Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Axitinib in the treatment of renal cell carcinoma: design, development, and place in therapy

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
21 September 2017
Number of times this article has been viewed

Audrey Bellesoeur
Edith Carton
Jerome Alexandre
Francois Goldwasser
Olivier Huillard

Department of Medical Oncology, Hopital Cochin AP-HP, Paris, France

Abstract: Since 2005, the approved first-line treatment of metastatic renal cell carcinoma consists in tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptors (VEGFRs). Axitinib is an oral second-generation TKI and a potent VEGFR inhibitor with a half maximal inhibitory concentration for the VEGF family receptors 10-fold lower than other TKIs. Axitinib activity in renal cell carcinoma (RCC) patients has been studied in various settings and particularly as second-line treatment. In this setting, axitinib with clinically based dose escalation compared to sorafenib has demonstrated an improvement in progression-free survival in a randomized Phase III trial leading to US Food and Drug Administration approval. In the first-line setting, axitinib failed to demonstrate improved efficacy over sorafenib, but the field of RCC treatment is rapidly changing with novel TKIs as cabozantinib or the emergence of check point inhibitors as nivolumab and the place of axitinib in therapy is therefore challenged. In this review, we focus on axitinib pharmacological and clinical properties in RCC patients and discuss its place in the treatment of patients with RCC.

Keywords: renal cell carcinoma, tyrosine kinase inhibitors, vascular endothelial growth factor, axitinib, pharmacology

Introduction

Renal cell carcinoma (RCC) is a frequent cancer representing 5% of the estimated new cases of cancer in males and 3% of the estimated new cases of cancer in females and was responsible for 14,240 estimated deaths in 2016 in the USA.[1] When diagnosed at a local stage, RCC can be treated with curative intent surgery. When diagnosed at a metastatic stage, active surveillance can be an option in the case of indolent growth of metastases, but disease will eventually progress in most cases requiring systemic therapy.[2] Since 2005, the approved first-line treatment consists in tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptors (VEGFRs) (Table 1).[3,4] In the Phase III trial comparing pazopanib with sunitinib in the first-line setting, the median progression-free survival (PFS) was 8.4 months (95% confidence interval [CI] 8.3–10.9) for patients receiving pazopanib and 9.5 months (95% CI 8.3–11.1) for patients receiving sunitinib. Second-line therapies are therefore needed, and treatments targeting the mammalian target of rapamycin (mTOR) pathway, the VEGF pathway, and more recently immune checkpoints have been developed. Axitinib, a VEFGR targeted agent, is one of these second-line approved treatment (Table 1).

Pharmacodynamics and preclinical development

Axitinib (Inlyta®; Pfizer, New York, NY, USA) is an oral second-generation TKI whose significant feature is its VEGF receptor specificity. It is an indazole derivative produced

Correspondence: Olivier Huillard
Department of Medical Oncology, Hopital Cochin AP-HP, 123 Boulevard de Port Royal, 75014 Paris, France
Tel +33 1 5841 1439
Fax +33 1 5841 1434
Email olivier.huillard@aphp.fr

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/DDDT.S109640

Table 1 Treatment approved by the FDA for the treatment of patients with metastatic renal cell cancer

Drug	Molecular target	Year of first approval	Trial number	Control arm
Sorafenib	VEGFR1, 2, 3 c-Kit FLT3 PDGFRβ Raf Ret	2005	NCT00073307	Placebo
Sunitinib	VEGFR1, 2 c-Kit FLT3 PDGFRα PDGFRβ	2006	NCT00083889	Interferon-α
Everolimus	mTOR	2009	NCT00410124	Placebo
Bevacizumab + interferon-α	VEGF	2009	NCT00072046	Placebo + interferon-α
Pazopanib	VEGFR1, 2, 3 c-Kit PDGFR FGFR	2009	NCT00720941	Sunitinib
Temsirolimus	mTOR	2010	NCT00065468	Interferon-α and combination of both
Axitinib	VEGFR1, 2, 3 PDGFRα PDGFRβ c-Kit	2012	NCT00678392	Sorafenib
Nivolumab	PD-1 checkpoint inhibitor	2015	NCT01668784	Everolimus
Cabozantinib	VEGFR1, 2, 3 c-Met Kit Axl	2016	NCT01865747	Everolimus

Abbreviations: FDA, US Food and Drug Administration; mTOR, mammalian target of rapamycin; PDFGR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

by chemical synthesis, whose molecular weight is 38,647 Da. Axitinib inhibits VEGFR1, VEGFR2, and VEGFR3; but contrary to multiple TKIs, axitinib is weakly active on other receptors, such as KIT and platelet derived growth factor receptor (PDGFR). With half maximal inhibitory concentrations (IC_{50}) for the VEGF family receptors 10-fold lower than other TKI, axitinib is a potent VEGFR inhibitor. In vitro, with an inhibitory concentration ~0.2 nmol/L, axitinib selectively inhibits VEGF receptor activities and VEGF-based cell survival on various angiogenesis cellular models.[5] Inhibitory concentrations of axitinib are 0.1 nM for VEGFR1, 0.2 nM for VEGFR2, and 0.1–0.3 nM for VEGFR3,[6] whereas anti-PDGFR activity and anti-Kit activity are almost 10 times weaker (IC_{50}: 5 nM for PDGFRα, 1.6 nM for PDGFRβ, and 1.7 nM for Kit) (Table 2). In vivo, axitinib confirmed its dose-dependent inhibition on angiogenesis and tumor growth in mice, including in xenograft model of human tumor: axitinib caused regression of the tumor vasculature, with loss of endothelial sprouts and fenestration and decreased vessels density.[7]

Table 2 IC_{50} (nM) of multiple tyrosine kinase inhibitors against the indicated kinases

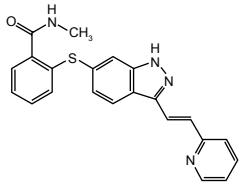
Drug	VEGFR1	VEGFR2	VEGFR3	PDGFRα	PDGFRβ	Kit	Ret	FLT3	Others
Sunitinib[75]	15	38	30	69	55	1–10	224	21	Csf1R: 35
Sorafenib[76]		90	20		57	68		58	BRAF: 30 CRAF: 6
Pazopanib[77]	10	30	47	71	84	74			
Axitinib[5]	0.1	0.2	0.2	5	1.6	1.7			
Cabozantinib[78]		14			575	752	8	21	Met: 2 FLT4: 3 Tie2: 13

Abbreviations: IC_{50}, half maximal inhibitory concentration; VEGFR, vascular endothelial growth factor receptor; PDFGR, platelet-derived growth factor receptor.

