

## Review

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# The Emerging Role of Combination Angiogenesis Inhibitors and Immune Checkpoint Inhibitors in the Treatment of Metastatic Renal Cell Cancer

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**Abstract.** The advent of vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) a decade ago revolutionized the treatment paradigm in advanced metastatic clear cell renal cell carcinoma (RCC) with improved survival rates compared to the pre-TKI era. Monotherapy with VEGF TKIs has remained first-line. However, sequencing of different TKIs, mammalian target of rapamycin (mTOR) inhibitors, or immune checkpoint inhibitors (ICIs) has been the subject of controversy in the treatment landscape of metastatic RCC. First-line treatment further evolved with the approval of nivolumab plus ipilimumab in intermediate- and poor-risk patients based on an overall survival (OS) benefit demonstrated in the CheckMate214 trial as well as a progression-free survival (PFS) benefit of cabozantinib in the CABOSUN trial. Optimal sequencing, patient selection, and understanding resistance pathways continue to be prominent concerns. Efforts to bypass resistance mechanisms have led to the study of combination therapies. Given enhancement of immune checkpoint inhibitor (ICI) T-cell mediated effects by VEGF-mediated immunosuppression, the combination of VEGF inhibitors and ICIs in treatment-naïve locally advanced and metastatic RCC has shown promise. Available results of phase III trials utilizing these combinations are discussed herein.

**Keywords:** Immunotherapy, VEGF inhibitors, immune checkpoint inhibitors (ICIs), advanced renal cell cancer

## INTRODUCTION

Renal cell carcinoma (RCC) accounts for 65,000 new cases and almost 15,000 deaths each year in the

United States [1]. While surgery is the cornerstone of treatment for localized or locally advanced kidney cancers, unresectable and metastatic RCC are usually treated with systemic therapy. However, ongoing controversy exists regarding upfront use of cytoreductive nephrectomy given the lack of survival benefit as shown in the CARMENA trial, especially in those with intermediate- or poor-risk disease [2]. The treatment landscape has evolved over the past several years since the initial use of angiogenesis inhibitors.

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Vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) have been used in predominantly favorable-risk patients, while the mammalian target of rapamycin (mTOR) inhibitor temsirolimus has been used in predominantly poor-risk patients [3].

Risk models incorporating different prognostic factors have played a critical role in stratifying patients not only for disease prognostication but also in treatment assignment. The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model utilizes five factors: two clinical factors including performance status and time from diagnosis to treatment of less than a year and three laboratory parameters including high lactic dehydrogenase (LDH), serum calcium level, and a low hemoglobin, to help stratify patients into favorable (those with 0 risk factors), intermediate (1 or 2 risk factors), or poor-risk (3 or more risk factors) categories. With the MSKCC model, the corresponding overall survival (OS) was incrementally worse for those with poor-risk compared to favorable or intermediate-risk disease (5 months for poor-risk compared to 30 months for favorable vs. 14 months for intermediate;  $P < 0.001$ ) [4]. Another more contemporary risk model in the era of VEGF-targeted agent use, called the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), utilizes the same prognostic factors, but with the addition of two laboratory parameters including high platelets and absolute neutrophil counts (ANC) in lieu of the LDH. The IMDC model also stratified patients into favorable, intermediate, or poor-risk. As in the MSKCC model, the IMDC model correlated with worse survival rates for the poor-risk group (8 months) vs. the favorable and intermediate-risk groups (43 months and 22 months, respectively) [5]. These use of these risk models in contemporary trials remains critical in the endeavor to further refine and personalize treatments.

The use of interferon and interleukin has almost historical significance given the potential durability of response, although they were generally considered more toxic therapies [6]. This has led to a great interest in using immunotherapies and immune checkpoint inhibitors (ICIs) in general for the treatment of advanced or metastatic RCC. Nivolumab, a PD-1 inhibitor, became the first ICI approved as 2nd line therapy for previously treated patients with VEGF TKIs. Further success of these agents has moved the combination of nivolumab and ipilimumab to the frontline setting. While VEGF TKIs such as cabozantinib are still utilized in the first-line setting, resistance develops in those treated with

single-agent VEGF inhibitors. Therefore, recent trials have attempted to combine agents in an effort to delay resistance to either agent alone. In the following sections, we further elucidate the current and emerging landscape of treatment in metastatic RCC with a discussion of these combination trials.

