC were randomly assigned to nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks (n = 550) or sunitinib 50 mg/day for 4 weeks in 6-week cycles (n = 546) [32]. Nivolumab plus ipilimumab significantly improved the coprimary endpoints of ORR and mOS (but not PFS) compared with sunitinib in patients with intermediate or poor IMDC risk (Table 1) [32]. ORR was 42% with nivolumab versus 27% with sunitinib (p < .001), mOS was not reached with nivolumab versus 26.0 months with sunitinib (HR, 0.63; 99.8% CI, 0.44–0.89; p < .001), and the between-group difference in mPFS did not reach the predefined criteria for statistical significance (11.6 vs. 8.4 months; p = .03 [threshold p = .009]). Conversely, patients with favorable IMDC risk had improved outcomes with sunitinib compared with nivolumab plus ipilimumab for ORR and PFS in an exploratory analysis [32]. Treatment-related grade 3/4 AEs were reported by 46% of patients with nivolumab plus ipilimumab and 63% of patients with sunitinib [32]. In April 2018, the U.S. FDA approved nivolumab plus ipilimumab for the treatment of patients with intermediate- or poor-risk, previously untreated aRCC [6], and NCCN guidelines now recommend nivolumab plus ipilimumab as one of the preferred agents for these patients with category 1 evidence (category 2B for favorable risk patients) [4].

More recently, results from the phase III IMmotion-151 study of atezolizumab (anti-PD-L1) plus bevacizumab versus sunitinib in patients with treatment-naive aRCC were reported [87]. Atezolizumab plus bevacizumab significantly improved the coprimary endpoint of PFS in PD-L1+ patients versus sunitinib (mPFS, 11.2 vs. 7.7 months; HR, 0.74; 95% CI, 0.57–0.96; p = .02); this PFS benefit was also observed in intention-to-treat (ITT) patients (HR, 0.83; 95% CI, 0.70–0.97; descriptive p = .02 [secondary endpoint]). OS data were immature at first interim analysis, prohibiting analysis of the coprimary endpoint of OS in ITT patients. ORR in PD-L1+ patients was 43% with atezolizumab plus bevacizumab versus 35% with sunitinib, and grade 3/4 AEs were reported by 40% and 54% of patients with atezolizumab plus bevacizumab and sunitinib, respectively. Pending OS data, results from IMmotion-151 may support the approval of atezolizumab plus bevacizumab as another first-line treatment option in aRCC.

First-Line Treatment Selection

Historically, favorable- and intermediate-risk patients have been grouped together for treatment guideline recommendations. Recently, use of this grouping has been rethought. Although the orally administered TKIs sunitinib and pazopanib and the intravenously administered bevacizumab plus IFN-α have category 1 level evidence in the first-line treatment setting in trials conducted predominantly in favorable- or intermediate-risk patients, [4, 5, 10] the treatment with the better tolerability/QoL profile and more convenient administration route would receive preference. Table 2 summarizes efficacy (PFS and OS) by risk group for pivotal trials of first-line agents. The CheckMate-214 study intriguingly found superior efficacy with nivolumab plus ipilimumab in intermediate-/poor-risk patients but superior efficacy with sunitinib in favorable-risk patients, and it would be interesting to see whether patients in the intermediate group with only one risk factor (vs. two risk factors) benefit from TKI monotherapy over nivolumab plus ipilimumab. Cabozantinib has also demonstrated efficacy in

Table 2. Efficacy by prognostic risk group from pivotal trials of first-line agents with category 1 evidence in treatment guideline recommendations, and first-line agents anticipated to be added to treatment guidelines soon