Pharmacokinetics

Orally taken, axitinib is rapidly absorbed and achieves maximal plasma concentration after 4 h (median T_{max} from 2.5 to 4.1 h). Regarding bioavailability, there is no clinically significant difference between fasted and fed states,[8] with a mean bioavailability of 58%.[9] Administration with a moderate calorie meal decreases axitinib exposure from 10% compared to overnight fasting, whereas high fat meal results in 19% higher exposure compared to an overnight fast. Axitinib absorption is pH dependent, with higher absorption in acidic pH, but antiacid agents have a limited impact on axitinib area under the curve and therefore are not contraindicated during axitinib treatment. At therapeutic dose axitinib has a high protein-binding rate exceeding 99% and preferentially binds to albumin. Particular attention must therefore be paid to patient with hypoalbuminemia. Axitinib apparent volume of distribution is 160 L. At steady-state axitinib pharmacokinetic is approximately linear over a dosing range of 1–20 mg.[10] Axitinib is mainly metabolized in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, 2C19, and UGT1A1, producing pharmacologically inactive metabolites. Attention should therefore be paid when axitinib is prescribed with known CYP3A4/5 inducer or inhibitor. However, axitinib is not considered as a cytochrome inducer or inhibitor but is a substrate for the efflux transporter P-glycoprotein (P-gp) and for the hepatic organic anion-transporting polypeptides (OATP1B1). Axitinib has been shown to inhibit the efflux transporter P-gp in vitro but not at therapeutic plasma concentration. Axitinib is mainly eliminated in feces due to hepatobiliary excretion, whereas axitinib renal excretion accounts for <20%. Unchanged axitinib is detected only in feces and not in urine.[11] A significant increase in axitinib plasma concentration has been observed in patients with moderate hepatic impairment (Child-Pugh B) but not for mild impairment (Child-Pugh A). Axitinib elimination remains constant during chronic dosing, without argument for autoinduction or autoinhibition.[10] Axitinib half-life is shorter than other TKI and varies from 2.5 to 6.1 h, justifying its twice daily schedule of prescription. Due to this short half-life, steady state is expected in <3 days, and plasma concentration quickly decreases after treatment interruption. After axitinib 5 mg bid administration, the median plasma concentration–time curve at steady state is 322 ng h/mL and the median maximum observed plasma concentration is 28.5 ng/mL. Axitinib, as most TKI, shows an important pharmacokinetic variability. Interindividual variability for area under the plasma concentration–time curve (AUC) at the 5 mg bid standard dose is estimated ~80%.

Table 3 Summary of axitinib pharmacokinetic parameters in patients with advanced renal cell carcinoma treated with axitinib 5 mg bid

Axitinib structure and pharmacokinetics Geometric mean (% CV)	
Chemical structure	
Bioavalibility[a]	54%–58%
C_{max} (ng/mL)	27.8 (79)
AUC_{0-24} (ng h/mL)	265 (77)
T_{max} (h)[b]	2.00 (1.00–2.50)
Plasma protein binding[a]	>99%
V_Z/F (L)	160 (105)
Metabolism	CYP3A4/5 (CYP1A2, CYP2C19, UGT1A1)
CL/F (L/h)	37.8 (80)
$t_{1/2}$ (h)	2.92 (144)

Notes: AUC_{0-24}, area under the plasma concentration–time curve from 0 to 24 h; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; $t_{1/2}$, apparent plasma half-life; T_{max}, time of maximal plasma concentration; V_Z/F, apparent volume of distribution after oral administration. [a]Mean. [b]Median with range.

This interindividual variability is quite the same after intravenous or oral administration, suggesting a greater role of metabolism than absorption.[10] Intraindividual variability is estimated ~20% to 22% (Table 3).[9]

Pharmacokinetics/pharmacodynamics (PK/PD) analysis

An increase in blood pressure (BP) is common under VEGFR-TKI treatment. The axitinib Phase I trial suggested a relationship between axitinib exposure and BP.[11] Thus, Rini et al[12] evaluated diastolic blood pressure (dBP) as a biomarker of axitinib efficacy in solid tumors. They demonstrated that increased dBP >90 mmHg was associated with axitinib efficacy. The correlation between axitinib plasma exposure and BP elevation was evaluated in a dedicated PK/PD study. Using data from the Phase II study of axitinib with or without dose titration in previously untreated patients with metastatic RCC (mRCC), Chen et al[13] developed a PK/PD model showing that dBP increased with increasing drug exposure. This relationship was not proportional, suggesting that an increase in dBP was not entirely explained by axitinib exposure, and thus that dBP should not be used exclusively to guide axitinib dosing. In a retrospective study of five Phase II trials (including three trials from mRCC patients), Rini et al[14] found that higher exposure and dBP were independently associated with longer PFS and overall survival (OS) and higher probability

of partial response. A post hoc analysis of the prospective, randomized, double-blind axitinib with or without titration Phase II trial found that patients receiving axitinib dose titration for mRCC had an increased axitinib exposure and a significantly higher objective response rate (ORR) than those with placebo titration (54% versus 34%; P=0.019).[15] Pharmacokinetics and BP data from this trial suggest a positive correlation of ORR, but not PFS, with plasma concentration of axitinib in the titration arm.[16] Regarding BP, a correlation between increased dBP and longer PFS was observed. This study demonstrated that axitinib exposure could be increased with individual dose titration, leading to a greater response rate. However, this work could not identify an optimal drug exposure target, perhaps due to the short axitinib half-life and the inter- and intrapatient variabilities. Moreover, there was no improvement in PFS when axitinib plasma exposure increased, possibly due to toxicity from titration and necessity of dose reduction after initial dose titration. Last, the correlation between axitinib plasma exposure and efficacy as well as axitinib plasma exposure and dBP was weak. These results suggest pharmacokinetic and BP measurements are not sufficient to be used exclusively to guide axitinib dose adaptation. This is consistent with axitinib current prescription guidelines, which consider not only BP measurement but also individual tolerability (with no grade >2 adverse event) (Table 4).