## BACKGROUND ON SYSTEMIC THERAPY FOR ADVANCED RCC

### *VEGF inhibitors in the frontline setting*

Sorafenib was the first VEGF TKI that was approved for advanced RCC in 2005 based on the TARGET trial which showed improvement of median progression-free survival (PFS) in sorafenib of 5.5 months compared to placebo at 2.8 months (HR, 0.44; 95% confidence interval [CI], 0.35 to 0.55;  $P < 0.01$ ) [7]. Furthermore, partial response was the best response seen in only 10% of patients compared to 2% in those who received placebo. Toxicities observed limited the routine first-line use of sorafenib.

Sunitinib became the mainstay of TKI monotherapy approved as first-line treatment for metastatic RCC in 2007. In a multicenter, randomized, phase 3 trial of sunitinib vs. interferon alfa in 750 patients with untreated metastatic RCC, sunitinib demonstrated longer PFS (11 months vs. 5 months;  $P < 0.001$ ) and a higher response rate (31% vs. 6%;  $P < 0.001$ ) compared to interferon alfa [8]. Pazopanib is another TKI later approved in 2009 [9] as first-line monotherapy in treatment-naïve and cytokine-pretreated patients with metastatic RCC. Its approval was based on demonstrated improvement in PFS (median PFS 9.2 months vs. 4.2 months;  $P < 0.001$ ) and tumor response rate (30% vs. 3%, respectively;  $P < 0.001$ ) compared to placebo. Notably, a more discernible benefit in PFS was observed in the treatment-naïve group (11.1 months vs. 2.8 months;  $P < 0.001$ ) [10].

Bevacizumab, a VEGF antibody, was studied as an adjunct to interferon alfa in comparison to interferon alfa monotherapy in a randomized, phase III trial in treatment-naïve metastatic clear cell RCC patients, and was approved as a combination therapy in 2009 [11]. While the primary endpoint of OS favored bevacizumab plus interferon alfa, it did not meet predefined criteria for significance but did show improved PFS (median PFS 8.5 months vs. 5.2 months;  $P < 0.001$ ) [12].

The COMPARZ trial demonstrated non-inferiority of pazopanib to sunitinib with regard to the primary endpoint of PFS (8.4 months vs. 9.5 months) [13]. A subsequent cross-over, randomized trial (PISCES) revealed a patient preference for pazopanib over sunitinib (70% vs. 22% vs. 8% no preference;  $P < 0.001$ ) given better health-related quality of life [14].

Cabozantinib emerged as a unique TKI with inhibition of multiple receptor tyrosine kinases including VEGF, MET, and AXL, which are involved in tumor cell proliferation and immune cell regulation. Cabozantinib is hypothesized to act synergistically with ICIs by promoting a more favorable immune environment in which ICIs are better able to have an effect [15, 16]. In the phase II CABOSUN trial comparing cabozantinib vs. sunitinib as initial treatment for patients with IMDC-defined intermediate- or poor-risk advanced RCC, investigator-assessed PFS favored cabozantinib vs. sunitinib (median 8.6 months vs. 5.3 months; two-sided  $P = 0.0008$ ), moving cabozantinib to the frontline for treatment of intermediate- or poor-risk untreated advanced RCC [17].

#### *mTOR Inhibitors*

mTOR inhibitors have been studied in both the first and subsequent-line settings. The pivotal trial that led to the approval of temsirolimus in 2007 [18] demonstrated an overall survival benefit of temsirolimus over interferon alfa monotherapy [19] but no benefit with temsirolimus plus interferon alfa in the first-line setting for patients with poor-risk metastatic RCC (10.9 months vs. 7.3 months vs. 8.4 months, respectively). On the basis of this trial, temsirolimus had initially been a preferred first-line treatment in poor-risk untreated advanced RCC, although the treatment landscape has since changed with the advent of data from cabozantinib and the use of ICI in this setting.

