

Efficacy and Safety of Axitinib Versus Sorafenib in Metastatic Renal Cell Carcinoma: Subgroup Analysis of Japanese Patients from the Global Randomized Phase 3 AXIS Trial

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Objective: Axitinib is a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors 1, 2 and 3. The efficacy and safety of axitinib in Japanese patients with metastatic renal cell carcinoma were evaluated.

Methods: A subgroup analysis was conducted in Japanese patients enrolled in the randomized Phase III trial of axitinib versus sorafenib after failure of one prior systemic therapy for metastatic renal cell carcinoma.

Results: Twenty-five (of 361) and 29 (of 362) patients randomized to the axitinib and sorafenib arms, respectively, were Japanese and included in this analysis. Median progression-free survival in Japanese patients was 12.1 months (95% confidence interval 8.6 to not estimable) for axitinib and 4.9 months (95% confidence interval 2.8–6.6) for sorafenib (hazard ratio 0.390; 95% confidence interval 0.130–1.173; stratified one-sided $P = 0.0401$). The objective response rate was 52.0% for axitinib and 3.4% for sorafenib ($P = 0.0001$). The common all-causality adverse events (all grades) in Japanese patients were dysphonia (68%), hypertension (64%), hand–foot syndrome (64%) and diarrhea (56%) for axitinib, and hand–foot syndrome (86%), hypertension (62%) and diarrhea (52%) for sorafenib. The safety profiles of axitinib and sorafenib in Japanese patients were generally similar to those observed in the overall population, with the exceptions of higher incidences of hypertension, dysphonia, hand–foot syndrome, hypothyroidism and stomatitis.

Conclusions: Axitinib is efficacious and well tolerated in Japanese patients with previously treated metastatic renal cell carcinoma, consistent with the results in the overall population, providing a new targeted therapy for these Japanese patients.

Key words: axitinib – renal cell carcinoma – vascular endothelial growth factor receptors – clinical trial – phase III

INTRODUCTION

Kidney cancer accounts for 2.2% of all malignancies worldwide (1), with steady increases in global incidence over the past several decades (2–5). Renal cell carcinoma (RCC) is the most common form of kidney cancer (5). When RCC is diagnosed early, surgical resection of localized tumors is the primary and often curative treatment (6–8). However, due to lack of symptoms with early stage RCC, ~30% of patients are not diagnosed until their disease is advanced or metastatic (2,9). Until recently, immunotherapy with interleukin-2 or interferon (IFN)- α was the established systemic therapy for patients with metastatic RCC (mRCC), generally with modest clinical benefits (10). Advanced understanding of the molecular biology of RCC led to the development and approval of several drugs that inhibit vascular endothelial growth factor receptor (VEGFR) signaling pathways (i.e. sorafenib, sunitinib, bevacizumab/IFN- α , pazopanib and axitinib) (9,11–17) or mammalian target of rapamycin pathways (i.e. temsirolimus and everolimus) (18,19).

Axitinib is a potent and selective second-generation inhibitor of VEGFR-1, 2 and 3 (20–24). Axitinib has shown anti-tumor activity as a single agent with acceptable safety profile against several advanced solid tumors, including previously treated mRCC, in Phase II clinical trials conducted in the United States and Europe (25–29). Axitinib has also been evaluated in a Phase II clinical trial for cytokine-refractory mRCC in Japan, with promising outcomes (9). A pivotal randomized Phase III trial (AXIS trial; ClinicalTrials.gov identifier: NCT00678392) was conducted globally to compare effectiveness of axitinib against another targeted agent, sorafenib, in patients with previously treated mRCC (15). Results from AXIS demonstrated a significant improvement in progression-free survival (PFS) for axitinib over sorafenib; median PFS assessed by Independent Review Committee (IRC) was 6.7 vs. 4.7 months, respectively (hazard ratio [HR] 0.665; 95% confidence interval [95% CI] 0.544–0.812; $P < 0.0001$, stratified one-sided log-rank test), leading to its recent approval in several countries including the United States and Japan.

Epidemiologic studies have shown that incidence and mortality rates for RCC vary substantially among different ethnic and geographical populations in the world (1,30,31). The reasons for such differences are not fully understood, but may include differences in the use of diagnostic surveillance, inherited susceptibility due to genetic variations in key genes involved in the pathophysiology of the disease and environmental risk factors such as cigarette smoking, obesity and hypertension. Advanced RCC is less common in Japan than in countries in Europe and North America, but is more prevalent than in other Asian countries; the incidence of RCC is also increasing in Japan (30,32). With disparities in efficacy and toxicities reported for some anti-cancer agents in different ethnic populations (33,34), it is critical to evaluate new anti-cancer agents in different ethnic populations in order to optimize their clinical benefits while

minimizing potential toxicities. The aim of this subgroup analysis was to evaluate the efficacy and safety of axitinib compared with sorafenib in Japanese patients with mRCC enrolled in AXIS trial.