Other pharmacodynamic biomarkers have been explored for VEGFR inhibitors, in particular dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Previous studies have proved that DCE-MRI could detect biological modification due to VEGFR inhibition but failed to demonstrate its predictive value. Axitinib Phase I trial explored DCE-MRI as a pharmacodynamics biomarker and found a correlation between axitinib exposure and changes in DCE-MRI in favor of a dose-dependent effect of axitinib.[17]

Toxicity

Axitinib is well tolerated, with the expected adverse events of VEGFR-TKI. Most of the time, these adverse events are manageable and reversible with dose adaptation or interruption and supportive care. According to the AXIS Phase III trial, the most common adverse events observed were digestive troubles (diarrhea principally, nausea and anorexia), antiangiogenic known adverse events (such as hypertension), fatigue, and dysphonia.[18] They occurred in more than one-third of the treated population. Laboratory examination of serum samples revealed, mainly creatinine elevation, hypocalcemia, anemia, and lymphopenia. Unusual adverse events were rare, mostly dysphonia, and hemoglobin elevation. There was no death related to axitinib treatment. Limited data on long-term exposure show a favorable toxicity profile with declining or stable rates of most adverse events.[19] In patients receiving axitinib for >2 years, an increase in adverse events rates was observed for proteinuria, peripheral edema, increased blood creatinine, increased amylase, and myocardial infarction. This warrants further monitoring since rare VEGFR-TKI class toxicities may be possible.[20–22] Cardiovascular events are frequent with VEGFR-TKI and can be severe.[23,24] Hypertension is common during axitinib treatment. It was the first dose-limiting toxicity in the Phase I

Table 4 Results of major studies regarding relationship between axitinib plasma exposure, diastolic blood pressure, and efficacy

References	Study population	Correlation between						
		dBP and axitinib exposure	dBP and efficacy			Axitinib plasma exposure and efficacy		
			PFS	OS	ORR	PFS	OS	ORR
Rini et al[12] (2011)	mRCC, NSCLC, melanoma and thyroid cancer (n=238)		HR=0.76 (0.54–1.06) P=0.107	HR=0.55 (0.39–0.77) P<0.001	P<0.001			
Chen[13] (2015)	mRCC (n=62)	Relationship between dBP and axitinib exposure, without proportionality						
Rini[14] (2013)	Solid tumors and mRCC (n=207)	Weak correlation r^2<0.10	HR=0.66 (0.52–0.84) P<0.001	HR=0.74 (0.59–0.93) P=0.010	P=0.004	HR=0.91 (0.83–0.99) P=0.035	HR=0.866 (0.77–0.97) P=0.012	P<0.001
Rini et al[15] (2015)	mRCC (n=213)	Weak correlation r^2=0.225	HR=0.40 (0.25–0.65) P<0.001			HR=0.83 (0.55–1.24) P=0.355		

Abbreviations: dBP, diastolic blood pressure; HR, hazard radio; mRCC, metastatic renal cell carcinoma; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Table 5 Axitinib major clinical and biological adverse events from the Phase III AXIS trial

Adverse events	Axitinib (n=359)	
	All grades (%)	Grade ≥3 (%)
Clinical adverse events		
Diarrhea	197 (55)	38 (11)
Hypertension	145 (40)	56 (16)
Fatigue	140 (39)	41 (11)
Decreased appetite	123 (34)	18 (5)
Nausea	116 (32)	9 (3)
Dysphonia	111 (31)	0
Palmar-plantar erythrodysesthesia	98 (27)	18 (5)
Weight decreased	89 (25)	8 (2)
Asthenia	74 (21)	19 (5)
Hypothyroidism	69 (19)	1 (<1)
Stomatitis	54 (15)	5 (1)
Biological adverse events		
Anemia	13/320 (35)	1/320 (<1)
Hemoglobin elevation	31/320 (10)	NA
Neutropenia	19/316 (6)	2/316 (1)
Thrombocytopenia	48/312 (15)	1/312 (<1)
Lymphopenia	106/317 (33)	10/317 (3)
Creatinine elevation	185/336 (55)	0

Abbreviation: NA, not available.

study, and hypertension was reported in 40.4% of treated patients in the Phase III AXIS trial, with 15.6% of grade 3–4 hypertension.[25] BP increase usually starts within the first month of treatment, sometimes within the first week. Similar to other antiangiogenic agents, hypertension should be controlled prior to initiating axitinib and cautiously monitored and treated during treatment (using appropriate antihypertensive agents) with a goal of BP <140/90 mmHg, in accordance with the Cardiovascular Toxicities Panel, convened by the Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee.[26] As for other TKIs, thyroid function should be monitored before starting treatment and regularly during treatment and supplemented in case of hypothyroidism (Table 5).