Everolimus has been largely relegated to the second-line setting based on the phase III RECORD-1 trial demonstrating prolonged PFS with everolimus compared to placebo (4.9 months vs. 1.9 months;  $P < 0.0001$ ), but with only a 1.8% overall response rates [20]. The use of everolimus in the second-line setting was further supported by results of the RECORD-3 trial, which compared first-line everolimus followed by second-line sunitinib to the standard order of first-line sunitinib followed by second-line everolimus. Everolimus failed to demonstrate noninferiority to sunitinib as the primary endpoint of PFS noninferiority was not met (21.1

months vs. 25.8 months) [21]. This led to the initial FDA approval of everolimus in the 2nd line setting in 2009.

#### *VEGF inhibitors in the subsequent-line setting*

Given the poor response rates with second-line mTOR inhibitors, several studies have attempted to elucidate the role of VEGF TKIs following progression on standard therapy. Axitinib was the first VEGF TKI to be studied compared to sorafenib in a phase III randomized trial in advanced RCC refractory to prior agents. The primary endpoint of PFS was met, favoring axitinib over sorafenib (6.7 months vs. 4.7 months;  $P < 0.0001$ ). The greatest benefit in PFS was seen in patients previously treated with cytokines (median PFS 12.1 months for axitinib vs. 6.5 months for sorafenib;  $P < 0.0001$ ), while those refractory to sunitinib were found to have worse PFS (median PFS 4.8 months for axitinib vs. 3.4 months for sorafenib;  $P = 0.0107$ ), [22] thus garnering FDA approval for axitinib in 2012.

The phase III METEOR trial comparing cabozantinib with everolimus in the second-line setting established cabozantinib as another standard of care treatment for advanced RCC refractory to first-line VEGF TKIs on the basis of increased OS (21.4 months vs. 17.1 months;  $P = 0.0002$ ), longer PFS (7.4 months vs. 3.9 months;  $P < 0.0001$ ), and increased objective response rate (ORR) (17% vs. 3%;  $P < 0.001$ ). Notably, cabozantinib is the only TKI to demonstrate benefit in all three endpoints following progression on VEGF TKIs [23, 24]. The trial results led to the initial FDA approval of cabozantinib in the 2nd line post-TKI failure setting [25].

Although VEGF inhibitors and mTOR inhibitors have improved response rates and prolonged PFS, resistance develops in almost all patients treated with these single-agent regimens [3]. Efforts to combine agents to avert resistance led to a randomized, phase II trial evaluating the combination of lenvatinib, a dual VEGFR-fibroblast growth factor receptor (FGFR) inhibitor and a multi-kinase inhibitor (including VEGF, RET and KIT), with the mTOR inhibitor everolimus in the second-line setting. In a 3-arm randomization of lenvatinib plus everolimus, lenvatinib alone, or everolimus alone, lenvatinib plus everolimus resulted in prolonged PFS (14.6 months vs. 5.5 months;  $P = 0.0005$ ) and median OS (25.5 months vs. 15.4 months;  $P = 0.024$ ) compared to everolimus alone [26]. This led to the FDA approval of the combination in 2016.

### Immune checkpoint Inhibitors

Nivolumab, a programmed death 1 (PD-1) inhibitor, was approved as second-line treatment of advanced RCC following failure of standard antiangiogenic treatment after demonstrating an OS benefit and fewer grade 3/4 adverse events in comparison to everolimus in the CheckMate 025 trial (25 months vs. 19.6 months;  $P < 0.002$ ) [27]. The CheckMate 214 trial further expanded on the previous success of nivolumab, comparing the combination of nivolumab and ipilimumab, a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, with sunitinib monotherapy in IMDC-defined intermediate- and poor-risk patients with previously untreated advanced RCC [28]. The combination demonstrated a higher 18-month OS rate of 75% vs. 60% (median OS not reached in the combination group vs. 26 months), and a higher ORR of 42% vs. 27%, favoring nivolumab plus ipilimumab over sunitinib monotherapy, effectively moving immunotherapy to the frontline setting for untreated advanced RCC after US FDA approval in April 2018 [29]. However, in an exploratory subgroup analysis of favorable-risk patients, sunitinib maintained a benefit in PFS (15.3 months vs. 25.1 months,  $P < 0.0001$ ) and ORR (29% vs. 52%;  $P = 0.0002$ ) compared to the combination regimen, preserving a role for TKIs in favorable-risk groups [30].

