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Axitinib for the Management of Metastatic Renal Cell Carcinoma

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Abstract

In recent years, targeted agents have changed the treatment landscape for patients with advanced renal cell carcinoma (RCC), greatly improving treatment outcomes. Several targeted agents are now licensed for the treatment of metastatic RCC (mRCC), and a number of new agents are under investigation. Axitinib, a small molecule indazole derivative is an oral, potent multitargeted tyrosine kinase receptor inhibitor, which selectively inhibits vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 at subnanomolar concentrations, *in vitro*. In various nonclinical models, axitinib has demonstrated *in vivo* target modulation and antiangiogenesis. In pharmacokinetic studies, axitinib administered orally with food at the proposed regimen of 5 mg twice daily continuous daily dosing, is rapidly absorbed, reaching peak concentrations within 2–6 hours. Axitinib is metabolized primarily in the liver via the cytochrome P450 (CYP) system with less than 1% of the administered drug passing unchanged in the urine. The pharmacokinetics of axitinib do not appear to be altered by coadministered

chemotherapies, and antacids do not have a clinically significant effect. However, coadministration with CYP3A4 and 1A2 inducers is contraindicated. In addition, proton pump inhibitors reduce the rate of axitinib absorption. Increased axitinib exposure is associated with higher efficacy indicated by decreased tumor perfusion and volume. In three phase II clinical trials in patients with advanced RCC previously treated with cytokines, chemotherapy or targeted agents, axitinib has demonstrated antitumor activity with a favorable noncumulative toxicity profile. In one study of Western patients with cytokine-refractory mRCC, an objective response rate (ORR) of 44.2% (95% CI 30.5, 58.7) was achieved. The median time to progression was 15.7 months (95% CI 8.4, 23.4) and the median overall survival (OS) was 29.9 months (95% CI 20.3, not estimable). In the second study of patients with sorafenib-refractory mRCC, ORR was 22.6% (95% CI 12.9, 35.0). The median progression-free survival (PFS) was 7.4 months (95% CI 6.7, 11.0) and a median OS of 13.6 months (95% CI 8.4, 18.8) was achieved. Results from the third study in Japanese patients with cytokine-refractory mRCC reported an ORR of 55% and median PFS of 12.9 months (95% CI 9.8, 15.6).

In the three studies, the most common adverse events reported were fatigue, hypertension, hand-foot syndrome (HFS), and gastrointestinal toxicity, which were generally manageable with standard medical intervention. Of note, the incidence of HFS and proteinuria in the Japanese study was higher than that reported in the Western study in cytokine-refractory mRCC patients.

An observed association between diastolic blood pressure ≥90 mmHg and increased efficacy suggests potential use as a prognostic biomarker. However, this requires further investigation. Two randomized phase III clinical trials are ongoing to determine the efficacy of axitinib in patients with mRCC in the first- and second-line setting. These results will help to determine the place of axitinib in the mRCC treatment algorithm.

1. Introduction

Renal cell carcinoma (RCC) is the most common form of kidney cancer. It is diagnosed in more than 200 000 patients worldwide every year and accounts for approximately 100 000 deaths annually.[1,2] In the last half-century, the incidence of RCC has increased; in the US alone, there has been a 126% increase in incidence and a 36.5% increase in mortality since 1950, with a corresponding increase in annual mortality, possibly due to the continuing development of advanced screening techniques.[3,4]

Most cases of RCC are of clear cell histology, which is often associated with mutations of the Von Hippel-Lindau (VHL) tumor suppressor gene, resulting in an increased transcription of several hypoxia-inducible genes including vascular endothelial growth factor (VEGF), a potent signaling molecule involved in inhibition of dendritic cell maturation, tumor cell apoptosis, and promotion of tumor angiogenesis.[5-8] The incidence of metastatic RCC (mRCC) is highest in developed regions, such as the US and Europe.[9] mRCC is highly resistant to conventional treatments, with a 5-year survival rate with stage IV disease (of which one-third of patients present with at initial diagnosis) of just 0–10%.[9] Additionally, recurrence develops in approximately 20–40% of patients treated for a localized tumor.[9,10]

Until recently, standard treatment for mRCC has consisted of immunotherapy with either interleukin-2 (IL-2) or interferon-α (IFNα), both of which are associated with overall response rates (ORRs) of 5–20%, and significant clinical toxicities.[11-15] In randomized controlled trials,

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IFNα has been associated with a median overall survival (OS) of 12–19 months,[16-18] and high-dose IL-2 can result in disease cure in 5–10% of patients.[19] Additionally, treatment options were scarce for those patients who progressed on cytokine therapy.