			Median PFS by risk group, mo			Median OS by risk group, mo		
Study	**Agent**	**Comparator arm**	**Favorable**	**Intermediate**	**Poor**	**Favorable**	**Intermediate**	**Poor**
Phase III RCT [17, 18]	Sunitinib	IFN-α	**NR** vs. 8[a]	**11** vs. 4[a]	**4** vs. 1[a]	**NR** vs. NR[a]	**20.7** vs. 15.4[a]	**5.3** vs. 4.0[a]
Phase III RCT (VEG105192) [44, 45]	Pazopanib	Placebo	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Phase III RCT (AVOREN) [58, 60]	Bevacizumab + IFN-α	Placebo + IFN-α	**12.9** vs. 7.6[a]	**10.2** vs. 4.5[a]	**2.2** vs. 2.1[a]	**35.1** vs. 37.2[a] (p = .6798)	**22.6** vs. 19.3[a] (p = .1230)	**6.0** vs. 5.1[a] (p = .5594)
Phase III RCT(CALGB 90206) [59, 61]	Bevacizumab + IFN-α	IFN-α	**11.1** vs. 5.7[a]	**8.4** vs. 5.3[a]	**3.3** vs. 2.6[a]	**32.5** vs. 33.5[a] (p = .5189)	**17.7** vs. 16.1[a] (p = .1688)	**6.6** vs. 5.7[a] (p = .2439)
Phase II RCT (CABOSUN) [31] [68] (int/poor-risk pts only)	Cabozantinib	Sunitinib	NA	**8.3** vs. 6.2[b]	**6.1** vs. 2.8[b]	Not reported	Not reported	Not reported
Phase III RCT (TIVO-1) [71]	Tivozanib	Sorafenib	**16.7** vs. 10.8[a] (p = .018)	**9.4** vs. 7.4[a] (p = .076	**3.7** vs. 10.9[a] (p = .504)	Not reported	Not reported	Not reported
Phase III RCT [81] (poor-risk pts only)	Temsirolimus	IFN-α vs. temsirolimus + INF-α	NA	NA	**5.5** vs. 3.1 vs. 4.7[c] (p < .001 for temsirolimus vs. IFN-α)	NA	NA	**10.9** vs. 7.3 vs. 8.4[c] (p = .008 for temsirolimus vs. IFN-α)
Phase III RCT (CheckMate-214) [32]	Nivolumab + ipilimumab	Sunitinib	**15.3** vs. 25.1[b] (p < .001)	**11.6** vs. 8.4[b,d] (p = .03)		NR vs. 32.9 (p = .27)	**NR** vs. 26.0[b] (p < .001)	

[a]Risk grouping per Memorial Sloan Kettering Cancer Center criteria.
[b]Risk grouping per International Metastatic Renal Cell Carcinoma Database Consortium criteria.
[c]Patients were designated poor risk based on the presence of ≥3 predictors of survival (serum lactate dehydrogenase >1.5 × upper limit of normal, hemoglobin <lower limit of normal, corrected serum calcium >10 mg/dL, time from initial diagnosis of renal cell carcinoma to randomization <1 year, Karnofsky performance status 60–70, or metastases in multiple organs.
[d]Predefined threshold for statistical significance: p = .009.
Abbreviations: IFN-α, interferon-α; int, intermediate; NA, not applicable; NR, not reached; OS, overall survival; PFS, progression-free survival; pts, patients; RCC, renal cell carcinoma; RCT, randomized controlled trial.

Table 3. Ongoing phase III trials in the first-line treatment setting in patients with advanced or metastatic renal cell carcinoma

Trial (Clinicaltrials.gov Identifier)	MOA	Agents	Comparator arm	Primary data expected	Primary endpoint(s)	Estimated/ actual enrollment (*n*)
KEYNOTE-426 (NCT02853331)	PD-1 inhibitor + TKI	Pembrolizumab + axitinib	Sunitinib	January 2020	PFS and OS	862
CLEAR (NCT02811861)	PD-1 inhibitor + TKI *or* TKI + mTOR inhibitor	Pembrolizumab + lenvatinib or lenvatinib + everolimus	Sunitinib	October 2019	PFS	735
CheckMate 9ER (NCT03141177)	PD-1 inhibitor + TKI	Nivolumab + cabozantinib	Sunitinib	September 2019	PFS	630
IMmotion151 (NCT02420821)	PD-L1 inhibitor + anti-VEGF mAb	Atezolizumab + bevacizumab	Sunitinib	PFS reported February 2018 [87]; OS data awaited	PFS in pts with detectable PD-L1; OS in ITT pts	915
JAVELIN Renal 101 (NCT02684006)	PD-L1 inhibitor + TKI	Avelumab + axitinib	Sunitinib	December 2018	PFS in PD-L1+ pts; OS in PD-L1+ pts	830

Abbreviations: ITT, intention-to-treat; mAb, monoclonal antibody; MOA, mechanism of action; mTOR, mammalian target of rapamycin; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