### EMERGING DATA ON VEGF INHIBITORS AND IMMUNE CHECKPOINT INHIBITORS (ICI)

The rationale regarding combination of VEGF inhibitors with immune checkpoint inhibitors centers on effects of VEGF-mediated immunosuppression by modifying the tumor microenvironment resulting in a decline in the Treg population as well as myeloid-derived suppressor cells [31]. Specifically, VEGF has been found to play a pivotal role in permissive immune suppression of the tumor microenvironment in part by enhancing PD-1 and other T-cell inhibitory checkpoints which theoretically could be reversed by the use of VEGF inhibitors [32]. In addition, tumor hypoxia with resultant recruitment of Treg cells poses an additional mechanism for immune evasion [33]. Thus, reversal of these immunosuppressive effects of VEGF through the use of VEGF inhibitors may further enhance the inherent T-cell mediated effects of the use of ICIs in this setting. Initial early phase combination trials were wrought with potential hepatotoxicity, limiting the development of combination trials such

as nivolumab with sunitinib or pazopanib [34] and pembrolizumab with pazopanib [35]. However, later combination trials with more selective agents and optimal dosing showed early safety and efficacy signals, leading to the further advancement into phase III randomized trials (see Table 1) that compared these combinations to the current standard of sunitinib in the first-line metastatic setting.

### A. IMMOTION 151: ATEZOLIZUMAB + BEVACIZUMAB VS. SUNITINIB

The combination of atezolizumab plus bevacizumab was compared to sunitinib in an earlier hypothesis-generating phase II trial, IMmotion 150, which randomized 305 patients to either atezolizumab plus bevacizumab vs. atezolizumab vs. sunitinib [36]. Cross-over was allowed after progression on atezolizumab or sunitinib monotherapy, with the primary endpoint of PFS in both intent-to-treat (ITT) analyses and patients with PD-L1+ in  $\geq 1\%$  of immune cells. While anti-tumor activity was observed and median PFS favored the combination of atezolizumab plus bevacizumab (14.7 months vs. 7.8 months), the PFS hazard ratio (HR) of 0.64 for atezolizumab plus bevacizumab vs. sunitinib in PD-L1+ patients was not statistically significant ( $P = .095$ ). However, mechanistic insights reveal overcoming resistance to immune checkpoint inhibitors is possible through VEGF inhibition [37]. Regardless, the results were encouraging enough to lead to further advancement to the randomized phase III trial, IMmotion 151. In this trial, atezolizumab plus bevacizumab vs. sunitinib were studied in the first-line setting for patients with previously untreated advanced or metastatic clear cell and/or sarcomatoid RCC [38]. The trial enrolled 915 patients with similar baseline characteristics who were stratified by MSKCC prognostic risk criteria, presence of liver metastases, and PD-L1+ expression in tumor tissue ( $< 1\%$  or  $> 1\%$  of immune cells). Patients were randomized to receive either atezolizumab plus bevacizumab or sunitinib monotherapy. The co-primary endpoints were PFS by investigator assessment in PD-L1+ patients and OS in the ITT population. Key secondary endpoints included PFS in ITT, OS in PD-L1+ patients, ORR, patient-reported outcomes (PROs), as well as safety profile. Of the ITT population, a majority of patients fell within the intermediate MSKCC risk category and 362 (40%) of the patients were PD-L1+. Notably, PD-L1+ patients who received

Table 1  
Ongoing Phase III trials utilizing the combination of VEGF TKIs and Immune Checkpoint Inhibitors (ICIs)

