

# VEGF Inhibitors in Renal Cell Carcinoma

Pankit Vachhani, MD, and Saby George, MD

Dr Vachhani is a hematology and oncology fellow and Dr George is an associate professor in the Department of Medicine at Roswell Park Cancer Institute in Buffalo, New York.

Corresponding author:  
Pankit Vachhani, MD  
Department of Medicine  
Roswell Park Cancer Institute  
Elm and Carlton Streets  
Buffalo, NY 14263  
Tel: (716) 845-3880  
Fax: (716) 845-4620  
E-mail: [pankit.vachhani@roswellpark.org](mailto:pankit.vachhani@roswellpark.org)

**Abstract:** The arrival of targeted therapies—vascular endothelial growth factor (VEGF) pathway inhibitors and mammalian target of rapamycin (mTOR) inhibitors—and programmed death 1 (PD-1) inhibitors has transformed the management of renal cell carcinoma (RCC). Once considered fatal, with a median survival of approximately 1 year, these agents have nearly tripled overall survival and have raised hopes of a possible cure for advanced RCC. This review begins with a brief discussion of the seminal von Hippel-Lindau/hypoxia-inducible factor axis in RCC. It then discusses the pivotal trials that have investigated VEGF inhibitors in metastatic RCC, as well as in adjuvant and neoadjuvant settings. Finally, it addresses some practical considerations and future directions in the use of VEGF inhibitors in RCC.

## Introduction

The last decade has witnessed tremendous advances in the management of renal cell carcinoma (RCC). Interleukin 2 (IL-2) and interferon alfa (IFN- $\alpha$ ), the staple treatments for metastatic RCC (mRCC) from the 1980s to 2005, have been largely relegated to history. IL-2 and IFN- $\alpha$  provided response rates in the range of 5% to 20% and led to a median overall survival (OS) of approximately 10 to 15 months.<sup>1-5</sup> Between 2005 and 2016, however, the US Food and Drug Administration (FDA) approved 10 novel drugs for the treatment of mRCC. Unprecedented results, in the form of overall response rates (ORRs) of 20% to 40% and a median OS of greater than 24 months, have been noted.<sup>6,7</sup> These FDA-approved drugs belong to 3 large categories: (1) vascular endothelial growth factor (VEGF) inhibitors (Table 1), (2) mammalian target of rapamycin (mTOR) inhibitors, and (3) programmed death 1 (PD-1) inhibitors. The VEGF inhibitors are sorafenib (Nexavar, Bayer), sunitinib (Sutent, Pfizer), bevacizumab (Avastin, Genentech), pazopanib (Votrient, Novartis), axitinib (Inlyta, Pfizer), cabozantinib (Cometriq, Exelixis), and lenvatinib (Lenvima, Eisai); the mTOR inhibitors are everolimus (Afinitor, Novartis) and temsirolimus (Torisel, Pfizer); and the anti-PD-1 agent is nivolumab (Opdivo, Merck). Both the VEGF and mTOR inhibitors constitute targeted therapies, and, with the exceptions of bevacizumab and temsirolimus, they are all oral agents. This review briefly discusses the key pathogenic von Hippel-Lindau (VHL) pathway in RCC before delving into a discussion of the pivotal clinical trials that have contributed to the approval of various VEGF inhibitors.

### Keywords

mTOR inhibitors, programmed death 1 inhibitors, RCC, renal cell carcinoma, VEGF inhibitors, VEGFR

**Table 1.** Anti-VEGF Inhibitors in Renal Cell Carcinoma and Approved Doses

Drug	FDA Approval Date	Line of Therapy	Recommended Starting Dose	Comments
Sorafenib	December 20, 2005	1st	400 mg orally twice daily	Obsolete in current practice; drug of choice in resource-limited setting
Sunitinib	January 26, 2006	1st	50 mg orally once daily for 4 weeks of a 6-week cycle (4 weeks on, 2 weeks off)	Frontline drug of choice along with pazopanib; 2-weeks on, 1-week off schedule may be used
Bevacizumab	July 31, 2009	1st	10 mg/kg intravenously every 2 weeks	Obsolete in current practice; given in combination with interferon
Pazopanib	October 19, 2009	1st	800 mg orally daily	Frontline drug of choice along with sunitinib
Axitinib	January 27, 2012	2nd	5 mg orally twice daily	Use likely to decrease given approval of nivolumab, cabozantinib, and lenvatinib
Cabozantinib	April 25, 2016	2nd	60 mg orally daily	Exact sequence in comparison to lenvatinib and nivolumab needs to be determined; may come in frontline setting
Lenvatinib	May 13, 2016	2nd	18 mg orally daily	Exact sequence in comparison to cabozantinib and nivolumab needs to be determined; given in combination with everolimus

FDA, US Food and Drug Administration; VEGF, vascular endothelial growth factor.

### VHL/HIF Axis in Clear Cell RCC

The advances in the management of mRCC can be directly traced back to the identification of the *VHL* gene on chromosome 3, cytoband 3p25-26, which is a tumor suppressor gene involved in the pathogenesis of VHL disease.<sup>8,9</sup> Various studies have shown that somatic biallelic inactivation of *VHL*, from either mutations or hypermethylation, occurs in approximately 50% or more of sporadic clear cell RCC, which constitutes approximately 70% of all RCC.<sup>10-14</sup> Additionally, loss of heterozygosity of *VHL* has been noted in up to 98% of patients with sporadic RCC.<sup>13,15</sup>

Under conditions of normoxia, the protein product of *VHL* inhibits hypoxia-inducible factor (HIF)—a heterodimeric transcription factor consisting of an unstable  $\alpha$  subunit (HIF-1 $\alpha$ , HIF-2 $\alpha$ , or HIF-3 $\alpha$ ) and a stable  $\beta$  subunit (HIF-1 $\beta$ ).<sup>16-18</sup> The HIF inhibition is secondary to hydroxylation of HIF- $\alpha$  by prolyl hydroxylases (PHDs) and factor-inhibiting HIF (FIH). HIF- $\alpha$  hydroxylation allows VHL to bind to it and to elongin C, which recruits elongin B, cullin 2 (CUL2), and ring-box 1 (RBX1) of an E3 ubiquitin ligase.<sup>19,20</sup> This helps target the HIF- $\alpha$  for polyubiquitination and degradation by the 26S proteasome.<sup>19,21</sup> However, under hypoxia, HIF- $\alpha$  hydroxylation is prevented.<sup>19</sup> VHL does not bind to unhydroxylated

HIF- $\alpha$ , which then accumulates in the cell.<sup>22,23</sup> HIF-1 $\alpha$  and HIF-2 $\alpha$  are stabilized by heterodimerization with HIF- $\beta$ .<sup>19</sup> This HIF- $\alpha/\beta$  complex binds to hypoxia response elements on DNA, recruits coactivators, and leads to transcription of target genes that include VEGF, platelet-derived growth factor (PDGF), transforming growth factor  $\alpha$  (TGF- $\alpha$ ), insulin-like growth factor (IGF), and epidermal growth factor receptor (EGFR).<sup>23</sup>

Overall, these genes are implicated in angiogenesis, pH regulation, glycolysis, glucose transport, cell cycle, chemotaxis, signaling, and apoptosis.<sup>19,24,25</sup> Thus, in patients with RCC who have had biallelic inactivation of VHL, there is increased transcription of HIF-targeted genes.

VEGF, which is one such protein with increased expression in such conditions, is a potent mediator of angiogenesis. It binds to VEGF receptor (VEGFR) on endothelial cells, leading to increased vascular permeability; inducing endothelial cell proliferation, survival, migration, and differentiation; and promoting degradation of extracellular matrix around endothelial cells.<sup>19,26</sup> This explains why VEGF inhibitors have seen tremendous success in RCC. Similarly, the efficacy of mTOR inhibitors is explained by the fact that HIF- $\alpha$  expression is mTOR-dependent. These pathways, including their various intricate details and their clinical implications, have been reviewed in many excellent papers.<sup>10,11,19,24,27,28</sup>

Also, work from The Cancer Genome Atlas (TCGA) Research Network helped to identify 19 significantly mutated genes in clear cell RCC.<sup>29</sup> In that landmark TCGA study and subsequent analysis, upregulation of the pentose phosphate pathway and fatty acid synthesis pathway genes, and downregulation of the tricarboxylic acid (TCA) cycle genes, were shown to correlate with worse survival.<sup>30</sup> A detailed description of those findings, the recently created comprehensive metabolomics dataset, and the demonstration of intratumoral heterogeneity—all of which can guide the design of future therapies, and aid in the understanding of treatment failures and differential responses—are beyond the scope of this review.<sup>29-32</sup>

### VEGF Inhibitors in mRCC

The low response rates and meager or absent improvements in survival outcomes with nonspecific therapies such as cytokines, chemotherapy, and their combination left much room for improvement.<sup>33-37</sup> In this context, VEGF pathway inhibitors represented rational treatments. To date, these VEGF inhibitors belong to either of the 2 main classes; bevacizumab is a monoclonal antibody and all the rest are tyrosine kinase inhibitors (TKIs). Below, we discuss the pivotal trials that contributed to the FDA approval of these drugs in the management of RCC (Table 2). IFN- $\alpha$  served as the control in the first few trials, given its demonstrated survival advantage. However, with the emergence of data as shown below, IFN- $\alpha$  as a control was fast replaced by VEGF pathway inhibitors such as sunitinib in the first-line setting, and sorafenib or an mTOR inhibitor such as everolimus in the second-line setting.