In recent years, targeted agents have changed the treatment landscape for patients with advanced RCC, greatly improving treatment outcomes. Several targeted agents are now licensed for the treatment of mRCC, including the multitargeted tyrosine kinase inhibitors sunitinib, sorafenib and pazopanib; the mammalian target inhibitor of rapamycin (mTOR) kinase inhibitors temsirolimus and everolimus; and the VEGF monoclonal antibody bevacizumab in combination with IFNα.[20-25]

ORRs of 26–46% have been reported with these targeted agents in patients with mRCC.[20,23,25] Median progression-free survival (PFS) of 6–11 months has been achieved in treatment-naïve patients,[20,22,23,25] and 5–6 months in previously treated patients.[21,24] Targeted agents have also been associated with a significantly increased median OS of up to 18 months in previously treated patients,[21,24] while in treatment-naïve patients, median OS greater than 2 years has been attained with sunitinib.[26] Targeted agents have also shown efficacy in previously untreated patients with poor prognosis, with the mTOR inhibitor temsirolimus improving median OS by 49% compared with IFNα alone.[22]

A number of second-generation targeted therapies are on the horizon, including axitinib, a potent and selective inhibitor of VEGF receptor tyrosine kinases (VEGF RTK)-1, -2, and -3 that has shown substantial anticancer activity in phase II trials in patients with RCC. This article discusses the preclinical and clinical data for axitinib for the management of RCC.

2. Mode of Action and Rationale

2.1 Vascular Endothelial Growth Factor Receptor (VEGFR) Signaling Pathway

Among other factors, the VEGFR signaling pathway plays a key role in the pathogenesis and progression of several tumor types as a pivotal mediator of tumor angiogenesis.[27,28] VEGFR-1, -2, and -3 are expressed in vascular sprouts, although VEGFR-3 is found primarily in the lymphatic system.[28-31] Indeed, signaling via the VEGFR family plays a role in regulating all three key tumor processes: growth, vascular angiogenesis, and metastatic spread.[27] VEGFR-1 is involved in angiogenesis and tumor growth; VEGFR-2 is involved in endothelial cell proliferation, migration and survival, and angiogenesis; and VEGFR-3 is involved in lymphangiogenesis.[28,30]

2.2 Axitinib Anti-VEGFR Activity

Axitinib, a small molecule indazole derivative, is an oral, potent, and highly selective inhibitor of VEGFR-1, -2, and -3. The structure-based drug design of axitinib allows strategic optimization of critical binding elements, with the tight fit of axitinib into the 'deep pocket' conformation of the kinase domain of VEGFRs resulting in high potency and selectivity (figure 1).[32]

In vitro, axitinib inhibits VEGFR-1, -2, and -3 autophosphorylation at picomolar concentrations, consistent with its potent and highly selective activity against these receptors. Indeed, the half maximal inhibitory concentration (IC_{50}) for axitinib is 10-fold lower for the VEGF family receptors than for RTKs of other family receptors.[32] The IC_{50} for axitinib is also lower than other RTK inhibitors for most of the targets of interest (table I).[33-38] The relative potencies of axitinib

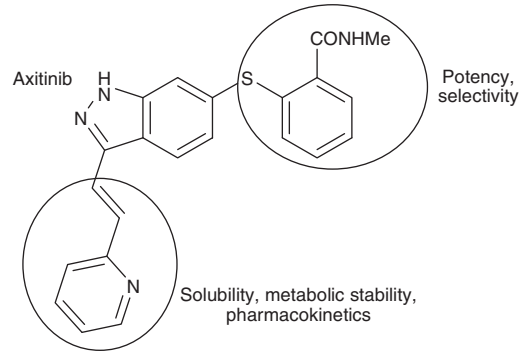

Fig. 1. Axitinib drug design. Reproduced from Hu-Lowe et al.,[32] with permission.

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Table I. IC_{50} for selected targeted agents. Reproduced from Bellmunt et al.,[33] with permission

Target	IC_{50} (nM)			
	sunitinib[34,35]	sorafenib[35-37]	pazopanib[35,38]	axitinib[32]
VEGFR-1	2	NR	10	0.1[a]
VEGFR-2	10	90	30	0.2
VEGFR-3	17	20	47	0.1–0.3
PDGFR-β	8	57	84	1.6
EGFR	880	58	NR	NR
c-KIT	10	68	74	1.7
FGF-1R	880	580	14	231
FLT-3	14	58	NR	>1000
Raf-1	NR	6	NR	NR
CSF-1R	100	NR	NR	73

a Converted from value obtained in the presence of 2.3% bovine serum albumin.

c-KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; **CSF** = colony-stimulating factor; **EGFR** = endothelial growth factor receptor; **FGF** = fibroblast growth factor; **FLT** = FMS-like tyrosine kinase; **IC_{50}** = concentration of a drug that is required to achieve 50% inhibition of the enzyme in a biochemical assay; **NR** = not reported; **PDGFR** = platelet-derived growth factor; **Raf** = v-raf-1 murine leukemia viral oncogene homolog 1; **VEGFR** = vascular endothelial growth factor receptor.