Trial	Mechanism of Action	Experimental Arms	Primary Endpoints	Secondary Endpoints	Associated Phase I/II trial
IMmotion 151 (NCT02420821) [38]	PD-L1 + TKI	Atezolizumab 1200 mg IV + bevacizumab 15 mg/kg IV q 3 weeks (6-week cycle) vs. sunitinib 50 mg daily (4 weeks on/2 weeks off) ( <i>n</i> = 915)	PFS in PD-L1+; OS in ITT	OS in PD-L1+; PFS in ITT; ORR, PROs, and safety in overall population	IMmotion 150 (NCT01984242) [36]
JAVELIN 101 (NCT02684006) [41]	PD-L1 + TKI	Avelumab 10 mg/kg IV q2 weeks + Axitinib 5 mg BID (6-week cycle) vs. sunitinib 50 mg daily (4 weeks on/2 weeks off) ( <i>n</i> = 886)	PFS, OS in PD-L1+	PFS in ITT; ORR, treatment-related AEs	JAVELIN 100 (NCT02493751)[40]
KEYNOTE-426 (NCT02853331) [43]	PD-1 + TKI	Pembrolizumab 200 mg IV q 3 weeks + axitinib 5 mg BID (6-week cycle) vs. sunitinib 50 mg daily (4 weeks on/2 weeks off) ( <i>n</i> = 840)	PFS, OS	ORR, DCR, DOR, PFS, OS, AEs	NCT02133742 [42]
KEYNOTE-581/ CLEAR (NCT02811861) [44]	PD-1 + TKI	Pembrolizumab 200 mg IV q 3 weeks + lenvatinib 20 mg/day vs. everolimus 5 mg/day + lenvatinib 18 mg/day vs. sunitinib 50 mg daily (4 weeks on/2 weeks off) ( <i>n</i> = 735)	PFS	ORR, OS, HRQOL, safety	NCT02501096 [45]

VEGF = vascular endothelial growth factor; TKI = tyrosine kinase inhibitor; PD-1 = programmed cell death protein 1; PD-L1 – programmed death-ligand 1; *n* = number; q = every; BID = twice a day; ORR = objective response rate; OS = Overall survival; PFS = progression-free survival; ITT = intention-to-treat population; PRO = patient-reported outcomes; AE = adverse event; DCR = disease control rate; DOR = duration of response; HRQOL = health-related quality of life.

atezolizumab plus bevacizumab had a PFS of 11.2 months (95% CI: 8.9–15.0) compared to 7.7 months for those who received sunitinib (95% CI: 6.8–9.7; HR: 0.74; *P* = 0.02). Similarly, the secondary endpoint of PFS in the ITT population was 11.2 months (95% CI: 9.6–13.3) in the atezolizumab plus bevacizumab arm compared to 8.4 months in the sunitinib arm (95% CI: 7.5–9.7; HR: 0.83; *P* = 0.02). For unclear reasons, PFS as assessed by independent review committee improved to a lesser degree for those in the atezolizumab plus bevacizumab arm as compared to the sunitinib arm alone in both the PD-L1+ (8.9 months vs 7.2 months, respectively) and ITT (9.6 months vs. 8.3 months, respectively) groups. The ORR for combination therapy was 43% in the PD-L1+ group and 37% in the ITT group compared to 35% and 33%, respectively, for those treated with sunitinib alone. Though median OS has yet to be reached, preliminary data favors combination therapy in both the PD-L1+ (HR: 0.67; *P* = 0.05) and ITT (HR: 0.83; *P* = 0.09) populations. Importantly, the safety profile and patient reported outcomes also favor atezolizumab plus bevacizumab over sunitinib [39]. Grade 3 or 4 treatment-related adverse events

occurred in 40% of patients in the atezolizumab plus bevacizumab arm compared to 54% in the sunitinib arm. 16% of patients treated with the combination required systemic corticosteroids within 30 days. Compared to those treated with sunitinib, patients who received the combination reported milder symptoms with overall better perceived quality of life. Given the significant improvement in PFS and the relatively favorable side-effect profile, the combination atezolizumab plus bevacizumab reflects well within the current treatment framework of mRCC.

## B. JAVELIN RENAL 101: AVELUMAB + AXITINIB VS. SUNITINIB

Early phase 1b results from the JAVELIN Renal 100 study showed feasibility of the combination of the PD-L1 inhibitor avelumab with axitinib [40]. This open-label, multicenter dose-finding trial showed objective responses in 6 out of 6 patients (100%, 95% CI: 54–100) in the initial dose-finding cohort and 26 out of 49 patients (53%, 38–68) in the dose-expansion cohort. These results paved the way for the phase III