Axitinib prescription

Axitinib is available as 1, 3, 5, and 7 mg coated tablets. The recommended starting dose is 5 mg twice daily, taken with or without food. Treatment is administered with continuous daily dosing. Dose adjustments are recommended according to individual tolerability. For patients with good tolerance after 2 weeks (no adverse event grade >2 and no increase in BP >150/90 mmHg or introduction of antihypertensive treatment), the dose should be increased to 7 mg twice daily. With the same criteria, a good tolerance of axitinib 7 mg bid may lead to increase the dose to 10 mg twice daily. Conversely, adverse reaction could require treatment interruption and reintroduction after dose reduction to 3 mg bid and further to 2 mg bid. No dose adjustment is recommended according to age, race,[27] gender, weight,[10] renal function,[28] or drug-metabolizing enzymes genotype.[29] Axitinib clearance decreased modestly in subjects older than 60 years, but these changes were not considered clinically significant, and no dose adjustment is recommended according to age.[10] No association has been identified between genetic polymorphisms in drug-metabolizing enzymes or transporters and axitinib pharmacokinetic variability.[29] As it has been described with the use of other VEGFR-TKI in mRCC patients, sarcopenia associated with a body mass index of <25 kg/m^2 could help identifying patients at high risk of severe toxicity in whom particular attention may be needed at treatment initiation.[30,31] For patients with moderate hepatic impairment (Child-Pugh B), a twofold higher axitinib exposure has been observed. A decrease in half the dose is recommended for these patients.[32] Given the lack of studies, axitinib is not recommended for patients with severe hepatic impairment. Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are not unusual in mRCC patients because of comorbidities and previous local treatments. However, there are few available data regarding the use of axitinib in patients with renal insufficiency, especially for patients with creatinine clearance <15 mL/min. A population pharmacokinetic model found no difference according to basal renal function, in favor of no dose adjustment in patients with renal impairment.[28] Because mRCC patients with CKD and ESRD were excluded from clinical trials, formal evidence lacks regarding the most suitable targeted drug and appropriate dose of each drug for this population. In a case reporting a patient undergoing hemodialysis, axitinib was introduced at 6 mg/day. Because no elevation in patient's BP was observed, axitinib dose was increased to 10 mg/day and continued safely for a total duration of 6 months, allowing a 4-month stability of the disease.[33] Another case reported axitinib pharmacokinetics in a patient undergoing hemodialysis and found no influence of hemodialysis on axitinib blood concentration.[34] Axitinib was administered at a dose of 6 mg twice a day and was well tolerated, with 12 months of disease control. The maximal fraction of axitinib in dialysates was estimated to be <0.62%. This minimal rate of drug removal by hemodialysis is in accordance with axitinib pharmacokinetic parameters (high level of protein binding, primary hepatobiliary excretion, and negligible urinary excretion). Therefore, axitinib could be used in patients with kidney failure, even for ESRD. It should be recommended to begin axitinib treatment with an initial low dose and, if the treatment is well tolerated, to increase axitinib dose using therapeutic dose monitoring.

No data are currently available regarding axitinib treatment in mRCC patients with kidney transplant, but this situation is rare. Immunosuppressive drugs prescribed for the kidney transplant need to be considered: the most frequently used agents are calcineurin inhibitors, inosine monophosphate deshydrogenase inhibitors, and mTOR inhibitors. Calcineurin inhibitors induce nephrotoxicity and drug interaction by CYP3A4 and P-gp and OATP inhibition. A published case reports renal impairment and nephrotic-range proteinuria in a patient treated with anticalcineurin and the antiangiogenic agent sorafenib.[35] Anticalcineurin prescription with antiangiogenic agent such as axitinib should probably be avoided. The same applies for anticalcineurin and mTOR inhibitors, since a single-center cohort study has reported an increased risk of thrombotic microangiopathy.[36] The risk of interaction between axitinib and inhibitors of inosine monophosphate deshydrogenase seems lower, involving mostly OATP transporter, but the safest option may probably be the mTOR inhibitors, since they have both immunosuppressive and anticancer properties.

Drug interaction

Solubility of axitinib is pH dependent, but antacids agents such as proton pump inhibitor decrease mostly the maximum observed plasma concentration (C_{max}) without significant impact on the AUC.[11] Acids suppressing agents have a slight effect on axitinib overall exposure and, thus, are not contraindicated during axitinib treatment. CYP3A4/5 inhibitors[37] may increase axitinib plasma concentration[38] resulting in clinically significant effects.[39,40] If an alternative treatment is not possible, a dose decrease in axitinib is recommended (approximately half the dose). CYP3A4/5 inducers[37] may decrease axitinib exposure.[41] When CYP3A4/5 inducer cannot be discontinued, axitinib dose should be increased progressively with enhanced toxicity monitoring and therapeutic drug monitoring. In case of CYP3A4/5 secondary discontinuation, axitinib should be immediately returned to standard dose.

Clinical development in Phase I and II studies

The first-in-human axitinib trial was a dose escalation study ranging from 5 to 30 mg bid[11] and identified 5 mg bid as the recommended Phase II dose. This study included 36 patients with advanced solid tumors. Partial responses according to Response Evaluation Criteria In Solid Tumors (RECIST) were observed in two of the six patients with mRCC, leading to further development in this disease.[42] A third partial response occurred in a patient with adenoid cystic carcinoma. At higher dose levels, dose-limiting toxicities were hypertension, hemoptysis, and stomatitis. Phase I studies were specifically conducted in Japanese population and confirmed the 5 mg twice daily starting dose, along with similar pharmacokinetics and adverse effect profile.[43] Regarding efficacy, axitinib was then evaluated in three Phase II studies. The initial Phase II study evaluated axitinib efficacy in 52 cytokine-refractory mRCC patients. With two complete and 21 partial responses, ORR was 44%, with median time to progression 15.7 months, median response duration 23 months, and median OS 29.9 months.[44] These results confirmed axitinib potency in mRCC treatment, with unusually high ORR and OS. Long-term follow-up reported a 5-year OS of 20.6%[45] with classical toxicity manageable through dose modification and/or supportive care. The second Phase II trial evaluated axitinib in 62 patients previously treated with sorafenib.[46] ORR was 22.6%, with a median duration of response of 17.5 months, a median PFS of 7.4 months, and a median OS of 13.6 months. These weaker results suggested that pretreatment with a VEGFR inhibitor could induce resistance to this class of agents and significantly decrease the efficacy of a second inhibitor. Another Phase II was specifically conducted in Japanese patients (n=64) after cytokine therapy.[47] ORR was 51.6%, with median PFS 11 months and median OS 37.3 months. A randomized double-blind Phase II study of axitinib with or without dose titration was then conducted in 213 treatment-naive mRCC patients. After 4 weeks of treatment, patients were eligible for titration if they had no grade >2 adverse events and BP <150/90 mmHg with no more than two antihypertensive agents.[15] ORR was statistically different between the two arms (54% for axitinib titration and 34% for axitinib without titration, P=0.019), with no translation in terms of PFS. A follow-up analysis with pharmacokinetic data showed that patients eligible to dose titration had lower axitinib plasma exposure compared with the group not eligible for titration and that axitinib plasma exposure increased with an increasing dose.[16]