and other agents targeting VEGFRs -1, -2, and -3 in mRCC are illustrated in figure 2.[33,39-45] Additionally, studies carried out *in vitro* showed that axitinib did not significantly inhibit other receptor kinases that were tested, including colony-stimulating factor (CSF)-1R, fms-like tyrosine kinase (Flt)-3, fibroblast growth factor receptor (FGFR)-1, ret proto-oncogene (RET), epidermal growth factor receptor (EGFR), and met proto-oncogene encoding hepatocyte growth factor (c-Met).[32]

2.3 Axitinib Antitumor Activity

Axitinib has demonstrated *in vivo* target modulation and antiangiogenesis in several nonclinical models.[32] In xenograft tumor mouse models across various tumor types, axitinib antitumor activity was associated with marked reduction in tumor vascularization and blood flow, and tumor shrinkage. These were achieved at a range of plasma concentrations consistent with its *in vitro* potency and were dose dependent.[32] The C_{target} value (required *in vivo* pharmacologic concentration) was determined to be ~0.5 nmol/L (unbound), which in humans would be equivalent to a C_{target} of ~100 nmol/L (total).

In a phase I study of axitinib in patients with advanced solid tumors, the maximum tolerated dose and recommended dose in humans was determined to be 5 mg twice daily on a continuous daily dosing schedule.[46] Hypertension and stomatitis were the main dose-limiting toxicities seen during the phase I study; these were mainly observed with higher doses of axitinib. Other adverse events (AEs) included fatigue, diarrhea, nausea, and vomiting.[46]

3. Pharmacokinetics/Pharmacodynamics

3.1 Pharmacokinetics

Axitinib is administered orally on a proposed standard dosing regimen of 5 mg twice daily with titration as required, and is rapidly absorbed, with peak plasma concentrations measurable within 2–6 hours after dosing in the fed state.[46] Axitinib exhibits linear pharmacokinetics at doses of 2–10 mg twice daily.[46] Peak plasma concentrations are reached in 1–2 hours after dosing in the fasted state, while plasma half-life remains unchanged.[46] Axitinib exists in different crystal forms. With crystal polymorph Form IV, higher plasma levels were observed after overnight fasting, but not with shorter fasting times (e.g. fasting 1 or 2 hours before and after each dose).[47] Findings for polymorph Form XLI are awaited.

Axitinib primarily undergoes hepatic metabolism via the cytochrome P450 (CYP) 3A4 isozyme,

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with some additional metabolism occurring via oxidation by CYP2C19 and CYP1A2 and glucuronidation via uridine diphosphate glucuronosyltransferase (UGT) 1A1.[46] The major circulating axitinib metabolites, the glucuronide and the sulfoxide, are not active. Less than 1% of the administered drug appears as unchanged drug in the urine.[46]

No changes in the pharmacokinetic profile of axitinib or comparator agents were observed when axitinib was administered in combination with chemotherapies including paclitaxel, docetaxel, cisplatin, carboplatin, oxaliplatin, 5-fluorouracil, irinotecan, and/or gemcitabine.[48-52]

As both CYP3A4 and 1A2 are known to be inducible, coadministration of axitinib with agents known to be potent inducers is contraindicated. Data from a single patient in a phase I study demonstrated an interaction between axitinib and phenytoin, a potent inducer of several CYP450 isozymes.[46] In this patient, the area under the concentration-time curve from 0 to 24 hours (AUC_{24}) and the peak plasma concentration (C_{max}) of axitinib were reduced by 10-fold, and the patient subsequently experienced disease progression, despite earlier response to axitinib, which ultimately led to their discontinuation from treatment. As a result of this, concomitant use of potent inducers of the CYP3A4 and CYP1A2 isozymes was subsequently excluded during axitinib treatment. In a phase I two-way crossover study of axitinib given with or without rifampicin in Japanese and Caucasian healthy volunteers (n = 40), rifampicin (a potent inducer of drug-metabolizing enzymes including CYP3A4, CYP1A2, and UGT1A1) decreased the AUC from time zero extrapolated to infinity (AUC_{∞}) and C_{max} of axitinib (geometric mean reduced to 79% and 71%, respectively).[53] No differences in pharmacokinetics were observed between Japanese and Caucasian subjects.