trial, Javelin 101, comparing avelumab plus axitinib vs. sunitinib in 886 patients with treatment-naïve, advanced RCC, with updated data recently presented at the European Society of Medical Oncology (ESMO) 2018 conference [41]. Patients were stratified by PD-L1 expression, with 560 patients of the 886 randomized patients in the PD-L1+ group, and randomized in 1:1 fashion to receive either avelumab 10 mg/kg IV every 2 weeks plus axitinib 5 mg orally twice daily for a 6-week cycle or sunitinib 50 mg orally daily for 4 weeks on, followed by 2 weeks off. The co-primary endpoints were PFS and OS in patients with PD-L1+ tumor expression. Key secondary endpoints included PFS in the ITT population, ORR, and treatment-related adverse events. Among the PD-L1+ group, patients who received combination therapy had a median PFS of 13.8 months vs. 7.2 months in those who received sunitinib, corresponding to a 39% reduction in disease progression or death in the avelumab plus axitinib arm compared to the sunitinib arm (HR: 0.61,  $P = .001$ ). Notably, median PFS in the overall population was similar to that of the PD-L1+ group with a PFS of 13.8 months in the avelumab plus axitinib arm compared to 8.4 months in the sunitinib arm (HR: 0.61,  $P = 0.001$ ). ORR improved significantly irrespective of PD-L1 status in the overall population. Similar rates of treatment-related adverse events occurred among both treatment arms. Median duration of response and OS have yet to be reached, however current data favors treatment with the combination.

### **C. KEYNOTE-426: PEMBROLIZUMAB + AXITINIB VS. SUNITINIB**

Axitinib was combined with the anti-PD-1 antibody, pembrolizumab, in an initial dose-finding phase Ib trial that enrolled 52 patients with treatment-naïve, metastatic clear cell renal cell carcinoma and good performance status [42]. In the dose-finding phase, the primary endpoint was maximum tolerated dose (MTD) as determined by dose-limiting toxicity (DLT) in the first 2 cycles (6 weeks). 3 of the 11 patients had DLTs, rendering a MTD of axitinib 5 mg twice daily and pembrolizumab 2 mg/kg every 3 weeks.

This was followed by a dose-expansion phase, in which an additional 41 patients were enrolled, with a vast majority of patients meeting IMDC criteria of favorable or intermediate-risk disease. The side effect profile was favorable, with hypertension

as the most common adverse event (23.1%), and lower rates of fatigue (13.4%) and hepatotoxicity (11.5%) compared to previous trials utilizing VEGF inhibitors and PD-1 inhibitors. Best overall response was a complete response in 4 patients (7.7%), partial response in 34 (65.4%), and stable disease in 8 patients (15.4%). The median PFS was 20.9 months (95% CI), but median OS was not reached at a minimum follow-up of 17.6 months. The encouraging findings from this early-phase study led to an open-label phase III multicenter study, KEYNOTE-426, comparing the combination of pembrolizumab plus axitinib to sunitinib in patients with advanced or metastatic renal cell carcinoma (mRCC). Accrual has completed in 840 patients randomly assigned in a 1:1 fashion to receive pembrolizumab 200 mg every 3 weeks plus axitinib 5 mg twice daily or sunitinib 50 mg once daily for 4 weeks, followed by 2 weeks off. Based on the first interim analysis by the independent Data Monitoring Committee, the combination of pembrolizumab plus axitinib resulted in statistically significant improvements in OS and PFS compared to sunitinib monotherapy [43]. Full results are anticipated to be reported at the 2019 ASCO Genitourinary Cancers Symposium.

### **D. KEYNOTE-581/CLEAR: LENVATINIB + EVEROLIMUS VS. PEMBROLIZUMAB + LENVATINIB VS. SUNITINIB**

KEYNOTE-581/CLEAR is a multicenter, open-label, phase III study evaluating the efficacy and safety of lenvatinib in combination with everolimus, compared to the combination of pembrolizumab plus lenvatinib, and sunitinib monotherapy as first-line treatment for advanced renal cell carcinoma [44]. An early phase 1b/II trial of lenvatinib plus pembrolizumab in patients with solid tumors showed impressive efficacy data with an ORR of 66.7% (95% CI, 47.2–82.7) and a median PFS of 17.7 months (95% CI, 9.6–NE), [45] leading to the current phase III trial of KEYNOTE-581/CLEAR. Enrolled patients (target enrollment of 735 patients) were randomized 1:1:1 to three arms including lenvatinib 18 mg/day plus everolimus 5 mg/day, lenvatinib 20 mg/day plus pembrolizumab 200 mg every three weeks, or sunitinib 50 mg/day in a 4-week on, 2-week off cycle. The primary endpoint of the trial is PFS lenvatinib plus everolimus or lenvatinib plus pembrolizumab over single-agent sunitinib, as first-line treatment for advanced RCC in improving PFS. Sec-

ondary endpoints include the ORR, OS, health related quality of life, and safety profiles. Further exploratory endpoints compare duration of response, disease control rate, and clinical benefit rate between groups, as well as analysis of the relationship between blood biomarkers and outcome. There is no planned interim analysis.