#### **Sorafenib**

Sorafenib is an orally administered TKI that inhibits VEGFR, PDGF receptor  $\beta$  (PDGFR- $\beta$ ), FMS-like tyrosine kinase 3 (FLT3), c-KIT protein, RAF, and RET receptor tyrosine kinases.<sup>38-40</sup> Sorafenib demonstrated tolerability in various phase 1 studies.<sup>41-44</sup> Similarly, a phase 2 study showed that the drug was well tolerated and had significant disease-stabilizing activity; the PFS was 29 weeks.<sup>45</sup>

TARGET (Study of BAY43-9006 in Patients With Unresectable and/or Metastatic Renal Cell Cancer), the randomized, double-blind, placebo-controlled phase 3 study, recruited patients with histologically confirmed clear cell mRCC who had progressed after 1 systemic treatment.<sup>38</sup> Those with high-risk RCC as per Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score were excluded. A total of 903 patients were randomly assigned to receive either sorafenib or placebo. The first preplanned interim analysis via independent assessment demonstrated that patients in the sorafenib group had significantly improved progression-free survival (PFS) compared with those in the placebo group

(5.5 vs 2.8 months; hazard ratio [HR], 0.44; 95% CI, 0.35-0.55;  $P < .001$ ). This result led to the halting of the trial, the decision to allow patients who had received placebo to receive sorafenib, and FDA approval of the drug. The overall response rate (ORR) was 10% for sorafenib and 2% for placebo. OS data favored sorafenib over placebo just prior to crossover (HR, 0.71;  $P = .015$ ) and approximately 6 months later (HR, 0.77;  $P = .015$ ), but neither finding was statistically significant, according to the O'Brien-Fleming threshold. In the final analysis done 16 months after crossover, OS in the sorafenib group was not superior to placebo (17.8 vs 15.2 months; HR, 0.88; 95% CI, 0.74-1.04;  $P = .146$ ) by intent-to-treat analysis.<sup>46</sup> However, when results were analyzed after censoring of placebo-assigned patients, treatment with sorafenib was associated with significantly improved OS compared with placebo (17.8 vs 14.3 months; HR, 0.78; 95% CI, 0.62-0.97;  $P = .0287$ ). Univariate analyses of VEGF levels vs outcome in placebo-treated patients showed that VEGF levels correlated inversely with PFS ( $P = .0013$ ) and OS ( $P = .0009$ ). Through multivariate analyses, baseline VEGF level was an independent prognostic factor for OS in both placebo-treated and sorafenib-treated patients. Using the 25th and 75th percentiles to define low vs high VEGF levels, the investigators noted that sorafenib benefited those with high VEGF levels more than those with low VEGF levels (HR, 0.27 vs 0.58, respectively). Grade 3 or 4 toxicities were noted in 29% of all patients who took sorafenib, with hand-foot syndrome, hypertension, fatigue, and diarrhea being the main adverse events (AEs). A retrospective subgroup analysis showed that PFS was similar in younger patients (<70 years; 23.9 weeks; HR, 0.55; 95% CI, 0.47-0.66) and older patients ( $\geq 70$  years; 26.3 weeks; HR, 0.43; 95% CI, 0.26-0.69).<sup>47</sup> Clinical benefit rates (complete response + partial response + stable disease) among younger and older sorafenib-treated patients also were similar. AEs were manageable regardless of age. However, gastrointestinal AEs were more frequent in older than younger patients among those treated with sorafenib.

#### **Sunitinib**

Sunitinib inhibits VEGFR and PDGFR besides having activity against RAF, fibroblast growth factor receptor (FGFR), FLT3, KIT, and FMS receptors.<sup>48</sup> A phase 1 trial in advanced malignancies showed that sunitinib had manageable toxicities.<sup>49</sup> However, it was the impressive results from a phase 2 trial showing an ORR of 34% (95% CI, 25%-44%) that drew attention and propelled the drug ahead.<sup>50</sup>

In the international, multicenter phase 3 trial, 750 patients with previously untreated mRCC with a clear cell histologic component were enrolled.<sup>51,52</sup> Patients were randomly assigned to receive either repeated 6-week cycles

**Table 2.** Pivotal Randomized Phase 2/3 Clinical Trials of VEGF Inhibitors in Renal Cell Carcinoma

Trial	Line of Therapy, Phase, n	Disease Setting	Treatment Arms	Results		
				ORR	PFS	OS
TARGET; NCT00073307	2nd, 3, 903	Met CC RCC	Sor vs p	10% (Sor) vs 2% (p)	5.5 mo (Sor) vs 2.8 mo (p); HR, 0.44; <i>P</i> <.01	17.8 mo (Sor) vs 15.2 mo (p); HR, 0.88; <i>P</i> =.146
NCT00098657 and NCT00083889	1st, 3, 750	Met RCC w CC compo- nent	Sun vs I	47% (Sun) vs 12% (I); <i>P</i> <.001	11 mo (Sun) vs 5 mo (I); HR, 0.539; <i>P</i> <.001	26.4 mo (Sun) vs 21.8 mo (I); HR, 0.821; <i>P</i> =.051
AVOREN; NCT00738530	1st, 3, 649	Met RCC w >50% CC histology	B + I vs I + p	31% (B + I) vs 13% (I + p); <i>P</i> =.0001	10.2 mo (B + I) vs 5.4 mo (I + p); HR, 0.63; <i>P</i> =.0001	23.3 mo (B + I) vs 21.3 mo (I + p); HR, 0.91; <i>P</i> =.3360
CALGB 90206; NCT00072046	1st, 3, 732	Met RCC w CC compo- nent	B + I vs I	25.5% (B + I) vs 13.1% (I); <i>P</i> <.0001	8.5 mo (B + I) vs 5.2 mo (I); HR, 0.71; <i>P</i> <.0001	18.3 mo (B + I) vs 17.4 mo (I); HR, 0.86; <i>P</i> =.069
VEG105192; NCT00334282	1st or cytokine pretreated, 3, 435	Locally adv or met CC or pred CC RCC	Pazo vs p	30% (Pazo) vs 3% (p); <i>P</i> <.001	9.2 mo (Pazo) vs 4.2 mo (p); HR, 0.46; <i>P</i> <.0001	22.9 mo (Pazo) vs 20.5 mo (p); HR, 0.91; <i>P</i> =.224
COMPARZ; NCT00720941	1st, 3, 1110	Adv or met RCC w CC component	Pazo vs Sun	31% (Pazo) vs 25% (Sun); <i>P</i> =.03	8.4 mo (Pazo) vs 9.5 mo (Sun); HR, 1.05	28.3 mo (Pazo) vs 29.1 mo (Sun); HR, 0.92; <i>P</i> =.24
AXIS; NCT00678392	2nd, 3, 723	Met CC RCC	Axi vs Sor	23% (Axi) vs 12% (Sor); <i>P</i> =.0001	8.3 mo (Axi) vs 5.7 mo (Sor); HR, 0.656; 95% CI, 0.552-0.779; <i>P</i> <.0001	20.1 mo (Axi) vs 19.2 mo (Sor); HR, 0.969; <i>P</i> =.3744
NCT00920816	1st, 3, 288	Met RCC w CC compo- nent	Axi vs Sor	32% (Axi) vs 15% (Sor); <i>P</i> =.0006	10.1 mo (Axi) vs 6.5 mo (Sor); HR, 0.77; <i>P</i> =.038	21.7 mo (Axi) vs 23.3 mo (Sor); HR, 0.995; <i>P</i> =.4883
METEOR; NCT01865747	≥2nd (≥1 VEGFR- targeting TKI), 3, 658	Adv or met RCC w CC component	Cabo vs E	17% (Cabo) vs 3% (E); <i>P</i> <.0001	7.4 mo (Cabo) vs 3.9 mo (E); HR, 0.51; <i>P</i> <.0001	21.4 mo (Cabo) vs 16.5 mo (E); HR, 0.66; <i>P</i> =.00026
NCT01136733	2nd (1 prior VEGF-tar- geted tx), 2, 153	Adv or met CC RCC	L vs E vs L + E	43% (L + E) vs 6% (E) vs 27% (L), w <i>P</i> <.0001 for L + E vs E; <i>P</i> =.10 for L vs E; <i>P</i> =.0067 for L vs L + E	14.6 mo (L + E) vs 5.5 mo (E); HR, 0.40; <i>P</i> =.0005; 14.6 mo (L + E) vs 7.4 mo (L); HR, 0.66; <i>P</i> =.12	25.5 mo (L + E) vs 19.1 mo (L) vs 15.4 mo (E); HR, 0.59; <i>P</i> =.065 for L + E vs E

adv, advanced; Axi, axitinib; B, bevacizumab; Cabo, cabozantinib; CC, clear cell histology; E, everolimus; HR, hazard ratio; I, IFN- $\alpha$ ; L, lenvatinib; mo, months; met, metastatic; ORR, overall response rate; OS, overall survival; p, placebo; Pazo, pazopanib; PFS, progression-free survival; pred, predominately; RCC, renal cell carcinoma; Sor, sorafenib; Sun, sunitinib; TKI, tyrosine kinase inhibitor; tx, treatment; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; w, with.