Place in therapy

Second-line therapy

Axitinib was approved by both American and European Agencies in 2012 for the treatment of advanced RCC after failure of one prior systemic therapy.[48] The demonstration of clinical benefit for axitinib was based on a Phase III, randomized, open-label, multicenter study of axitinib compared to sorafenib in patients with advanced RCC after failure of a prior systemic first-line regimen containing one

or more of the following agents: sunitinib, bevacizumab with interferon-α, temsirolimus, or cytokines.[49] In this multicentric randomized study, 723 patients were assigned to receive axitinib (n=361) or sorafenib (n=362). The median PFS was 6.7 months with axitinib compared to 4.7 months with sorafenib (hazard ratio [HR] 0.665; 95% CI 0.544–0.812; one-sided $P<0.0001$). However, the updated median OS was 20.1 months (95% CI 16.7–23.4) with axitinib and 19.2 months (17.5–22.3) with sorafenib (HR 0.969; 95% CI 0.800–1.174; one-sided $P=0.3744$). Importantly, axitinib dose increases to 7 mg and then to 10 mg, twice daily, were allowed for those patients without hypertension or adverse reactions grade >2, but dose increase was not allowed for patients receiving sorafenib. This difference could explain the difference in efficacy between axitinib and sorafenib[50] and sorafenib with plasma monitoring[51] and, therefore, represents a valid alternative to axitinib. Plasma monitoring can help identifying disease progression linked with sorafenib underexposure and lead to dose optimization to restore efficacy.[52–55] Since then, several other drugs have been approved in the treatment of mRCC. Pazopanib has been fully approved in first-line treatment in 2013, providing the opportunity to use either pazopanib or sunitinib in first-line treatment[3] and raising the question of which TKI should be preferred in first-line[56] and second-line therapies.[57] To date, only indirect comparison between pazopanib and axitinib is available and pointed out a similar response rate, but a higher risk of treatment discontinuation for pazopanib due to adverse events.[58] Several authors evaluated the safety profile of axitinib in second-line therapy, especially in the elderly population. There was no difference regarding adverse events' rate or response rate between patients aged <75 years or older.[59] Other authors reported their "patients' real-life experience" of axitinib and pointed out its tolerance and feasibility.[60,61]

Recently, two other drugs have been approved in RCC. A Phase III trial randomly assigned nivolumab or everolimus to 821 pretreated clear-cell RCC patients.[62] The median OS was 25.0 months (95% CI 21.8 to not estimable [NE]) with nivolumab and 19.6 months (95% CI 17.6–23.1) with everolimus. The HR for death with nivolumab versus everolimus was 0.73 (98.5% CI 0.57–0.93; $P=0.002$), leading to an approval by the US Food and Drug Administration (FDA) in November 2015 and by the European Medicines Agency (EMA) in February 2016. Additionally, another randomized Phase III trial assessed the efficacy of cabozantinib over everolimus in 658 pretreated clear-cell RCC patients.[63,64] The median OS was 21.4 months (95% CI 18.7 to NE) with cabozantinib and 16.5 months (95% CI 14.7–18.8) with everolimus (HR 0.66; 95% CI 0.53–0.83; $P=0.00026$). These results led to another approval by both the FDA (in April 2016) and the EMA (in September 2016). Moreover, a randomized Phase II trial including 157 clear-cell mRCC patients reported the efficacy of cabozantinib over sunitinib as first-line therapy.[65] The median PFS was 8.2 months (95% CI 6.2–8.8 months) with cabozantinib and 5.6 months (95% CI 3.4–8.1 months) with sunitinib. Cabozantinib reduced the rate of disease progression or death by 34% compared to sunitinib (adjusted HR for progression or death 0.66; 95% CI 0.46–0.95; one-sided $P=0.012$). The second-line therapy recommendations of the European Society for Medical Oncology (ESMO) include both cabozantinib and nivolumab,[66] which question the role of axitinib in this setting and make the discussion between axitinib and everolimus outdated.[67,68]

First line/adjuvant/neoadjuvant

Axitinib was also compared with sorafenib in first-line treatment of mRCC, showing no significant difference neither in median PFS (10.1 months [95% CI 7.2–12.1] versus 6.5 months [95% CI 4.7–8.3], respectively) nor in OS (21.7 months [95% CI 18.0–31.7] versus 23.3 months [95% CI 18.1–33.2]).[69,70] The authors concluded that axitinib demonstrated clinical activity with an acceptable safety profile. However, no comparison with any other first-line therapy is available. Currently, axitinib is not approved in first-line therapy.

Furthermore, axitinib was tested in the neoadjuvant setting.[71,72] A Phase II trial conducted from 2011 to 2013 reported a partial response after 12 weeks under treatment in nearly half of the patients (N=24) with locally advanced clear-cell carcinoma prior to surgery, leading to five partial nephrectomies. A higher rate of adverse events was observed compared to that reported in metastatic setting, with an acceptable level of postoperative complications (n=2). So far, no survival data are reported. Another Phase II neoadjuvant trial (Axipan) is ongoing to assess the efficacy of axitinib to enable partial nephrectomy after treatment for kidney tumors measuring 7–10 cm (NCT01599754). Similar trials are also ongoing with other drugs in neoadjuvant setting. The role of axitinib in the adjuvant setting is being evaluated with the ATLAS trial, conducted in patients with high-risk clear-cell carcinoma (NCT01599754). Axitinib or placebo is given for 3 years after nephrectomy, and the first results should be available in 2017. To date, the role of sunitinib as adjuvant therapy has been reported in two trials with conflicting results. The ECOG-ACRIN E2805 randomly assigned 1,943 patients to receive sunitinib (N=647), sorafenib (N=649), or placebo

(N=647) for 54 weeks.[73] There was no significant difference in median disease-free survival between groups (5.8 years [interquartile range {IQR} 1.6−8.2] for sunitinib [HR 1.02; 97.5% CI 0.85–1.23; *P*=0.8038), 6.1 years [IQR 1.7 to NE] for sorafenib [HR 0.97; 97.5% CI 0.80–1.17; *P*=0.7184], and 6.6 years [IQR 1.5–NE] for placebo). Conversely, the ASSURE trial randomized 615 patients with locoregional, high-risk clear-cell RRC to receive either sunitinib or placebo for 1 year after prior nephrectomy.[74] The authors reported a significant difference in median duration of disease-free survival (6.8 years [95% CI 5.8 to not reached] in the sunitinib group and 5.6 years [95% CI 3.8–6.6] in the placebo group [HR 0.76; 95% CI 0.59–0.98; *P*=0.03]). All in all, the use of TKI in adjuvant setting is not recommended and we look forward for the results of other trials.