Since axitinib is predominantly metabolized by CYP3A4, concomitant use of potent inhibitors with axitinib is also excluded. Data from a phase I two-way crossover study of axitinib alone or coadministered with ketoconazole (a potent CYP3A inhibitor) in healthy volunteers (n = 32) demonstrated that concurrent administration of ketoconazole increased axitinib plasma exposure (AUC_{∞}) and C_{max} with approximate

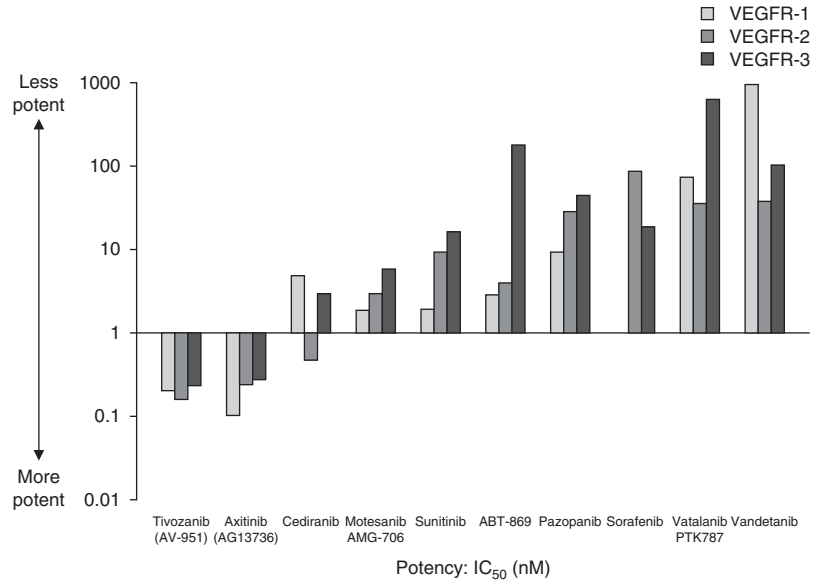

Fig. 2. Relative potency of targeted agents in metastatic renal cell carcinoma (mRCC).[32,33,39-45] **IC_{50}** = concentration that produces 50% inhibition; **VEGFR** = vascular endothelial growth factor receptor. Reproduced from Bellmunt et al.,[33] with permission.

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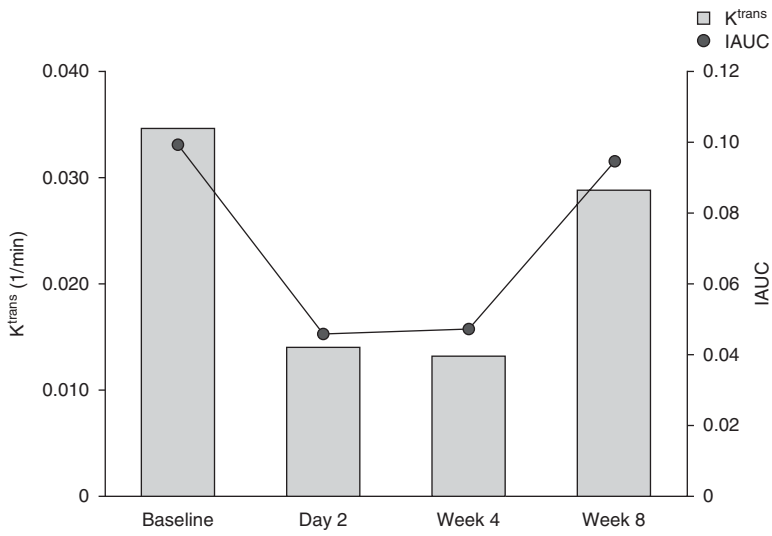

Fig. 3. Quantitative representation of tumor initial area under the curve (IAUC) values mapped over the tumor region K^{trans}, volume transfer constant. Reproduced from Liu et al.,[55] with permission.

2- and 1.5-fold increases in the geometric mean values, respectively.[54] In addition, C_{max} occurred 1.5 hours after dosing with axitinib alone compared with 2.0 hours after coadministration with ketoconazole.

Antacids do not have a clinically significant effect on axitinib pharmacokinetics.[46] Coadministration with the proton pump inhibitor, rabeprazole, reduced the rate of axitinib absorption, leading to a decrease in C_{max}, but had only marginal impact on AUC.[46]

3.2 Pharmacodynamics

In a study measuring the exposure-response relationship of axitinib in patients with advanced solid tumors, a >50% decrease in the volume transfer coefficient (K^{trans}) and initial area under the curve was demonstrated by day 2 of therapy, and persisted through week 4 of treatment (figure 3).[55] A linear correlation suggested that increased axitinib exposure is associated with higher efficacy, as indicated by decreased tumor perfusion and volume.