of sunitinib (daily for 4 weeks, then 2 weeks off; 4/2) or IFN- $\alpha$ . Prespecified dose reductions of sunitinib and IFN- $\alpha$  were allowed for management of AEs. The ORR was 47% (95% CI, 42%-52%) for sunitinib vs 12% (95% CI, 9%-16%) for IFN- $\alpha$  ( $P<.001$ ). PFS was 11 months (95% CI, 11-13 months) in the sunitinib group compared with 5 months (95% CI, 4-6 months) in the IFN- $\alpha$  group (HR, 0.539; 95% CI, 0.451-0.643;  $P<.001$ ). There was a trend toward better OS in the sunitinib group (26.4 months; 95% CI, 23.0-32.9 months) than in the IFN- $\alpha$  group (21.8 months; 95% CI, 17.9-26.9 months), but it did not reach statistical significance (HR, 0.821;  $P=.051$ ). When 25 patients from the IFN- $\alpha$  group who had crossed over to receive sunitinib on study were censored, the OS was 26.4 months (95% CI, 23.0-32.9 months) for those in the sunitinib group vs 20.0 months (95% CI, 17.8-26.9 months) for those in the IFN- $\alpha$  group, which was a statistically significant difference (HR, 0.808;  $P=.036$ ). Further, in the subset of patients who did not receive any cancer treatment after the study, the investigators found that OS was significantly improved with sunitinib vs IFN- $\alpha$  only (28.1 vs 14.1 months; HR, 0.647;  $P=.003$ ). Thus, these analyses confirmed the hypothesis that the OS benefits of sunitinib had been confounded by crossover treatment and by the use of anticancer agents after the study. Sunitinib also was well tolerated. Major grade 3 AEs included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%); none of these reached grade 4 severity. Major grade 3 or 4 laboratory abnormalities were neutropenia, lymphopenia, and lipase elevation (all 18%) for the sunitinib group. Quality of life (QOL) was significantly better with sunitinib than with IFN- $\alpha$ .<sup>53</sup>

Nevertheless, the high occurrence rate of any-grade AEs such as diarrhea (61%), fatigue (54%), and nausea (52%) and of laboratory abnormalities such as neutropenia (77%), anemia (79%), thrombocytopenia (68%), and increased creatinine (70%) led to testing of alternative schedules and dose intensities. Of note, a large, multicenter, retrospective analysis (the RAINBOW study) investigated sunitinib administration in a 2-weeks-on, 1-week-off (2/1) schedule.<sup>54</sup> A total of 208 patients started sunitinib on the 4/2 schedule and then were switched to the 2/1 schedule because of toxicity (group 4/2 $\rightarrow$ 2/1), and 41 patients started first-line sunitinib with the 2/1 schedule because of suboptimal clinical conditions (group 2/1). A total of 211 patients treated with the 4/2 schedule (group 4/2) served as external controls. Median PFS was 30.2, 10.4, and 9.7 months in the 3 groups, respectively. Median OS was not reached, 23.2 months, and 27.8 months, respectively. The incidence of grade 3 or higher toxicities was significantly reduced (45.7% to 8.2%;  $P<.001$ ) after the switch to the 2/1 schedule in group 4/2 $\rightarrow$ 2/1. The results indicated that the overall safety

profile also improved after those patients switched to the 2/1 schedule, and no decrease in efficacy was seen. An ongoing prospective study (NCT02060370) may confirm this finding.

In another retrospective study, of 186 patients with mRCC who were treated with sunitinib alone or in combination, 34 patients (18%) were identified who either had a durable complete response or remained progression-free while receiving sunitinib for more than 18 months. A lack of bone or lung metastasis and good MSKCC risk status were predictive for durable PFS.<sup>55</sup>

### **Bevacizumab**

Unlike the VEGF receptor inhibitors, bevacizumab is a humanized monoclonal antibody that inhibits VEGF. Bevacizumab demonstrated clinical activity in multiple phase 2 studies.<sup>56-59</sup> PFS in previously untreated patients was 8.5 months in one study, and another study found that PFS in previously treated patients was significantly improved with bevacizumab monotherapy vs placebo (4.8 vs 2.5 months; HR, 0.39,  $P<.001$ ).<sup>56,59</sup> Two major phase 3 trials were conducted on the back of these findings.

In the double-blind AVOREN trial (A Study of Avastin Added to Interferon Alfa-2a Therapy in Patients With Metastatic Renal Cell Cancer With Nephrectomy), 649 previously untreated patients with predominantly (>50%) clear cell mRCC were randomly assigned (1:1) to receive bevacizumab plus IFN- $\alpha$  to progression or for a maximum of 52 weeks, or placebo plus IFN- $\alpha$ .<sup>60,61</sup> PFS was improved in the bevacizumab plus IFN- $\alpha$  group (10.2 vs 5.4 months; HR, 0.63; 95% CI, 0.52-0.75;  $P=.0001$ ) irrespective of MSKCC risk group. Censoring patients on the day they received subsequent therapy had no effect on the efficacy of bevacizumab (HR, 0.62). The ORR was significantly higher with bevacizumab plus IFN- $\alpha$  (31% vs 13%;  $P=.0001$ ). OS was 23.3 months with bevacizumab plus IFN- $\alpha$  and 21.3 months with IFN- $\alpha$  plus placebo (unstratified HR, 0.91; 95% CI, 0.76-1.10; stratified HR, 0.86; 95% CI, 0.72-1.04). Treatment after the protocol in both arms may have confounded OS analyses. Patients who received a postprotocol TKI had longer OS if they were in the bevacizumab/IFN- $\alpha$  arm than in the control arm (38.6 vs 33.6 months; HR, 0.80; 95% CI, 0.56-1.13), suggesting that sequential therapy could be a promising approach.<sup>62</sup>

In comparing the bevacizumab-containing arm with the control arm, fatigue (13% vs 8%) and asthenia (11% vs 7%), both IFN- $\alpha$  related AEs, were the most commonly reported grade 3 AEs. Proteinuria (8%) and hypertension (6%) were the most common grade 3 or 4 AEs associated with bevacizumab. Given that the IFN- $\alpha$  dose had to be reduced in both the experimental and control arms, the investigators assessed whether this led to alterations in outcomes. PFS in the bevacizumab/reduced-dose IFN- $\alpha$

group was comparable with that in the overall cohort, suggesting that IFN- $\alpha$  could be dose-reduced to manage AEs without compromising efficacy.<sup>63</sup>

In the CALGB 90206 trial from the Cancer and Leukemia Group B, 732 patients were randomly assigned (1:1) to receive either open-label bevacizumab plus IFN- $\alpha$  or IFN- $\alpha$  monotherapy.<sup>64,65</sup> PFS was significantly better in patients receiving bevacizumab plus IFN- $\alpha$  than in those receiving IFN- $\alpha$  alone (8.5 vs 5.2 months; adjusted HR, 0.71; 95% CI, 0.61-0.83,  $P=$ .0001). The ORR was higher with combination therapy as well (25.5% vs 13.1%;  $P=$ .0001). However, there was no OS benefit. OS was 18.3 months for bevacizumab plus IFN- $\alpha$  and 17.4 months for IFN- $\alpha$  monotherapy (unstratified log-rank  $P=$ .097; with adjustment of stratification factors, HR, 0.86; 95% CI, 0.73-1.01;  $P=$ .069).