Current development of axitinib and future directions

Several studies involving axitinib are currently ongoing (Table 6). Previous trials were mainly conducted on patients with clear-cell RCC, and therefore, data are not available for rare histology, such as papillary RCC, which is diagnosed in ~10% to 15% of patients with kidney cancer. This is the reason of the ongoing multicenter Phase II study, Axipap, assessing the efficacy of axitinib as first-line treatment of advanced or mRCC (NCT02489695). The first results are expected for January 2018. Another promising field of research for RCC is combining TKI and immunotherapy, in which axitinib is a leader. Thus, a Phase III study assessing the efficacy and safety of pembrolizumab (a PD-1 inhibitor) in combination with axitinib versus sunitinib monotherapy as a first-line treatment for patients with advanced or mRCC is ongoing since July 2016 (NCT02853331). Another Phase III randomized trial evaluating the antitumor activity and safety of avelumab (a PD-L1 inhibitor) in combination with axitinib and of sunitinib monotherapy, administered as first-line treatment, in patients with advanced RCC is ongoing since January 2016 (NCT02684006). Finally, a Phase II study comparing the efficacy of X4P-001 in combination with axitinib versus axitinib alone in pretreated mRCC patients started on January 2016 (NCT02667886). X4P-001 is an orally bioavailable CXCR4 antagonist, which is the receptor of CXCL12. CXCL12 has potent chemotactic activity for lymphocytes and is important in homing of hematopoietic stem cells to the bone marrow. A different approach consists in combining two angiogenesis inhibitors. This is the purpose of the ongoing Phase II study, comparing dalantercept (a subcutaneous Activin receptor-like kinase 1) in combination with axitinib versus axitinib alone in patients with pretreated advanced RCC (NCT01727336), for which results are expected in December 2017. Another ongoing Phase II study compares mRCC patients treated with axitinib and TRC105 (an antibody that binds to CD105, an important angiogenic target on vascular endothelial cells) with those treated with axitinib alone, after following failure of one prior VEGF TKI (NCT01806064).

Conclusion

Axitinib is an oral TKI that has been mainly developed for the treatment of RCC. Its advantages over other TKIs are a potent VEGFR inhibition, little off VEGFR-targeted effect,

Table 6 Ongoing clinical trials with axitinib

Clinical trial number	Purpose of the study	Estimated primary completion date	Phase
NCT02700568	Efficacy and safety of axitinib in mRCC patients with favorable IMDC prognostic factors who had progressed on sunitinib or pazopanib	January 2018	IV
NCT02639182	Progression-free survival of AGS-16C3F compared to axitinib in mRCC	June 2018	II
NCT02489695	Axitinib in first-line treatment in locally advanced or metastatic papillary renal cell carcinoma	January 2019	II
NCT01727336	Safety and tolerability of dalantercept in combination with axitinib in mRCC	December 2018	II
NCT01806064	Safety and tolerability and determine a recommended Phase II dose for TRC105 when added to standard dose axitinib in patients with advanced RCC	June 2017	I and II
NCT02853331	Efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy as a first-line treatment in mRCC	December 2019	III
NCT02493751	To estimate the maximum tolerated dose and select the Phase II dose of avelumab (MSB0010718C) in combination with axitinib	April 2018	I
NCT02684006	Efficacy and safety of avelumab in combination with axitinib compared to sunitinib monotherapy, as first-line treatment, in mRCC	June 2018	III
NCT02667886	Safety and tolerability of X4P-001 given alone and in combination with axitinib in mRCC	March 2019	I and II
NCT02535533	Safety and preliminary efficacy of the combination of axitinib and selenomethionine in mRCC	September 2019	I
NCT02579811	To figure out which dose of axitinib each patient should receive based on the side effects in mRCC	August 2018	II

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell cancer.