### E. TIVOZANIB + NIVOLUMAB

Tivozanib is a highly specific VEGF TKI known to have a lower incidence of class effect adverse events. In a phase II cross-over trial with sorafenib, tivozanib demonstrated potent anti-tumor activity with acceptable safety profiles [46]. Given its high specificity and favorable safety profile, it has been explored as a possible combination treatment with immune checkpoint inhibition. In a phase Ib/II study, tivozanib is studied in combination with the ICI, nivolumab [47].

In the now-complete phase Ib portion, two dose levels of tivozanib, 1.0 mg and 1.5 mg, once daily for 21 days were studied in combination with nivolumab 240 mg every 14 days in a 28-day cycle. In the phase Ib trials, 18 patients were enrolled and none experienced a DLT. Patients progressing to phase II received 1.5 mg of tivozanib. While all of the enrolled patients experienced some adverse effect, a majority were limited to grades 1-2. Of the 5 patients (38%) who experienced grade 3-4 adverse events, one had significant malignant hypertension that was complicated by seizure. Other grade 3-4 adverse events included pneumonitis, stomatitis, and elevated ALT. Hypertension, asthenia and mucositis of all grades each occurred in 31% of patients. As hypothesized, the combination of highly specific tivozanib with nivolumab appears to be a safe approach to combination therapy with both drugs administered at a full dose, although current data is limited and should be interpreted with caution. As the study enrolls additional patients for the phase II portion, additional data will allow for analysis of efficacy.

### DISCUSSION

The treatment landscape for advanced renal cell carcinoma has evolved considerably since the introduction of TKIs. However, the role of TKI monotherapy and immunotherapy has shifted based on the approval of nivolumab and ipilimumab as well as cabozantinib in the frontline settings. While

the combination of nivolumab and ipilimumab comprises current first-line treatment in intermediate- and poor-risk patients, there remains a role for TKI monotherapy in favorable-risk populations, as demonstrated in the subgroup analyses of the CheckMate214 trial [30]. Furthermore, cabozantinib has emerged as a new frontline TKI after being studied in a similar population as the CheckMate 214 trial. Although it has garnered the same FDA approval as nivolumab plus ipilimumab, it is theoretically not limited to only intermediate- or poor-risk patients based on its unique mechanism involving VEGF, MET, and AXL inhibition. TKI monotherapy may move to the second-line setting based on retrospective data showing a benefit in those with progressive disease following initial therapy with ICIs [48]. This is particularly relevant given the implications of sequencing regimens if patients fail first-line therapies with immunotherapy and TKI combinations.

Building upon the success of previous regimens that took advantage of complementary mechanisms of action, such as CTLA-4 inhibition and PD-1 inhibition, there is a strong rationale for combining VEGF inhibitors and immunotherapy based on the enhancement of ICI T-cell mediated effects of VEGF-mediated immunosuppression. Based on the trials discussed above, VEGF inhibition plus immunotherapy increases response rate, tumor shrinkage rates, and PFS compared to immunotherapy combinations alone, with suggestions that this may extend to OS benefits as well. The addition of VEGF inhibitors also extends benefit to favorable-risk patients compared to intermediate- and poor-risk patients with immunotherapy combinations alone. With improvement in PFS and OS, complete response (CR) may become a new benchmark for determining efficacy of these regimens. To this end, combinations utilizing VEGF inhibitors with PD-1 inhibitors and CTLA-4 inhibitors are underway and appear to be feasible [49].