Although crossover was not allowed, a substantial portion of patients (408/732) received postprogression therapy with sunitinib or sorafenib. The investigators performed additional OS analysis based on whether patients received subsequent therapy (received: HR, 0.80;  $P=$ .055; not received: HR, 0.82;  $P=$ .108), and this showed a consistent trend toward OS benefit, although it was not statistically significant. The less impressive, though still beneficial, results in the CALGB-90206 trial as compared with the AVOREN trial were attributed to several possible factors: worse risk group distribution of treated patients, the lack of nephrectomy in a substantial proportion of patients, and the requirement for only a component of clear cell histology as compared with the clear cell-predominant requirement in the AVOREN trial. Grade 3 or higher toxicities were more common in the bevacizumab/IFN- $\alpha$  arm than in the IFN- $\alpha$  monotherapy arm, and included hypertension (11% vs 0%), anorexia (17% vs 8%), fatigue (37% vs 30%), and proteinuria (15% vs 1%).

### **Pazopanib**

Pazopanib is an inhibitor of VEGFR, PDGFR, and c-KIT that showed single-agent activity in RCC in multiple phase 1 and 2 trials.<sup>66-68</sup> Subsequently, it was studied in 2 major phase 3 trials.

The VEG105192 trial was a double-blind study that enrolled 435 patients (233 treatment-naïve; 202 cytokine-pretreated) with advanced and/or metastatic RCC with clear cell or predominantly clear cell histology. Patients were randomly assigned (2:1) to receive either pazopanib or placebo.<sup>69,70</sup> Pazopanib significantly prolonged PFS compared with placebo in the overall population (9.2 vs 4.2 months; HR, 0.46; 95% CI, 0.34-0.62;  $P<$ .0001) as well as in the 2 subgroups of treatment-naïve patients (11.1 vs 2.8 months; HR, 0.40;  $P<$ .0001) and cytokine-pretreated patients (7.4 vs 4.2 months; HR, 0.54;  $P<$ .001). The ORR was significantly better for

pazopanib than for placebo (30% vs 3%). OS, as with many other trials, was not significantly better for pazopanib than for placebo (22.9 vs 20.5 months; HR, 0.91; 95% CI, 0.71-1.16;  $P=$ .224). Crossover to pazopanib, as well as postprotocol treatments, was thought to have confounded the OS analysis. Post hoc analysis using statistical tools to compensate for crossover-related bias showed that pazopanib likely had mortality benefit. Diarrhea (52%), hypertension (40%), hair color changes (38%), nausea (26%), anorexia (22%), and vomiting (21%) were the most common AEs reported, with hypertension (4%) and diarrhea (4%) constituting the most common grade 3/4 AEs in the pazopanib arm. Despite more toxicity in the pazopanib group, there was no significant difference in the QOL measurements between the 2 groups.

The COMPARZ trial (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma) was an open-label noninferiority study that randomly assigned (1:1) 1100 patients with advanced or metastatic RCC with a clear cell histologic component and no prior systemic treatment to receive pazopanib or sunitinib.<sup>71,72</sup> PFS was 8.4 months with pazopanib and 9.5 months with sunitinib; the HR for disease progression or death showed noninferiority for pazopanib (HR, 1.05; 95% CI, 0.90-1.22). The investigator-assessed ORR was similar between pazopanib and sunitinib (33% vs 29%;  $P=$ .12). OS also was comparable between the pazopanib and sunitinib (28.3 vs 29.1 months; HR, 0.92; 95% CI, 0.79-1.06;  $P=$ .24) groups, with subgroup analyses across MSKCC risk groups showing similar results. The safety profiles of the drugs differed. More patients with sunitinib than pazopanib had hand-foot syndrome (50% vs 29%), mucosal inflammation (26% vs 11%), stomatitis (27% vs 14%), hypothyroidism (24% vs 12%), dysgeusia (36% vs 26%), dyspepsia (24% vs 14%), epistaxis (18% vs 9%), fatigue (63% vs 55%), thrombocytopenia (78% vs 41%), anemia (60% vs 31%), and leukopenia (78% vs 43%). The opposite was true for hair color changes (10% vs 30%), weight loss (6% vs 15%), and alopecia (7% vs 14%). Pazopanib was favored over sunitinib for 11 of 14 comparisons regarding health-related QOL.

PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer), an innovative double-blind, multicenter, phase 3b crossover trial with 169 patients, confirmed that patients preferred pazopanib over sunitinib (70% vs 22%; 8% expressed no preference;  $P<$ .001), largely based on the impact of AEs and health-related QOL.<sup>73</sup> Physician preferences were similar to patient preferences.

### **Axitinib**

Axitinib is a second-generation TKI with relative specificity for VEGFR.<sup>74</sup> Following impressive ORRs in multiple

phase 2 trials, in the range of 23% to 55%, 2 major phase 3 trials of axitinib were launched.<sup>75-77</sup>

The AXIS trial (Axitinib as Second Line Therapy for Metastatic Renal Cell Cancer) enrolled 723 patients with mRCC with a clear cell component who had progressed on a systemic therapy (sunitinib, 54%; cytokines, 35%; bevacizumab, 8%; temsirolimus, 3%).<sup>74,78</sup> Patients were randomly assigned (1:1) to receive open-label axitinib or sorafenib. PFS was 8.3 months with axitinib vs 5.7 months with sorafenib (HR, 0.656;  $P<.0001$ ). The PFS advantage in favor of axitinib was significant even in various subgroup analyses (age, MSKCC risk category, and cytokine- and sunitinib-treated patient subgroups). The ORR was significantly better with axitinib than with sorafenib (23% vs 12%;  $P=.0001$ ). However, there was no OS advantage with axitinib vs sorafenib (20.1 vs 19.2 months; HR, 0.969; 95% CI, 0.800-1.174;  $P=.3744$ ).

Those patients who had progressed fastest on sunitinib (0-25th percentile for time to progression) had shorter OS on axitinib, suggesting more aggressive biology and cross-resistance to VEGF inhibitors as possible reasons. Additional retrospective analysis concluded that OS with second-line therapy (sorafenib or axitinib) was better in both patients who received longer duration of prior therapy and those with a smaller tumor burden.<sup>79</sup> The most common grade 3 or higher AEs in the axitinib group were hypertension (17%), diarrhea (54%), and fatigue (37%). Treatment-related hypertension, nausea, dysphonia, and hypothyroidism were more common with axitinib, whereas hand-foot syndrome, alopecia, and rash were more common with sorafenib (greater than 10% difference between treatment groups).

Axitinib is not approved for frontline treatment based on an open-label trial wherein 192 patients with treatment-naïve clear cell mRCC were randomly assigned to receive either axitinib or sorafenib.<sup>80,81</sup> Although there was a trend in improved PFS with axitinib vs sorafenib, the difference was not statistically significant (10.1 vs 6.5 months; HR, 0.77; 95% CI, 0.56-1.05,  $P=.038$ ). Unsurprisingly, OS was similar for axitinib and sorafenib (21.7 vs 23.3 months; HR, 0.995; 95% CI, 0.731-1.356;  $P=.4883$ ). The ORR, however, was significantly improved with axitinib vs sorafenib (32% vs 15%; risk ratio, 2.21;  $P=.0006$ ). The safety profile for both sorafenib and axitinib was comparable with that in the AXIS trial. Overall, given that the primary endpoint of PFS was not met, axitinib was not approved in the first-line setting.

### **Cabozantinib**

Cabozantinib provides a theoretical advantage over other VEGF inhibitors because it inhibits not only VEGFR, but also AXL, MET, KIT, and RET.<sup>82</sup> Both AXL and MET are associated with poor prognosis and the development

of resistance to VEGF inhibitors in RCC. Having seen responses even in those patients treated with a median of 2 systemic therapies, the investigators swiftly took the drug to a phase 3 trial.<sup>83</sup>

In the METEOR trial (A Study of Cabozantinib vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma), 658 patients with advanced or metastatic RCC with a clear cell component who had progressed on a minimum of 1 VEGF inhibitor were randomly assigned (1:1) to receive open-label cabozantinib or everolimus.<sup>83,84</sup> The trial was designed to evaluate PFS in the first 375 randomly assigned patients at interim analysis and OS in all patients at final analysis, with adequate power for assessment of both these endpoints. OS eventually was found to be significantly different during an unplanned second interim analysis. The ORR for cabozantinib and everolimus was 17% vs 3% ( $P<.0001$ ), respectively. Both PFS (7.4 vs 3.9 months; HR, 0.51;  $P<.0001$ ) and OS (21.4 vs 16.5 months; HR, 0.66;  $P=.00026$ ) were significantly better in the cabozantinib group. The MET expression level, based on available archived samples, showed no correlation with outcomes. Overall, grade 3 or 4 AEs occurred in 71% of patients treated with cabozantinib and 60% of those treated with everolimus. The most common AEs included hypertension (15% vs 4%), diarrhea (13% vs 2%), fatigue (11% vs 7%), hand-foot syndrome (8% vs 1%), anemia (6% vs 17%), hyperglycemia (1% vs 5%), and hypomagnesemia (5% vs 0%).