and an individualized prescription based on clinical dose titration. These advantages led to the demonstration of a clinical benefit compared to standard dose sorafenib and approval of axitinib as second-line treatment in RCC patients, but axitinib failed to demonstrate its superior efficacy as first line over other TKIs. Recently, axitinib have been replaced with cabozantinib and nivolumab in the second-line setting in international guidelines and its place in therapy therefore remains to determine. Trials are currently ongoing to assess its efficacy in the adjuvant setting or in the first-line setting in combination with immunotherapies.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7–30.
2. Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. *Lancet Oncol*. 2016; 17(9):1317–1324.
3. 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.
4. 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.
5. Hu-Lowe DD, Zou HY, Grazzini ML, et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. *Clin Cancer Res*. 2008;14(22): 7272–7283.
6. Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. *Drugs R D*. 2011;11(2):113–126.
7. Inai T, Mancuso M, Hashizume H, et al. Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts. *Am J Pathol*. 2004;165(1):35–52.
8. Pithavala YK, Chen Y, Toh M, et al. Evaluation of the effect of food on the pharmacokinetics of axitinib in healthy volunteers. *Cancer Chemother Pharmacol*. 2012;70(1):103–112.
9. European Medicines Agency; Committee for Medicinal Products for Human Use (CHMP). *CHMP assessment report; Inlyta (axitinib)*; 2012. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002406/WC500132190.pdf. Accessed August 8, 2017.
10. Chen Y, Tortorici MA, Garrett M, Hee B, Klamerus KJ, Pithavala YK. Clinical pharmacology of axitinib. *Clin Pharmacokinet*. 2013;52(9): 713–725.
11. Rugo HS, Herbst RS, Liu G, et al. Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. *J Clin Oncol*. 2005;23(24): 5474–5483.
12. Rini BI, Schiller JH, Fruehauf JP, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. *Clin Cancer Res*. 2011; 17(11):3841–3849.
13. Chen Y, Rini BI, Bair AH, Mugundu GM, Pithavala YK. Population pharmacokinetic-pharmacodynamic modelling of 24-h diastolic ambulatory blood pressure changes mediated by axitinib in patients with metastatic renal cell carcinoma. *Clin Pharmacokinet*. 2015; 54(4):397–407.
14. Rini BI, Garrett M, Poland B, et al. Axitinib in metastatic renal cell carcinoma: results of a pharmacokinetic and pharmacodynamic analysis. *J Clin Pharmacol*. 2013;53(5):491–504.
15. Rini BI, Melichar B, Ueda T, et al. Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial. *Lancet Oncol*. 2013;14(12):1233–1242.
16. Rini BI, Melichar B, Fishman MN, et al. Axitinib dose titration: analyses of exposure, blood pressure and clinical response from a randomized phase II study in metastatic renal cell carcinoma. *Ann Oncol*. 2015; 26(7):1372–1377.
17. Grünwald V, Merseburger AS. Axitinib for the treatment of patients with advanced metastatic renal cell carcinoma (mRCC) after failure of prior systemic treatment. *Onco Targets Ther*. 2012;5:111–117.
18. 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.
19. Rini BI, Escudier B, Hariharan S, et al. Long-term safety with axitinib in previously treated patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer*. 2015;13(6):540–547.e1–7.
20. Loriot Y, Boudou-Rouquette P, Billemont B, Ropert S, Goldwasser F. Acute exacerbation of hemorrhagic rectocolitis during antiangiogenic therapy with sunitinib and sorafenib. *Ann Oncol*. 2008;19(11):1975.
21. Coriat R, Ropert S, Mir O, et al. Pneumatosis intestinalis associated with treatment of cancer patients with the vascular growth factor receptor tyrosine kinase inhibitors sorafenib and sunitinib. *Invest New Drugs*. 2011;29(5):1090–1093.
22. Hescot S, Vignaux O, Goldwasser F. Pancreatic atrophy – a new late toxic effect of sorafenib. *N Engl J Med*. 2013;369(15):1475–1476.
23. Alivon M, Giroux J, Briet M, Goldwasser F, Laurent S, Boutouyrie P. Large artery stiffness and hypertension after antiangiogenic drugs: influence on cancer progression. *J Hypertens*. 2015;33(6):1310–1317.
24. Ropert S, Vignaux O, Mir O, Goldwasser F. VEGF pathway inhibition by anticancer agent sunitinib and susceptibility to atherosclerosis plaque disruption. *Invest New Drugs*. 2011;29(6):1497–1499.
25. Rini BI, Quinn DI, Baum M, et al. Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial. *Target Oncol*. 2015;10(1): 45–53.
26. Maitland ML, Bakris GL, Black HR, et al; Cardiovascular Toxicities Panel, Convened by the Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst*. 2010;102(9):596–604.
27. Chen Y, Suzuki A, Tortorici MA, et al. Axitinib plasma pharmacokinetics and ethnic differences. *Invest New Drugs*. 2015;33(2):521–532.
28. Chen Y, Rini BI, Motzer RJ, et al. Effect of renal impairment on the pharmacokinetics and safety of axitinib. *Target Oncol*. 2016;11(2): 229–234.
29. Brennan M, Williams JA, Chen Y, Tortorici M, Pithavala Y, Liu YC. Meta-analysis of contribution of genetic polymorphisms in drug-metabolizing enzymes or transporters to axitinib pharmacokinetics. *Eur J Clin Pharmacol*. 2012;68(5):645–655.
30. Huillard O, Mir O, Peyromaure M, et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. *Br J Cancer*. 2013;108(5):1034–1041.
31. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Ann Oncol*. 2010;21(8): 1594–1598.
32. Tortorici MA, Toh M, Rahavendran SV, et al. Influence of mild and moderate hepatic impairment on axitinib pharmacokinetics. *Invest New Drugs*. 2011;29(6):1370–1380.
33. Nishida H, Fukuhara H, Yamagishi A, et al. Sequential molecularly targeted drug therapy including axitinib for a patient with end-stage renal failure and metastatic renal cell carcinoma. *Hemodial Int*. 2016; 20(2):E1–E4.