With evolving treatment combinations, potential toxicities of combination therapy must be considered carefully. Previous combination trials with VEGF inhibitors and immune checkpoint inhibitors have revealed high toxicity levels, leading to an increased effort to find at least additive antitumor activity in treatment-naive patients with advanced renal cell carcinoma. In CheckMate016, the combinations of sunitinib compared to pazopanib with nivolumab showed unacceptable toxicity levels precluding further study of these combination regimens. However, the potentially increased toxicities seen with these

Table 2  
Select early-phase trials utilizing the combination of VEGF TKIs and Immune Checkpoint Inhibitors (ICIs)

Trial	Phase	Mechanism of Action	Experimental Arms	Primary Endpoints	Secondary Endpoints	Associated Phase III trial
NCT03136627 [47]	Ib/II	PD-1 + TKI	Tivozanib 1.5 mg daily x21 days (of a 28-day cycle) + nivolumab 240 mg IV q 14 days ( <i>n</i> = 28)	MTD/DLT	Disease status q3 months in months 1–12, then q6 months	N/A
NCT02496208 [49]	Ib	PD-1 + TKI ± CTLA-4	Nivolumab 3 mg/kg q 14 days + cabozantinib 40 mg daily ( <i>n</i> = 49) ± ipilimumab 1 mg/kg q 21 days × 4 doses ( <i>n</i> = 29)	MTD/DLT; ORR	PFS	CHECKMATE 9ER (NCT03141177)[50]
COSMIC-021 (NCT03170960) [16]	Ib	PD-L1 + TKI	Cabozantinib 40 mg daily + atezolizumab 1200 mg q3 wk ( <i>n</i> = 12)	Dose Escalation: MTD/RD Dose Expansion: ORR	AEs and SAEs	N/A

VEGF = vascular endothelial growth factor; TKI = tyrosine kinase inhibitor; CTLA-4 = cytotoxic T-lymphocyte associated protein 4 antibody; *n* = number; q = every; MTD = maximum tolerated dose; DLT = dose-limiting toxicity; RD = recommended dose; AE = adverse event; SAE = serious adverse event; ORR = objective response rate; OS = Overall survival; PFS = progression-free survival; PD-1 = programmed cell death protein 1; PD-L1 – programmed death-ligand 1.

combination regimens will need to be weighed against the benefit gained in PFS and CR.

Finally, it is important to note that the majority of patients studied in established trials had a clear-cell histology with favorable- or intermediate-risk disease. Therefore, it is difficult to ascertain how these regimens compare in the setting of different histologic classifications and risk categories of disease, and this is a potential future area of research.

## FUTURE DIRECTIONS

The next wave of standard of care treatment will likely come in the form of trials that utilize the combination of ICIs with VEGF TKIs (see Table 2). Given the rapidly evolving field, current trials that utilize sunitinib alone as the control arm may soon no longer be suitable. On the other hand, questions remain regarding sequencing since these treatments are not expected to work indefinitely. Further understanding of different molecular signatures and biomarker expression in tailoring treatment may be helpful in stratifying patients to different modalities of treatment. Furthermore, combination therapies capitalize on the ability of VEGF TKIs in affecting tumors with high expression of a myeloid inflammatory signature compared to low myeloid suppression since these myeloid-derived suppressor cells are considered barriers to effective cancer immunotherapy effect. In addition, certain VEGF TKIs such as cabozantinib can mediate rapid remodeling of myeloid cells from an immunosuppressive to an antitumor phenotype with priming of circulating cytotoxic NK and T cells [15]. Cabozantinib is increasingly being combined

with other ICIs [16, 49, 50]. There are certainly implications of sequencing different agents after immune checkpoint inhibitor drugs have been exhausted. While there are insufficient data to suggest optimal outcomes with VEGF TKI treatment post-ICI therapy failure, small retrospective datasets suggest some response can still be seen [48, 51]. Further investigation into combination treatments and use of novel drugs with non-overlapping mechanisms of action would be of paramount importance.

## CONCLUSIONS

The treatment landscape for advanced and metastatic RCC is rapidly evolving. While the ICI combination of nivolumab and ipilimumab has changed the first-line treatment of metastatic RCC with intermediate- and poor-risk disease, the additional option of adding VEGF TKIs to immunotherapy serves as the next wave of revolutionary change in the landscape of treatment for advanced RCC given encouraging results. Established prognostic risk models, analysis of gene expression signatures, and further refinement of prognostic biomarkers will serve to further inform decisions on optimal treatment regimens for patients in the future.

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## CONFLICT OF INTEREST

AN, LR, BG have no conflicts to declare. JBAC serves on the Speakers' Bureau of Bristol Myers Squibb.

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