4. Phase II Clinical Study Results

Axitinib has been studied in three phase II, single-arm, multicenter, clinical trials investigating its efficacy, safety and pharmacodynamics in patients with mRCC (table II).[56,57]

4.1 Efficacy

In the first study, conducted in 52 patients with cytokine-refractory mRCC, patients received axitinib (administered as 5 mg twice daily) in the fasted state in 28-day treatment cycles until disease progression or unacceptable toxicity.[56,58] Results from this study demonstrated an ORR of

Table II. Summary of efficacy findings in key phase II studies [n (%)]

Best response	Cytokine refractory (n = 52)[56]	Sorafenib refractory (n = 62)[57]
Objective response rate	23 (44)	14 (23)
complete response	2 (4)	NR
partial response	21 (40)	14 (23)
Stable disease		11(18)
≥8 wk	22 (42)	
≥24 wk	13 (25)	
Disease progression	4 (8)	25 (40)
Missing data	3 (6)	12 (19)
PFS (mo)	13.7	7.4
OS (mo)	29.9	13.6

OS = overall survival; **NR** = not reported; **PFS** = progression-free survival.

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44.2% (23 patients; 95% CI 30.5, 58.7), as indicated by two complete responses (4%) and 21 partial responses (PR; 40%) based on the Response Evaluation Criteria In Solid Tumors (RECIST).[59] Additionally, 22 patients (42%) showed stable disease (SD) lasting for longer than 8 weeks, including 13 (25%) patients with SD for at least 24 weeks. The median duration of response was 23.0 months. The median time to progression was 15.7 months (95% CI 8.4, 23.4), and the median OS was 29.9 months (95% CI 20.3, not estimable). Maximum percentage decrease in target lesion size, based on RECIST is shown in figure 4a.

The second phase II study evaluated axitinib in 62 patients with advanced and refractory RCC who had not responded to sorafenib-based therapy.[57] In this study, prior therapies were not limited to sorafenib, but could also include cytotoxic therapies, cytokines and other targeted therapies such as sunitinib, bevacizumab, and temsirolimus. PR was observed in 14 patients giving an ORR of 22.6%, (95% CI 12.9, 35.0), SD

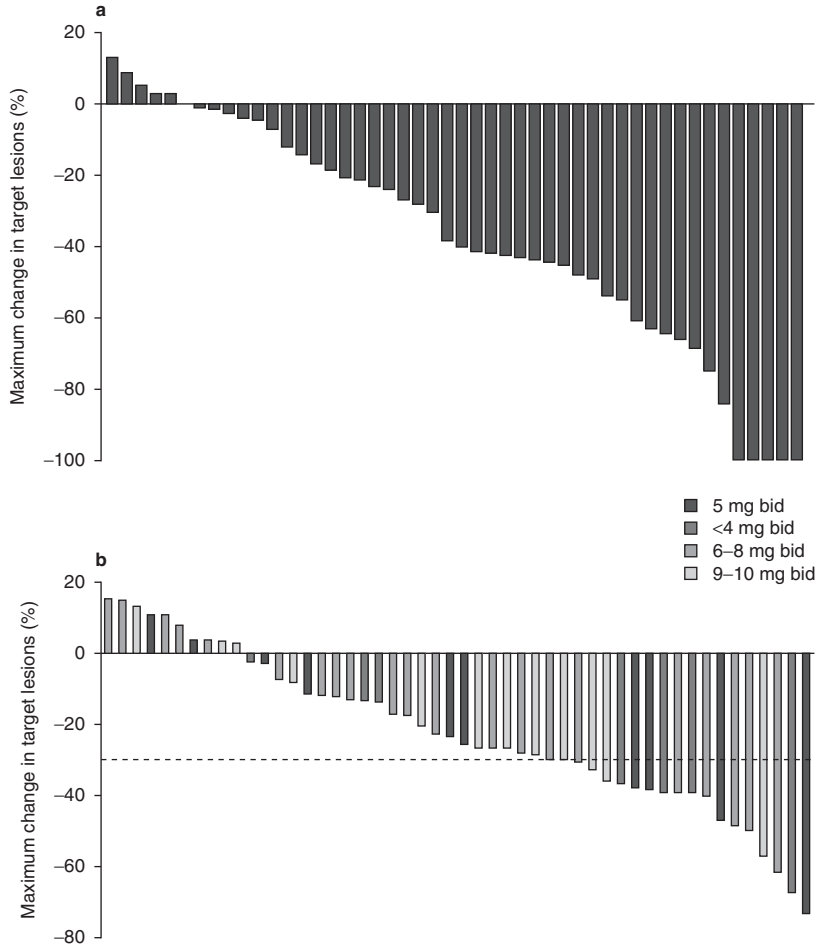

Fig. 4. Tumor responses from phase II trials of axitinib in patients with metastatic renal cell carcinoma (mRCC). Each bar represents one patient. Maximum percentage reduction in tumor size of target lesions by Response Evaluation Criteria In Solid Tumors (RECIST) [–100% = complete response; –30% = partial response; n = 48]. Reproduced from (**a**) Rini et al.[57] and (**b**) Rixe et al.,[56] with permission **bid** = twice daily; **CR** = complete response; **PR** = partial response.