On the back of successful results, including a benefit in OS, the FDA granted breakthrough therapy designation, fast track review, and priority review to cabozantinib, and consequent approval.

### **Lenvatinib**

Lenvatinib is an inhibitor of VEGFR, FGFR, PDGFR, RET, and KIT.<sup>85</sup> Studies in mouse models showed that a combination of lenvatinib and everolimus led to greater tumor volume reductions than either one alone. In response, a phase 1/2 study was launched.<sup>85</sup> The phase 2 component recruited 153 patients with clear cell locally advanced or metastatic RCC who had progressed on 1 previous VEGF inhibitor. Patients were randomly assigned (1:1:1) to receive either lenvatinib plus everolimus, single-agent lenvatinib, or single-agent everolimus. PFS for lenvatinib/everolimus, single-agent lenvatinib, and single-agent everolimus was 14.6 months, 7.4 months, and 5.5 months, respectively. PFS was significantly better with the combination compared with everolimus (HR, 0.40; 95% CI, 0.24-0.68;  $P=.0005$ ) but not when compared with single-agent lenvatinib (HR, 0.66; 95% CI, 0.39-1.10;  $P=.12$ ). ORRs in the lenvatinib/everolimus, single-agent lenvatinib, and single-agent everolimus groups were 43%, 27%, and 6%, respectively. OS for lenvatinib/

everolimus, single-agent lenvatinib, and single-agent everolimus was 25.5 months, 19.1 months, and 15.4 months, respectively. OS was significantly better in the combination group as compared with the everolimus group (HR, 0.51; 95% CI, 0.30-0.88;  $P=.024$ ). However, OS was not better in the lenvatinib group than in the everolimus group (HR, 0.68; 95% CI, 0.41-1.14;  $P=.12$ ). An ad hoc, retrospective, blinded, independent radiological review (IRR) confirmed that the PFS was significantly longer in patients receiving combination therapy than those receiving everolimus alone (HR, 0.45; 95% CI, 0.27-0.79).<sup>86</sup> No significant PFS difference was found between the combination group and the single-agent everolimus group (HR, 0.62; 95% CI, 0.37-1.04;  $P=.12$ ). The IRR-based ORRs in the lenvatinib/everolimus, single-agent lenvatinib, and single-agent everolimus groups were 35%, 39%, and 0%, respectively ( $P<.0001$  for both comparisons). Overall, the findings were largely consistent with the investigator-assessed findings.

The most common AEs of any grade in the lenvatinib/everolimus arm were diarrhea (85%), decreased appetite (51%), and fatigue or asthenia (49%). Otherwise, grade 3 and 4 events were less common in patients who received single-agent everolimus (50%) than in those who received single-agent lenvatinib (79%) or lenvatinib/everolimus (71%). Overall, both lenvatinib and the combination of lenvatinib and everolimus fared better than everolimus monotherapy. Lenvatinib, like cabozantinib, received a breakthrough designation and priority review. However, given the robustness of the improved outcomes with lenvatinib/everolimus—including OS benefits—the FDA approved the combination drug regimen rather than lenvatinib alone.

### VEGF Inhibitors in Neoadjuvant and Adjuvant Therapy of RCC

Neither IL-2 nor IFN- $\alpha$  demonstrated improvement in disease-free survival (DFS) or OS in randomized trials that investigated their use in adjuvant treatment of RCC.<sup>87</sup> The advent of VEGF inhibitors as part of mRCC management provided a natural foray into investigating these agents in the adjuvant setting (Table 3). Results are available from only 2 trials so far.

The ASSURE trial (Sunitinib Malate or Sorafenib Tosylate in Treating Patients With Kidney Cancer That Was Removed by Surgery) randomly assigned 1943 patients with completely resected RCC that was at least T1bNxM0 to receive adjuvant sunitinib, sorafenib, or placebo for 1 year.<sup>88</sup> Owing to intolerance, the starting doses of sorafenib and sunitinib were decreased midway through the trial. Disappointingly, both the VEGF inhibitors failed to improve 5-year DFS (sunitinib: HR,

1.02; 95% CI, 0.85-1.23; sorafenib: HR, 0.97; 95% CI, 0.80-1.17) or 5-year OS (sunitinib: HR, 1.17; 95% CI, 0.90-1.52; sorafenib: HR, 0.98; 95% CI, 0.75-1.28). Whether dose reduction, discontinuation rates, or shorter length of treatment duration may have contributed to the lack of benefits needs additional analysis and will be answered by future trials. The S-TRAC trial (Sunitinib Treatment of Renal Adjuvant Cancer) randomly assigned 615 patients (1:1) with resected locoregional RCC at high risk for disease recurrence as per UCLA Integrated Staging System (UISS) criteria to receive either sunitinib or placebo on a 4/2 schedule for 1 year.<sup>89</sup> Treatment completion was 55.6% for sunitinib and 69.4% for placebo. Dose reductions (34.3% vs 2%), dose interruptions (46.4% vs 13.2%), and drug discontinuations (28.1% vs 5.6%) were more frequent in the sunitinib group than the placebo group. The median treatment duration was 12.4 months, and the median duration of follow-up was 5.4 years. The median daily dose was 45.9 mg (range, 8.9-52.6 mg) in the sunitinib group. Blinded independent central review showed that median DFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group (HR, 0.76; 95% CI, 0.59-0.98;  $P=.03$ ). Investigator-assessed DFS was not significantly different between the 2 groups, however (HR, 0.81; 95% CI, 0.64-1.02;  $P=.08$ ). It should be noted that investigators called relapse earlier than the blinded independent central review more often for sunitinib than for placebo. Data for OS, a secondary endpoint, were not mature. Grade 3 or 4 AEs were more common in the sunitinib group than in the placebo group (60.5% vs 19.4%). The S-TRAC investigators noted that the lack of DFS benefit even in the clear cell histologic or high-risk subgroups of the ASSURE trial may possibly be secondary to distinct patient populations, dose regimens, and trial methods. For example, the ASSURE trial had many patients with lower-risk, stage 1 RCC disease (9%) and non-clear cell histology (21%). Further, the sunitinib dose was changed midtrial (from 50 mg to 37.5 mg daily, with dose reductions to 25 mg daily allowed; neither adjustment was done in S-TRAC). In addition, radiologic reviews, both at baseline and follow-ups, were done by investigators in the ASSURE trial.

The results of the SORCE trial (Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer) are highly anticipated as well. It is investigating sorafenib (1 year vs 3 years vs placebo) in adjuvant treatment of intermediate-risk and high-risk RCC. It will help answer the question of whether sorafenib is beneficial when given for 2 different periods in relatively high-risk RCC, rather than across the board as in the ASSURE trial. Additionally, the PROTECT (A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma; NCT01235962)



**Table 3.** Phase 3 Clinical Trials of VEGF Inhibitors in Adjuvant Treatment of Renal Cell Carcinoma

Trial	n	Estimated Study Completion Date	Disease Stage	Disease Histology	Treatment Arms	Outcomes
ASSURE; NCT00326898	1943	August 2015	pT1b(G3-4)N0M0 or pT2-4(Gx)N1-3M0	Any	Sunitinib vs sorafenib vs placebo	No improvement in 5-y DFS or OS with sunitinib or sorafenib
SORCE; NCT00492258	1656	December 2012	Intermediate- or high-risk (Leibovich score, 3-11)	Any	Sorafenib vs placebo	NA
S-TRAC; NCT00375674	615	August 2017	High-risk (modified UISS criteria)	Predominantly CC	Sunitinib vs placebo	DFS of 6.8 y for sunitinib vs 5.6 y for placebo (HR, 0.76; 95% CI, 0.59-0.98; <i>P</i> =.03)
ATLAS; NCT01599754	700	May 2019	pT2-4N0M0 or pTxN1M0	>50% CC RCC	Axitinib vs placebo	NA
PROTECT; NCT01235962	1540	April 2019	pT2(G3-4)N0 or pT3-4(Gx)N0 or pTx(Gx)N1M0	CC or predominantly CC	Pazopanib vs placebo	NA
ECOG-2810; NCT01575548	128	August 2022	pT1-4N0-1M1	CC component	Pazopanib vs placebo	NA

CC, clear cell histology; DFS, disease-free survival; HR, hazard ratio; NA, not available; OS, overall survival; RCC, renal cell carcinoma; UISS, UCLA Integrated Staging System; VEGF, vascular endothelial growth factor; y, year/years.

and ATLAS (Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients; NCT01599754) trials are investigating the roles of pazopanib and axitinib, respectively, in the adjuvant setting as well. Pazopanib is also being studied in the adjuvant setting after metastectomy in patients with no evidence of disease following surgery (ECOG-2810, Pazopanib Hydrochloride in Treating Patients With Metastatic Kidney Cancer Who Have No Evidence of Disease After Surgery; NCT01575548).