this setting versus sunitinib in a randomized phase II trial [31] but may be less preferable to nivolumab plus ipilimumab because of its safety profile and less solid study design. For patients with favorable risk, pazopanib and sunitinib are the preferred [4] and most commonly used [5] first-line treatments according to treatment guideline recommendations, and although bevacizumab plus interferon carries the same high level of evidence [4, 5, 10], it may be less preferable because of its less convenient administration regimen. Consideration of safety/tolerability profile, quality of life, and patient preference may inform treatment choice between pazopanib and sunitinib, based on results from phase III studies [34, 57], as well as other factors such as cost and reimbursement. For patients with intermediate or poor risk, combination nivolumab plus ipilimumab is now the preferred treatment option with category 1 level evidence in updated NCCN guidelines; cabozantinib is also an option for these patients, albeit at a lower level of evidence (category 2A) [4]. Although temsirolimus also carries a high level of evidence for patients with poor risk (category 1 in NCCN guidelines and [4] and level of evidence II, grade of recommendation A in ESMO guidelines [5]), both combination nivolumab plus ipilimumab (dosed intravenously every 3 weeks for 4 doses, followed by nivolumab every 2 weeks) and cabozantinib (oral daily doses) may be preferred because of their more convenient administration regimen compared with temsirolimus (once-weekly intravenous infusion), and based on an indirect comparison of clinical trial data suggesting poorer PFS, OS, and ORR for temsirolimus [31, 32, 68, 81].

There are currently no validated molecular biomarkers to predict treatment benefit with first-line agents. Perhaps the most promising potential predictive biomarker for the first-line treatment of aRCC is PD-L1 expression, based on recent results from the CheckMate-214 study. In this study, PD-L1 tumor expression ≥1% predicted improved PFS with nivolumab plus ipilimumab versus sunitinib in patients with intermediate or poor IMDC risk, but not in patients with PD-L1 <1%, suggesting that PD-L1 may be predictive of outcomes with nivolumab-ipilimumab combination therapy [32]. However, these findings are somewhat contradicted by the OS benefit reported for nivolumab-ipilimumab in all intermediate/poor IMDC-risk patients, regardless of PD-L1 status [32], indicating the limitations of PD-L1 in the field of immunotherapy. Furthermore, a recent meta-analysis demonstrated that high PD-L1 expression significantly increased the risk of death in patients with metastatic RCC regardless of treatment, confirming the prognostic role of PD-L1 expression in metastatic RCC [88]. Even more recently, results of the phase III study of first-line atezolizumab plus bevacizumab versus sunitinib in untreated metastatic RCC found that PD-L1+ patients treated with the combination had a significantly longer mPFS (11.2 vs. 7.7 months; HR, 0.74; 95% CI, 0.57–0.96; p = .02) [87].

No predictive biomarkers for first-line sunitinib versus the mTOR inhibitor everolimus were identified in a next-generation sequencing study of available tumor tissue from patients in the phase II RECORD-3 study, although significant differences were observed within treatment groups when comparing mutant and wild-type genes for *PBRM1*, *BAP1*, and *KDM5C* [89]. Panels comprising multiple biomarkers to generate a "tumor signature" may be a promising sign of treatment benefit. The ongoing phase II BIONIKK trial (Clinicaltrials.gov Identifier NCT02960906) is investigating molecular biomarker signatures by randomizing patients to nivolumab, nivolumab plus ipilimumab, or TKI (sunitinib or pazopanib) based on their molecular clear cell RCC subtype [90].

Although on-treatment biomarkers, such as treatment-emergent hypertension, have shown to predict treatment benefit in patients with aRCC [91, 92], these are less useful than predictive biomarkers in choosing between

treatments, as they require a period of treatment before assessing potential benefit.

Ongoing Studies of Investigational First-Line Regimens

Several other combination regimens of immune checkpoint inhibitors with VEGF-targeted therapies or other immunomodulating drugs are currently being assessed in phase III trials in the first-line setting (Table 3). VEGF-targeted agents induce immunomodulatory effects, such as tumor T-cell infiltration [93] and reducing proangiogenic and immunosuppressive cell populations [94–96], which may make tumors more susceptible to immune checkpoint inhibitor therapy [97]. IMmotion151 recently reported superior PFS with atezolizumab plus bevacizumab versus sunitinib in PD-L1+ patients (coprimary endpoint) and in ITT patients (secondary endpoint); the data for analysis of OS in ITT patients (coprimary endpoint) are not yet mature [87]. Early-phase trials suggest promising efficacy with avelumab plus axitinib, nivolumab plus cabozantinib, pembrolizumab plus axitinib, and pembrolizumab plus lenvatinib [98–103]. Results from phase III trials are expected beginning in late 2018, which will determine whether any of these combinations will be added to the RCC treatment armamentarium.

Conclusion

The first-line treatment paradigm for patients with aRCC is evolving rapidly, mainly as a result of the revolutionary incorporation of immune checkpoint inhibitors in this setting. The ongoing evolution will lead to further improvements in survival and other clinical outcomes for RCC patients, which may be aided by the addition of new first-line agents and combination therapies as well as the development of biomarkers that predict outcomes with various treatments. Clinicians should be aware of rapidly evolving first-line treatment options to ensure the best outcomes for their patients with RCC.

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Disclosures

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