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Table III. Common adverse events reported in phase II clinical trials[56,57]

Adverse event	Cytokine refractory (n = 52)[56]		Sorafenib refractory (n = 62)[57]	
	all grades [n (%)]	grade 3/4 [n (%)]	all grades [n (%)]	grade 3/4 [n (%)]
Diarrhea	31 (60)	5 (10)	38 (61)	9 (15)
Hypertension	30 (58)	8 (15)	28 (45)	10 (16)
Fatigue	27 (52)	4 (8)	48 (77)	10 (16)
Nausea	23 (44)	0	27 (44)	4 (7)
Hoarseness	19 (37)	0	NR	NR
Dyspnea	NR	NR	24 (39)	9 (15)
Dysphonia	NR	NR	23 (37)	0
Hand-foot syndrome	NR	NR	22 (36)	10 (16)
Anorexia	18 (35)	1 (2)	30 (48)	0
Mucosal inflammation	NR	NR	21 (34)	1 (2)
Dry skin	17 (33)	0	NR	NR
Weight loss	14 (27)	0	19 (31)	3 (5)
Dyspepsia	12 (23)	0	NR	NR
Vomiting	11 (21)	0	20 (32)	3 (5)
Cough	NR	NR	18 (29)	0
Headache	NR	NR	18 (29)	1 (2)
Arthralgia	NR	NR	17 (27)	2 (3)
Constipation	NR	NR	16 (26)	0
Dysgeusia	NR	NR	14 (23)	0
Abdominal pain	NR	NR	13 (21)	7 (11)
Pain in extremity	NR	NR	13 (21)	2 (3)

NR = not reported.

in 11 patients (18%), and progressive disease in 25 patients (40%). Some degree of tumor shrinkage was seen in 40 of 50 patients (80.0%) for whom post-baseline data were available.

In this study, tumor responses were observed within the group of patients who dose-titrated to >5 mg twice daily (7/33; 21%), as well as in patients who remained on 5 mg twice daily or who were dose-modified to <5 mg twice daily (7/29; 24%). Maximum percentage reduction in target lesions (by RECIST) during treatment with axitinib based on dose titration is illustrated in figure 4b. These results suggest that axitinib dose titration (i.e. axitinib given at a higher dose [above its standard starting dose]), may improve the response to treatment in some patients. This is being investigated in an ongoing randomized, double-blind, phase II study of axitinib with or without dose titration in patients with mRCC.[60]

After a median follow-up of 22.7 months (95% CI 6.7, 11.0), the median PFS was 7.4 months (95% CI 6.7, 11.0), and median OS was 13.6 months (95% CI 8.4, 18.8).

In the third phase II study in Japanese patients with mRCC refractory to previous cytokine-based treatment, patients (n = 64) received continuous dosing of axitinib (starting dose: 5 mg twice daily).[58] An ORR of 55% was reported in this study and median PFS was 12.9 months (95% CI 9.8, 15.6).

4.2 Safety and Tolerability

For single-agent axitinib, the most common AEs reported are hypertension, fatigue, and gastrointestinal toxicity (table III).[56,57] These AEs are an expected class effect due to the known mechanism of action of the drug. The majority of AEs are manageable with dose modification and supportive care; hypertension is generally easily managed with standard antihypertensive drugs.[56,57]

In the three phase II studies in renal carcinoma, no unexpected AEs occurred. In the Western

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trial of cytokine-refractory patients, the most common all-causality treatment-related AEs included diarrhea (60%), hypertension (58%), and fatigue (52%).[56] The most common grade 3–4 AEs were hypertension (15%), diarrhea (10%), and fatigue (8%), and no grade 3–4 hematologic toxicities were noted. Only four patients reported treatment-related proteinuria, all of which were grade 1–2. Of the 52 patients enrolled, ten patients discontinued due to treatment-related AEs.[56]

In sorafenib-refractory patients, the most common all-causality AEs were fatigue (77%), diarrhea (61%), anorexia (48%), and hypertension (45%).[57] All-causality grade 3–4 AEs included hand-foot syndrome (HFS; 16.1%), fatigue (16.1%), hypertension (16.1%), dyspnea (14.5%), diarrhea (14.5%), dehydration (8.1%), and hypotension (6.5%). Of 62 patients enrolled, treatment was discontinued in 22 patients due to AEs (of these, 12 were attributed to study treatment).[57]

Common treatment-related AEs reported in the Japanese trial of cytokine-refractory patients were HFS (73%), hypertension (66%), diarrhea (66%), and hoarseness (53%). In all, 18 patients developed proteinuria ≥2 g/24 hours during treatment and required dose reduction or treatment interruption/discontinuation.[58] Of note, the incidences of HFS and proteinuria in the Japanese study were higher than those reported in the Western study in cytokine-refractory mRCC patients.