There is paucity of high-quality data for using VEGF inhibitors in the neoadjuvant setting. Various small studies, including phase 2 trials, have demonstrated clinical efficacy of these agents (sorafenib, sunitinib, axitinib, and pazopanib) in this setting.<sup>90</sup> Tumor downsizing of up to 28.3% has been noted (with axitinib); however, neoadjuvant treatment is unlikely to downstage inferior vena cava thrombosis, which occasionally accompanies renal tumors. Nevertheless, randomized phase 3 trials are required for any conclusive evidence to emerge. Until then, the use of VEGF inhibitors in both the adjuvant and neoadjuvant settings remains limited to clinical trials.

## Discussion

VEGF inhibitors have ushered in a new era in the treatment of mRCC. Compared with just a decade ago, unprecedented OS and PFS have been achieved. VEGF inhibitors, along with anti-PD-1 agents and mTOR inhibitors, have raised hopes of long-term disease control and possibly even cure in the near future. However, their sudden burst on the RCC management scene has also brought forth many issues, and raised clinically relevant questions that need to be answered. One such question is how best to choose from and sequence the various available therapies. Cross-trial comparisons, such as cabozantinib from the METEOR trial vs lenvatinib in NCT01136733, are fraught with potential error given differences in trial design, treatments before and after protocol, crossover allowance, nephrectomy status at enrollment, RCC risk category, and histology (clear cell proportion), despite the fact that both had everolimus as the comparator. Indeed, we lack high-quality evidence on how to best treat patients with non-clear cell mRCC,

which accounts for approximately one-fourth of all RCC histologic subtypes.<sup>7</sup> For the most part, empiric evidence suggests that outcomes are much worse in non-clear cell mRCC. Evidence from 2 recent small phase 2 trials came to slightly different conclusions. Patients in the ESPN trial (Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma) had advanced papillary, chromophobe, Xp11.2 translocation, or unclassified RCC, or clear cell RCC with greater than 20% sarcomatoid features. They were randomly assigned to receive sunitinib (4/2) or everolimus, with crossover at disease progression.<sup>91</sup> An interim analysis of 68 patients showed that PFS was not significantly different for first-line sunitinib and everolimus (6.1 vs 4.1 months;  $P=.6$ ). Although median OS results initially favored sunitinib ( $P=.014$ ), the final analysis showed no difference in OS between the sunitinib and everolimus groups (16.2 vs 14.9 months;  $P=.18$ ). It should be noted that patients without sarcomatoid features ( $n=49$ ) did numerically much better with sunitinib than with everolimus (OS, 31.6 vs 10.5 months;  $P=.075$ ). However, in ASPEN, 108 mRCC patients with at least 50% papillary, chromophobe, or undifferentiated histology were randomly assigned to receive sunitinib (4/2) or everolimus.<sup>92</sup> PFS was significantly longer in the former group (8.3 vs 5.6 months; HR, 1.41;  $P=.16$ ). Substantial heterogeneity was noted, however, on subgroup analysis based upon risk status. Nevertheless, the overall results of ESPN, ASPEN, and the phase 2 RECORD-3 trial (Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of patients With Metastatic Renal Cell Carcinoma;  $n=66$  in subset of patients with non-clear cell RCC) trials show that sunitinib can be used in first-line treatment of mRCC with non-clear cell histology. That said, participation in a well-designed clinical trial should be recommended for all patients.

The flurry of treatment options in clear cell mRCC also has meant that some of the FDA-approved options are now obsolete in routine practice. Bevacizumab seems to have fallen out of favor, partly because of equal or better outcomes with the more recent TKIs and partly because of the inconvenience of its intravenous route of administration and the AEs secondary to the use of IFN- $\alpha$ . In this context, for the prototypical patient with clear cell mRCC, either pazopanib or sunitinib should be considered in the first-line setting, while noting that QOL measures favor pazopanib. Temsirolimus may be considered for those with poor-risk disease. Nevertheless, the combination of temsirolimus and bevacizumab was not superior to IFN- $\alpha$  and bevacizumab for first-line treatment in clear cell mRCC in the randomized, open-label, phase 3 INTORACT trial (Study Comparing Bevacizumab + Temsirolimus vs. Bevacizumab + Interferon-Alpha

in Advanced Renal Cell Carcinoma Subjects).<sup>93</sup> PFS was not significantly different between the 2 groups, even in the MSKCC poor-risk subgroup (HR, 0.8;  $P=.49$ ). Similarly, results from the randomized phase 2 BEST trial (Bevacizumab, Sorafenib Tosylate, and Temsirolimus in Treating Patients With Metastatic Kidney Cancer) showed no improvement in PFS in 3 combinations of targeted therapies (temsirolimus/bevacizumab, temsirolimus/sorafenib, and bevacizumab/sorafenib) over bevacizumab alone in first-line RCC.<sup>94</sup> Another combination of mTOR and VEGF inhibitors was explored in the first-line setting in the RECORD-2 trial (Phase II Randomized Study of Everolimus and Bevacizumab Versus Interferon  $\alpha$ -2a and Bevacizumab as First-Line Therapy in Patients With Metastatic Renal Cell Carcinoma); no significant PFS difference was identified between the everolimus/bevacizumab group and the IFN- $\alpha$ /bevacizumab group.<sup>95</sup> IL-2 is a valid option in selected patients with excellent performance status and good cardiopulmonary function; however, its use has significantly declined given the general decrease in centers that administer IL-2.

In the second-line setting after sunitinib, temsirolimus failed to improve PFS (HR, 0.87;  $P=.19$ ) and in fact had inferior OS compared with sorafenib (HR, 1.31;  $P=.01$ ) in the INTORSECT trial (Temsirolimus Versus Sorafenib as Second-Line Therapy in Patients With Advanced RCC Who Have Failed First-Line Sunitinib).<sup>96</sup> On the other hand, everolimus—once an option in the second-line setting—has been displaced by the newer agents nivolumab (based on CHECKMATE 025; Study of Nivolumab vs Everolimus in Pre-Treated Advanced or Metastatic Clear-Cell Renal Cell Carcinoma), cabozantinib (based on METEOR), and lenvatinib/everolimus (NCT01136733), all of which were compared against it. There is no good evidence regarding which of these should be preferred; however, nivolumab stands out for having shown OS benefit in the large CHECKMATE 025 trial and for having a different AE profile. It is worth mentioning that QOL improved significantly with nivolumab. Both cabozantinib and lenvatinib/everolimus are also competing in the same space with nivolumab. The dilemma now is the optimal sequence after first-line therapy, which represents an embarrassment of riches. It will be interesting to see how well cabozantinib and lenvatinib/everolimus patients would do after nivolumab, owing to the improvement in QOL with nivolumab and the fact that the AE profile may be different in the third-line setting. PFS may even improve owing to the sequence of drugs with differing mechanisms of action. It should be noted that the lenvatinib/everolimus trial (NCT01136733) had more MSKCC high-risk patients across the groups than the cabozantinib (METEOR) trial did (38%-44% vs 12%-16%). This is notable because

MSKCC high-risk patients have been shown to have miserable outcomes, even worse than poor-risk patients by the Heng criteria.<sup>97</sup> Regardless, it is obvious that additional research is needed on how best to sequence these regimens. Furthermore, the role of axitinib—also an option in second-line treatment—needs to be better defined.

Tivozanib, another TKI, which failed to show OS benefit despite PFS gain in the first-line setting (TIVO-1; A Study to Compare Tivozanib to Sorafenib in Subjects With Advanced Renal Cell Carcinoma), may potentially join the ranks in the future as well. The FDA had previously rejected it owing to inconsistent PFS and OS results, as well as imbalance in poststudy treatments. It currently is being studied in refractory advanced RCC in the third-line setting (the phase 3 TIVO-3 trial) and in combination with nivolumab (the phase 1/2 TiNivo trial). The latter, along with other trials like NCT02210117 (nivolumab vs nivolumab/bevacizumab vs nivolumab/ipilimumab), NCT02811861 (lenvatinib/everolimus or lenvatinib/pembrolizumab vs sunitinib), NCT02496208 (cabozantinib/nivolumab with or without ipilimumab), CHECKMATE 016 (NCT01472081; nivolumab in combination with sunitinib, pazopanib, or ipilimumab), KEYNOTE-018 (NCT02014636; pembrolizumab/pazopanib), KEYNOTE-426 (NCT02853331; pembrolizumab/axitinib vs sunitinib), JAVELIN Renal 100 (NCT02493751; avelumab/axitinib), JAVELIN Renal 101 (NCT02684006; avelumab/axitinib vs sunitinib), IMmotion151 (NCT02420821; atezolizumab/bevacizumab vs sunitinib) will also help demonstrate the efficacy of combined therapy, including novel immune checkpoint inhibitors with VEGF inhibitors, in advanced or mRCC. Further, the recent news of improved PFS with cabozantinib over sunitinib in previously untreated patients with intermediate- or high-risk locally advanced or metastatic RCC will significantly shake up the treatment algorithm, which is already in significant flux.