34. Thiery-Vuillemin A, Orillard E, Mouillet G, et al. Hemodialysis does not impact axitinib exposure: clinical case of a patient with metastatic renal cell carcinoma. *Cancer Chemother Pharmacol*. 2017;79(6):1273–1276.
35. Jonkers IJAM, van Buren M. Nephrotic-range proteinuria in a patient with a renal allograft treated with sorafenib for metastatic renal-cell carcinoma. *Clin Exp Nephrol*. 2009;13(4):397–401.
36. Fortin MC, Raymond MA, Madore F, et al. Increased risk of thrombotic microangiopathy in patients receiving a cyclosporin-sirolimus combination. *Am J Transplant*. 2004;4(6):946–952.
37. Thomas-Schoemann A, Blanchet B, Bardin C, et al. Drug interactions with solid tumour-targeted therapies. *Crit Rev Oncol Hematol*. 2014;89(1):179–196.
38. Pithavala YK, Tong W, Mount J, et al. Effect of ketoconazole on the pharmacokinetics of axitinib in healthy volunteers. *Invest New Drugs*. 2012;30(1):273–281.
39. Gomo C, Coriat R, Faivre L, et al. Pharmacokinetic interaction involving sorafenib and the calcium-channel blocker felodipine in a patient with hepatocellular carcinoma. *Invest New Drugs*. 2011;29(6):1511–1514.
40. Da Silva F, Thomas-Schoemann A, Huillard O, Goldwasser F, Blanchet B. Benefit of therapeutic drug monitoring to disclose pharmacokinetic interaction between sunitinib and calcium channel blocker. *Ann Oncol*. 2016;27(8):1651–1652.
41. Pithavala YK, Tortorici M, Toh M, et al. Effect of rifampin on the pharmacokinetics of axitinib (AG-013736) in Japanese and Caucasian healthy volunteers. *Cancer Chemother Pharmacol*. 2010;65(3):563–570.
42. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205–216.
43. Mukohara T, Nakajima H, Mukai H, et al. Effect of axitinib (AG-013736) on fatigue, thyroid-stimulating hormone, and biomarkers: a phase I study in Japanese patients. *Cancer Sci*. 2010;101(4):963–968.
44. 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.
45. Rini BI, de La Motte Rouge T, Harzstark AL, et al. Five-year survival in patients with cytokine-refractory metastatic renal cell carcinoma treated with axitinib. *Clin Genitourin Cancer*. 2013;11(2):107–114.
46. 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.
47. Eto M, Uemura H, Tomita Y, et al; Japan Axitinib Phase II Study Group. Overall survival and final efficacy and safety results from a Japanese phase II study of axitinib in cytokine-refractory metastatic renal cell carcinoma. *Cancer Sci*. 2014;105(12):1576–1583.
48. Tzogani K, Skibeli V, Westgaard I, et al. The European Medicines Agency approval of axitinib (Inlyta) for the treatment of advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine: summary of the scientific assessment of the committee for medicinal products for human use. *Oncologist*. 2015;20(2):196–201.
49. 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.
50. Huillard O, Boissier E, Blanchet B, et al. Drug safety evaluation of sorafenib for treatment of solid tumors: consequences for the risk assessment and management of cancer patients. *Expert Opin Drug Saf*. 2014;13(5):663–673.
51. Blanchet B, Billemont B, Cramard J, et al. Validation of an HPLC-UV method for sorafenib determination in human plasma and application to cancer patients in routine clinical practice. *J Pharm Biomed Anal*. 2009;49(4):1109–1114.
52. Arrondeau J, Mir O, Boudou-Rouquette P, et al. Sorafenib exposure decreases over time in patients with hepatocellular carcinoma. *Invest New Drugs*. 2012;30(5):2046–2049.
53. Boudou-Rouquette P, Ropert S, Mir O, et al. Variability of sorafenib toxicity and exposure over time: a pharmacokinetic/pharmacodynamic analysis. *Oncologist*. 2012;17(9):1204–1212.
54. Bellesoeur A, Carton E, Mir O, et al. Critical role of sorafenib exposure over time for its antitumor activity in thyroid cancer. *Invest New Drugs*. 2014;32(3):569–572.
55. Boudou-Rouquette P, Thomas-Schoemann A, Bellesoeur A, Goldwasser F. Sorafenib for patients with differentiated thyroid cancer. *Lancet*. 2015;385(9964):227–228.
56. Huillard O, Alexandre J, Goldwasser F. Treatment of advanced renal-cell carcinoma. *N Engl J Med*. 2016;374:888.
57. Powles T, Staehler M, Ljungberg B, et al. Updated EAU guidelines for clear cell renal cancer patients who fail VEGF targeted therapy. *Eur Urol*. 2016;69(1):4–6.
58. Dranitsaris G, Schmitz S, Broom RJ. Small molecule targeted therapies for the second-line treatment for metastatic renal cell carcinoma: a systematic review and indirect comparison of safety and efficacy. *J Cancer Res Clin Oncol*. 2013;139(11):1917–1926.
59. Miyake H, Harada K-I, Ozono S, Fujisawa M. Efficacy and safety of axitinib in elderly patients with metastatic renal cell carcinoma. *Med Oncol*. 2016;33(8):95.
60. D'Aniello C, Vitale MG, Farnesi A, et al. Axitinib after sunitinib in metastatic renal cancer: preliminary results from Italian 'real-world' SAX study. *Front Pharmacol*. 2016;7:331.
61. MacLean E, Cisar L, Mehle K, Eremina D, Quigley JM. Real-world axitinib use in the United States: a retrospective study using linked datasets. *J Manag Care Spec Pharm*. 2016;22(6):723u–732u.
62. Motzer RJ, Escudier B, McDermott DF, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803–1813.
63. 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.
64. Choueiri TK, Escudier B, Powles T, et al; METEOR Investigators. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1814–1823.
65. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol*. 2017;35(6):591–597.
66. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(suppl 5):v58–v68.
67. Wiecek W, Karcher H. Nivolumab versus cabozantinib: comparing overall survival in metastatic renal cell carcinoma. *PLoS One*. 2016;11(6):e0155389.
68. Wells JC, Stukalin I, Norton C, et al. Third-line targeted therapy in metastatic renal cell carcinoma: results from the international metastatic renal cell carcinoma database consortium. *Eur Urol*. 2017;71(2):204–209.
69. 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.
70. 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*. 2017;15(1):72–76.
71. Karam JA, Devine CE, Urbauer DL, et al. Phase 2 trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell renal cell carcinoma. *Eur Urol*. 2014;66(5):874–880.
72. Kawakami F, Rao P, Tamboli P, Wood CG, Karam JA. Study of the kidney tumor-parenchymal interface after neoadjuvant treatment with axitinib for locally advanced clear cell renal cell carcinoma: matched analysis from a phase II trial. *J Urol*. 2017;197(3 pt 1):559–565.

73. 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.
74. Ravaud A, Motzer RJ, Pandha HS, et al; S-TRAC Investigators. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*. 2016;375:2246–2254.
75. Roskoski R. Sunitinib: a VEGF and PDGF receptor protein kinase and angiogenesis inhibitor. *Biochem Biophys Res Commun*. 2007; 356(2):323–328.
76. 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.
77. Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther*. 2007;6(7):2012–2021.
78. Lacy S, Hsu B, Miles D, Aftab D, Wang R, Nguyen L. Metabolism and disposition of cabozantinib in healthy male volunteers and pharmacologic characterization of its major metabolites. *Drug Metab Dispos*. 2015;43(8):1190–1207.