These phase II data indicate that the continuous administration and the constant dose of axitinib appear to have acceptable tolerability and are compatible with long-term administration. Certainly, in the Western study in cytokine-refractory mRCC, patients have received axitinib for more than 3 years with no cumulative toxicity.[56]

4.3 Diastolic Blood Pressure and Clinical Efficacy

An interesting association between diastolic blood pressure (DBP) and clinical efficacy appears to exist with axitinib therapy. Hypertension is a commonly observed event during treatment with axitinib and other VEGF signal inhibitors, and is generally manageable with standard antihypertensive agents. In a retrospective analysis of axitinib treatment across multiple tumor types, the occurrence of DBP ≥90 mmHg was associated with increased OS.[61]

A pooled analysis of the two axitinib phase II mRCC studies (n = 114) explored the relationship between pharmacokinetics, DBP, and clinical efficacy.[61] Response was evaluated based on RECIST-defined ORR, OS, and changes in tumor size (the sum of lesion diameter; SLD). DBP and mean steady-state AUC during axitinib treatment were used as predictors of clinical efficacy in mRCC patients using logistic regression.

Using this methodology, DBP ≥90 mmHg and AUC appear to be independent predictors of clinical efficacy, with an improved clinical response (as indicated by a reduction in SLD) associated with increasing axitinib plasma exposure (AUC).

There was an increased probability ($p < 0.05$) of achieving a PR with increasing AUC, with a 47% and 22% increase in the probability of achieving a PR for every 100 ng/h/mL increase in AUC for cytokine-refractory and sorafenib-refractory patients, respectively. Additionally, improved clinical response was associated with greater changes in DBP. Logistic regression analysis showed that the probability of experiencing a PR increased with greater maximum DBP ($p < 0.05$), and patients had an 86% increase in the probability of achieving a PR for every 10 mmHg increase in DBP ($p < 0.05$; figure 5).[62]

OS was also longer in patients with at least one DBP measurement ≥90 mmHg during axitinib therapy ($p < 0.05$), with a median OS of 130 weeks for patients with DBP ≥90 mmHg compared with just 42 weeks for patients without DBP ≥90 mmHg. Interestingly, increases in AUC were not highly correlated with changes in DBP.

Logistic regression and Kaplan-Meier analyses showed that increased axitinib exposure and DBP ≥90 mmHg were independently associated with several measures of clinical improvement, including longer OS, greater probability of a PR, and greater reductions in SLD.

In the Japanese phase II study,[58] patients with at least one recorded DBP reading ≥90 mmHg during the first 28 days of treatment had significantly longer PFS compared with those without

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a DBP reading ≥90 mmHg (median PFS, 14.6 vs 9.8 months; p = 0.02).

These data suggest that in patients with mRCC, the occurrence of DBP ≥90 mmHg during axitinib treatment is not merely a reflection of higher axitinib drug levels and, therefore, may be of clinical interest and worthy of investigation as a potential prognostic biomarker.

5. Ongoing Clinical Studies

Clinical investigation of axitinib is ongoing in one phase II study[60,63] and two large-scale phase III trials in patients with mRCC.[64,65]

5.1 Ongoing Phase II Clinical Study: The AGILE 1046 Trial

The AGILE 1046 trial is a prospective, randomized trial to evaluate (i) the efficacy of axitinib treatment with or without dose titration in treatment-naïve mRCC patients; (ii) axitinib-related changes in blood pressure (BP) using 24-hour ambulatory BP monitoring and telemedicine in a subset of patients; and (iii) axitinib pharmacokinetics over 6 hours, time-matched with BP measurements prior to each pharmacokinetic sample.[63]

Patients will be randomized 1 : 1 to receive axitinib 5 mg twice daily plus dose titration with axitinib (Arm A) or placebo (Arm B). Only the dose titration portion will be blinded. Patients not meeting randomization (dose-titration) criteria will continue receiving axitinib without dose titration in a separate, non-randomized arm (Arm C).[60,63]

The primary endpoint is ORR, and secondary endpoints include PFS, OS, duration of response, safety, pharmacokinetics, BP, and translational medicine assessments.[60,63] Estimated enrollment is 200 and the trial is currently recruiting participants with an estimated enrollment period of 2 years.[63]

5.2 Ongoing Phase III Clinical Studies

5.2.1 The AGILE 1032 Trial

The AGILE 1032 trial is a global, phase III, randomized, open-label study that will compare the efficacy and safety of second-line axitinib 5 mg twice daily or sorafenib 400 mg twice daily (both with continuous dosing) therapy in 723 patients with mRCC refractory to one prior first-line therapy.[64] The primary endpoint is PFS, with secondary endpoints including OS, response rate, duration of response, safety and tolerability,