Besides the significance of diagnostic and prognostic biomarkers, the use of predictive biomarkers could hold the key to sequencing drugs in the future. The development of hypertension has been noted to predict improved outcomes in many of the above VEGF inhibitor trials. Nevertheless, it is a nonspecific finding and one that cannot be predicted before the start of a VEGF inhibitor. On the other hand, expression levels of miR-99b-5p, heme oxygenase-1 (HMOX1), IL-8, osteopontin, hepatocyte growth factor (HGF), TIMP1, VEGF, spinocerebellar ataxia 9 (sCA9), collagen type 4 (COL4), soluble VEGFR 2 (sVEGFR2), TNF-related apoptosis-inducing ligand (TRAIL), IL-6, FGF-basic (bFGF), VEGFR1, and the rs9582036 SNP have been associated with outcomes in VEGF pathway inhibitors.<sup>98-100</sup> Clinical translation of 1

or more robust biomarkers following prospective validation may help both in achieving the best possible outcomes and in minimizing toxicities, thus contributing to the delivery of personalized and cost-effective medicine. Similarly, understanding the development of primary and secondary resistance to VEGF inhibitors will prove crucial in designing rational therapies in future.

The role of cytoreductive nephrectomy in the treatment of mRCC was established in the era of immunotherapies. Although it was routinely recommended and performed even in the current VEGF inhibitor era, prospective evidence for cytoreductive nephrectomy is largely lacking in the era of targeted therapy. Two large ongoing phase 3 trials—CARMENA (Clinical Trial to Assess the Importance of Nephrectomy; NCT00930033) and SURTIME (Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer; NCT01099423) will seek the answer to this important question about the role of cytoreductive nephrectomy.<sup>101</sup> Finally, there is an urgent need for clinical trials that have increased homogeneity in patient population and tumor characteristics and that also employ up-to-date control agents. Clinical trials dedicated exclusively to the evaluation of newer therapies in patients with the more rare and aggressive histologies are awaited, despite the difficulty in designing these trials and recruiting patients to them. As new drugs gain indications in RCC, the financial burden on both the individual patient and health care in general needs to be addressed. Drug selection should increasingly take into account the 5 measures that the National Comprehensive Cancer Network is already taking account: the quality and consistency of supporting evidence, along with the efficacy, safety, and affordability of the drug.

### Disclosures

*Dr Vachhani has no conflicts of interest to report. Dr George has received grants from Acceleron, Agensys, Bayer, Bristol-Myers Squibb, Merck, Novartis, and Pfizer, and personal fees from Astellas, Bayer, Bristol-Myers Squibb, Novartis, OncLive, Exelixis, and Xcenda. No financial support was utilized in the preparation of this article.*

### References

1. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23(1):133-141.
2. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23(4):832-841.
3. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol*. 1999;17(8):2530-2540.
4. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma.

- Groupe Français d'Immunothérapie. *N Engl J Med*. 1998;338(18):1272-1278.
5. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. *J Clin Oncol*. 2003;21(16):3127-3132.
  6. Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1803-1813.
  7. Daste A, Grellety T, Gross-Goupil M, Ravaud A. Protein kinase inhibitors in renal cell carcinoma. *Expert Opin Pharmacother*. 2014;15(3):337-351.
  8. Latif F, Tory K, Gnarr J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260(5112):1317-1320.
  9. Maher ER, Bentley E, Yates JR, et al. Mapping of the von Hippel-Lindau disease locus to a small region of chromosome 3p by genetic linkage analysis. *Genomics*. 1991;10(4):957-960.
  10. Jonasch E, Gao J, Rathmell WK. Renal cell carcinoma. *BMJ*. 2014;349:g4797.
  11. Shen C, Kaelin WG Jr. The VHL/HIF axis in clear cell renal carcinoma. *Semin Cancer Biol*. 2013;23(1):18-25.
  12. Foster K, Prowse A, van den Berg A, et al. Somatic mutations of the von Hippel-Lindau disease tumour suppressor gene in non-familial clear cell renal carcinoma. *Hum Mol Genet*. 1994;3(12):2169-2173.
  13. Gnarr JR, Tory K, Weng Y, et al. Mutations of the VHL tumour suppressor gene in renal carcinoma. *Nat Genet*. 1994;7(1):85-90.
  14. Whaley JM, Naglich J, Gelbert L, et al. Germ-line mutations in the von Hippel-Lindau tumor-suppressor gene are similar to somatic von Hippel-Lindau aberrations in sporadic renal cell carcinoma. *Am J Hum Genet*. 1994;55(6):1092-1102.
  15. Young AC, Craven RA, Cohen D, et al. Analysis of VHL gene alterations and their relationship to clinical parameters in sporadic conventional renal cell carcinoma. *Clin Cancer Res*. 2009;15(24):7582-7592.
  16. Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer*. 2002;2(9):673-682.
  17. Semenza GL. HIF-1 and mechanisms of hypoxia sensing. *Curr Opin Cell Biol*. 2001;13(2):167-171.
  18. Jaakkola P, Mole DR, Tian YM, et al. Targeting of HIF- $\alpha$  to the von Hippel-Lindau ubiquitylation complex by O<sub>2</sub>-regulated prolyl hydroxylation. *Science*. 2001;292(5516):468-472.
  19. Baldewijns MM, van Vlodrop IJ, Vermeulen PB, Soetekouw PM, van Engeland M, de Bruïne AP. VHL and HIF signalling in renal cell carcinogenesis. *J Pathol*. 2010;221(2):125-138.
  20. Ohh M, Park CW, Ivan M, et al. Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol*. 2000;2(7):423-427.
  21. Tomlinson IP, Alam NA, Rowan AJ, et al; Multiple Leiomyoma Consortium. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. *Nat Genet*. 2002;30(4):406-410.
  22. Pugh CW, Ratcliffe PJ. The von Hippel-Lindau tumor suppressor, hypoxia-inducible factor-1 (HIF-1) degradation, and cancer pathogenesis. *Semin Cancer Biol*. 2003;13(1):83-89.
  23. Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer*. 2003;3(10):721-732.
  24. Koul H, Huh JS, Rove KO, et al. Molecular aspects of renal cell carcinoma: a review. *Am J Cancer Res*. 2011;1(2):240-254.
  25. Harris AL. Hypoxia—a key regulatory factor in tumour growth. *Nat Rev Cancer*. 2002;2(1):38-47.
  26. Ferrara N. Role of vascular endothelial growth factor in the regulation of angiogenesis. *Kidney Int*. 1999;56(3):794-814.
  27. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. *Nat Rev Cancer*. 2015;15(1):55-64.
  28. Haase VH. The VHL/HIF oxygen-sensing pathway and its relevance to kidney disease. *Kidney Int*. 2006;69(8):1302-1307.
  29. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature*. 2013;499(7456):43-49.
  30. Hakimi AA, Reznik E, Lee CH, et al. An integrated metabolic atlas of clear cell renal cell carcinoma. *Cancer Cell*. 2016;29(1):104-116.
  31. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med*. 2012;366(10):883-892.
  32. Gerlinger M, Horswell S, Larkin J, et al. Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing. *Nat Genet*. 2014;46(3):225-233.
  33. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet*. 2009;373(9669):1119-1132.
  34. Rini BI, Weinberg V, Small EJ. A phase I trial of fixed dose rate gemcitabine and capecitabine in metastatic renal cell carcinoma. *Cancer*. 2005;103(3):553-558.
  35. Stadler WM, Halabi S, Rini B, et al; Cancer and Leukemia Group B. A phase II study of gemcitabine and capecitabine in metastatic renal cancer: a report of Cancer and Leukemia Group B protocol 90008. *Cancer*. 2006;107(6):1273-1279.
  36. Atzpodien J, Kirchner H, Hänninen EL, Deckert M, Fenner M, Poliwooda H. Interleukin-2 in combination with interferon- $\alpha$  and 5-fluorouracil for metastatic renal cell cancer. *Eur J Cancer*. 1993;29A(suppl 5):S6-S8.
  37. Gore M. Interferon-alpha (IFN), interleukin-2 (IL2) and 5-fluorouracil (5FU) vs IFN alone in patients with metastatic renal cell carcinoma (mRCC): results of the randomised MRC/EORTC RE04 trial [ASCO abstract 5039]. *J Clin Oncol*. 2008;26(15)(suppl).
  38. Escudier B, Eisen T, Stadler WM, et al; TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356(2):125-134.
  39. Carlomagno F, Anaganti S, Guida T, et al. BAY 43-9006 inhibition of oncogenic RET mutants. *J Natl Cancer Inst*. 2006;98(5):326-334.
  40. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res*. 2004;64(19):7099-7109.
  41. Awada A, Hendlitz A, Gil T, et al. Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours. *Br J Cancer*. 2005;92(10):1855-1861.
  42. Clark JW, Eder JP, Ryan D, Lathia C, Lenz HJ. Safety and pharmacokinetics of the dual action Raf kinase and vascular endothelial growth factor receptor inhibitor, BAY 43-9006, in patients with advanced, refractory solid tumors. *Clin Cancer Res*. 2005;11(15):5472-5480.
  43. Moore M, Hirte HW, Siu L, et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. *Ann Oncol*. 2005;16(10):1688-1694.
  44. Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J Clin Oncol*. 2005;23(5):965-972.
  45. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24(16):2505-2512.
  46. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol*. 2009;27(20):3312-3318.
  47. Eisen T, Oudard S, Szczylik C, et al; TARGET Study Group. Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. *J Natl Cancer Inst*. 2008;100(20):1454-1463.
  48. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer*. 2008;8(8):579-591.
  49. Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. *J Clin Oncol*. 2006;24(1):25-35.
  50. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA*. 2006;295(21):2516-2524.
  51. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356(2):115-124.
  52. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27(22):3584-3590.
  53. Cella D, Li JZ, Cappelleri JC, et al. Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomized trial. *J Clin Oncol*. 2008;26(22):3763-3769.
  54. Bracarda S, Iacovelli R, Boni L, et al; Rainbow Group. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. *Ann Oncol*. 2015;26(10):2107-2113.
  55. Molina AM, Jia X, Feldman DR, et al. Long-term response to sunitinib therapy for metastatic renal cell carcinoma. *Clin Genitourin Cancer*. 2013;11(3):297-302.
  56. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med*. 2003;349(5):427-434.
  57. Thompson DS, Greco FA, Spigel DR, et al. Bevacizumab, erlotinib, and imatinib in the treatment of patients with advanced renal cell carcinoma: update of a multicenter phase II trial [ASCO abstract 4594]. *J Clin Oncol*. 2006;24(18)(suppl).

58. Hainsworth JD, Sosman JA, Spigel DR, Edwards DL, Baughman C, Greco A. Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib. *J Clin Oncol*. 2005;23(31):7889-7896.
59. Bukowski RM, Kabbinnar FF, Figlin RA, et al. Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. *J Clin Oncol*. 2007;25(29):4536-4541.
60. Escudier B, Pluzanska A, Koralewski P, et al; AVOREN Trial Investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*. 2007;370(9605):2103-2111.
61. Escudier B, Bellmunt J, Négrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol*. 2010;28(13):2144-2150.
62. Bracarda S, Bellmunt J, Melichar B, et al. Overall survival in patients with metastatic renal cell carcinoma initially treated with bevacizumab plus interferon- $\alpha$ 2a and subsequent therapy with tyrosine kinase inhibitors: a retrospective analysis of the phase III AVOREN trial. *BJU Int*. 2011;107(2):214-219.
63. Melichar B, Koralewski P, Ravaud A, et al. First-line bevacizumab combined with reduced dose interferon-alpha2a is active in patients with metastatic renal cell carcinoma. *Ann Oncol*. 2008;19(8):1470-1476.
64. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol*. 2008;26(33):5422-5428.
65. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol*. 2010;28(13):2137-2143.
66. Hurwitz H, Dowlati A, Savage S, et al. Safety, tolerability and pharmacokinetics of oral administration of GW786034 in pts with solid tumors [ASCO abstract 3012]. *J Clin Oncol*. 2005;23(16)(suppl).
67. Hutson TE, Davis ID, Machiels JH, et al. Biomarker analysis and final efficacy and safety results of a phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor [ASCO abstract 5046]. *J Clin Oncol*. 2008;26(15)(suppl).
68. Hutson TE, Davis ID, Machiels JP, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2010;28(3):475-480.
69. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. *Eur J Cancer*. 2013;49(6):1287-1296.
70. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28(6):1061-1068.
71. Motzer RJ, Hutson TE, McCann L, Deen K, Choueiri TK. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. *N Engl J Med*. 2014;370(18):1769-1770.
72. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369(8):722-731.
73. Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. *J Clin Oncol*. 2014;32(14):1412-1418.
74. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939.
75. Rixe O, Bukowski RM, Michaelson MD, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. *Lancet Oncol*. 2007;8(11):975-984.
76. Tomita Y, Uemura H, Fujimoto H, et al; Japan Axitinib Phase II Study Group. Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: a phase II study in Japanese patients with cytokine-refractory metastatic renal cell carcinoma. *Eur J Cancer*. 2011;47(17):2592-2602.
77. Rini BI, Wilding G, Hudes G, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27(27):4462-4468.
78. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*. 2013;14(6):552-562.
79. Escudier B, Michaelson MD, Motzer RJ, et al. Axitinib versus sorafenib in advanced renal cell carcinoma: subanalyses by prior therapy from a randomised phase III trial. *Br J Cancer*. 2014;110(12):2821-2828.
80. Hutson TE, Al-Shukri S, Stus VP, et al. Axitinib versus sorafenib in first-line metastatic renal cell carcinoma: overall survival from a randomized phase III trial. *Clin Genitourin Cancer*. 2016;S1558-7673(16)30134-3.
81. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol*. 2013;14(13):1287-1294.
82. Yakes FM, Chen J, Tan J, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther*. 2011;10(12):2298-2308.
83. Choueiri TK, Escudier B, Powles T, et al; METEOR Investigators. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373(19):1814-1823.
84. Choueiri TK, Escudier B, Powles T, et al; METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17(7):917-927.
85. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*. 2015;16(15):1473-1482.
86. Motzer RJ, Hutson TE, Ren M, Dutcuc C, Larkin J. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. *Lancet Oncol*. 2016;17(1):e4-e5.
87. Pal SK, Haas NB. Adjuvant therapy for renal cell carcinoma: past, present, and future. *Oncologist*. 2014;19(8):851-859.
88. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016;387(10032):2008-2016.
89. Ravaud A, Motzer RJ, Pandha HS, et al; S-TRAC Investigators. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy [published online October 10, 2016]. *N Engl J Med*. DOI:10.1056/NEJMoa1611406.
90. Borregales LD, Adibi M, Thomas AZ, Wood CG, Karam JA. The role of neo-adjuvant therapy in the management of locally advanced renal cell carcinoma. *Ther Adv Urol*. 2016;8(2):130-141.
91. Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): A randomized multicenter phase 2 trial. *Eur Urol*. 2016;69(5):866-874.
92. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol*. 2016;17(3):378-388.
93. Rini BI, Bellmunt J, Clancy J, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. *J Clin Oncol*. 2014;32(8):752-759.
94. Flaherty KT, Manola JB, Pins M, et al. BEST: A randomized phase II study of vascular endothelial growth factor, RAF kinase, and mammalian target of rapamycin combination targeted therapy with bevacizumab, sorafenib, and temsirolimus in advanced renal cell carcinoma—a trial of the ECOG-ACRIN cancer research group (E2804). *J Clin Oncol*. 2015;33(21):2384-2391.
95. Ravaud A, Barrios CH, Alekseev B, et al. RECORD-2: phase II randomized study of everolimus and bevacizumab versus interferon  $\alpha$ -2a and bevacizumab as first-line therapy in patients with metastatic renal cell carcinoma. *Ann Oncol*. 2015;26(7):1378-1384.
96. Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2014;32(8):760-767.
97. Noe A, Blank CU, Horenblas S, Haanen JB, Bex A. MSKCC and Heng prognostic risk assessment for synchronous metastatic renal cell carcinoma (sync-mRCC) and the tumor in place treated in the targeted therapy era [ASCO abstract e15525]. *J Clin Oncol*. 2013;31(15)(suppl).
98. Ngo TC, Wood CG, Karam JA. Biomarkers of renal cell carcinoma. *Urol Oncol*. 2014;32(3):243-251.
99. Zheng WX, Yan F, Xue Q, et al. Heme oxygenase-1 is a predictive biomarker for therapeutic targeting of advanced clear cell renal cell carcinoma treated with sorafenib or sunitinib. *Oncotargets Ther*. 2015;8:2081-2088.
100. Lukamowicz-Rajska M, Mittmann C, Prummer M, et al. MiR-99b-5p expression and response to tyrosine kinase inhibitor treatment in clear cell renal cell carcinoma patients [published online October 12, 2016]. *Oncotarget*. DOI:10.18632/oncotarget.12618.
101. Agarwal N, Shuch B, Pal SK. Up-front targeted therapy prior to cytoreductive nephrectomy in treatment-naïve patients with metastatic renal cell carcinoma. *JAMA Oncol*. 2016;2(10):1273-1274.