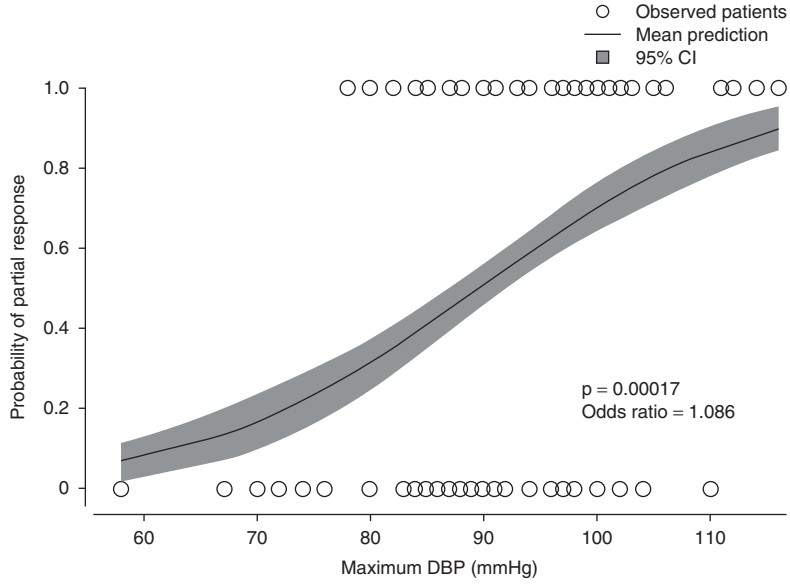

Fig. 5. Probability of a partial response with maximum diastolic blood pressure (DBP). Reproduced from Rixe et al.,[62] with permission.

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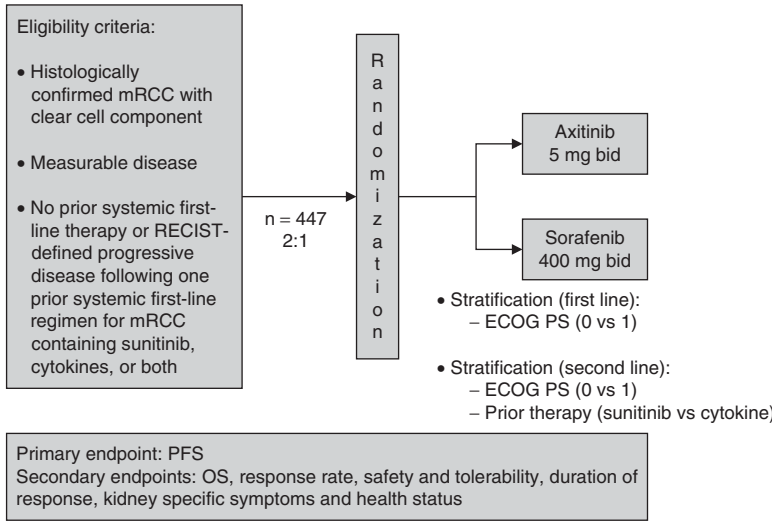

Fig. 6. Study schema for AGILE 1051.[65] **bid** = twice daily; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **mRCC** = metastatic renal cell carcinoma; **OS** = overall survival; **PFS** = progression-free survival; **RECIST** = Response Evaluation Criteria In Solid Tumors.

and specific renal symptoms and health status measures. This 3-year trial has completed accrual as of April 2010 and is expected to report out in 2011.

5.2.2 The AGILE 1051 Trial

The second trial is a randomized, open-label, phase III study (AGILE 1051 trial) evaluating first- and second-line axitinib 5 mg twice daily versus sorafenib 400 mg twice daily (again, both with continuous dosing) in Asian and non-Asian patients with mRCC who have either received no prior systemic first-line therapy or have progressed after one prior systemic first-line regimen for metastatic disease containing sunitinib, cytokines, or both.[65] The primary and secondary endpoints are the same as for the AGILE 1032 trial. At the time of writing, trial 1051 is still recruiting, and has an estimated enrollment of 447 patients. A schema for this trial is shown in figure 6.

6. Conclusions and Outlook

Axitinib is a potent and selective inhibitor of VEGFR-1, -2, and -3, delivered orally, with a convenient schedule of administration. Axitinib has been shown to reduce vascular permeability, tumor vascularization and tumor volume, and has demonstrated antitumor activity as a single agent in patients with cytokine- and/or sorafenib-refractory mRCC. The activity range of axitinib is the highest when compared with other active drugs currently approved for use in mRCC, and raises high expectations. Axitinib also has a favorable and non-cumulative tolerability profile associated with manageable AEs, which are generally mild to moderate in severity. Potential associations between the efficacy of axitinib and DBP are currently under evaluation, with promising preliminary results. The place of axitinib in the oncologist's armamentarium and the future role of the drug in the treatment algorithm for mRCC will be further elucidated in the two ongoing, large-scale, phase III studies in this disease.

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