PATIENTS AND METHODS

STUDY DESIGN

AXIS was a two-arm, multicenter, open-label, randomized, controlled Phase III clinical trial to evaluate efficacy and safety of axitinib versus sorafenib (as an active comparator) in patients with mRCC whose disease progressed following one prior systemic cytokine-, sunitinib-, bevacizumab/IFN- α - or temsirolimus-based regimen (15). The study was conducted at 175 centers in 22 countries, including 18 centers in Japan. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1) and by prior therapy and randomized in a 1:1 ratio to receive either axitinib or sorafenib. The study protocol, all amendments and informed consent forms were approved by the Institutional Review Boards or Independent Ethics Committees at each center. The study was conducted in compliance with Good Clinical Practice Guidelines, the Declaration of Helsinki and local regulatory requirements.

PATIENTS

Inclusion and exclusion criteria for patients enrolled in AXIS have previously been described in detail (15). In brief, key eligibility criteria were aged 18 years (20 years in Japan) or older; histologically or cytologically confirmed mRCC of clear-cell subtype; Response Evaluation Criteria in Solid Tumors (RECIST, v1.0)-defined progressive disease after one prior systemic first-line regimen; ECOG performance status 0 or 1; adequate bone marrow, hepatic and renal function; baseline proteinuria $< 2+$ by urine dipstick or < 2 g/24 h urine collection; and no uncontrolled hypertension, i.e. blood pressure (BP) $\leq 140/90$ mmHg at baseline (prior anti-hypertensive medications were permitted). Written informed consent was obtained from each patient prior to enrollment.

STUDY TREATMENT

Axitinib was administered orally at a starting dose of 5 mg twice daily (bid) taken with food. Axitinib dose could be increased to 7 mg bid, and then to a maximum of 10 mg bid, in patients who tolerated the starting dose with no treatment-related adverse events (AEs) above grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE, v3.0) for a consecutive 2-week period, at the discretion of a treating physician, unless the patient had BP $> 150/90$ mmHg or was receiving anti-hypertensive medications (15,35).

Axitinib dose reduction (3 mg bid, and then to 2 mg bid) or temporary interruption was permitted in patients to manage toxicities.

Sorafenib was administered at a dose of 400 mg bid taken orally without food (at least 1 h before or 2 h after eating). Sorafenib dose could be reduced to 400 mg once daily, and then to 400 mg once every other day, if necessary (15,36). Patients were treated with assigned drugs in 28-day cycles, until disease progression, occurrence of intolerable AE or withdrawal of consent. Patients and investigators were not masked to study treatment and crossover between study drugs was not allowed.

ASSESSMENTS

The primary efficacy evaluation was PFS assessed by a blinded IRC and secondary evaluations included overall survival (OS), objective response rate (ORR), safety, tolerability, and patient-reported outcomes (PROs) consisting of kidney-specific symptoms and health status. Tumors were radiologically assessed at baseline, 6 and 12 weeks and every 8 weeks thereafter and responses were evaluated according to RECIST v1.0.

Safety was assessed throughout the study by monitoring all AEs and conducting physical examinations, clinical laboratory tests and BP measurements. Severity of AEs was graded according to NCI-CTCAE v3.0. Thyroid function tests (free tri-iodothyronine [T_3], free thyroxine [T_4] and thyroid-stimulating hormone [TSH]) were performed at baseline. Subsequently, TSH measurements were repeated at 2, 4, 8 and 12 weeks and every 8 weeks thereafter, whereas free T_3 and free T_4 measurements were performed when clinically indicated. Protein, glucose and blood urinalysis were done at baseline and every 4 weeks. If patients had $\geq 2+$ proteinuria by semi-quantitative method (e.g. urine dipstick), protein was quantified by 24-h urine protein determination. BP readings were taken with patient in a seated position after 5-min rest at each clinic visit. Additionally, patients were provided with a BP monitor and instructed to measure BP at home prior to taking each dose and contact their physicians if systolic BP was > 150 mmHg or diastolic BP > 100 mmHg.

PROs were assessed using the validated Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI) and the FKSI–Disease-Related Symptoms (DRS) subscale, a validated questionnaire which measures quality of life (QOL) and symptoms related to advanced kidney cancer disease (37,38), at baseline and every 4 weeks. They were measured as the summary scores of the 15-item (i.e. lack of energy, bone pain, short of breath, coughing, hematuria, bothered by fever, pain, fatigue, losing weight, appetite, side effects, enjoying life, worsened condition, ability to work and sleep) FKSI-15 and 9-item (i.e. the first nine items listed under FKSI-15) FKSI-DRS questionnaires, respectively. A higher score is better (i.e. less symptoms). Japanese patients completed a validated Japanese translation of the FKSI questionnaire, conducted by experienced and trained

translators according to established Functional Assessment of Chronic Illness Therapy (FACIT) Multilingual Translations Methodology (39–41). The minimally important difference (MID) was predefined as 5 points for the FKSI-15 and 3 points for the FKSI-DRS subscale, as previously established (37,38). Lastly, a pre-specified time to deterioration (TTD) composite endpoint was examined, which was comprised of the combined endpoints of death, disease progression or clinically meaningful worsening of symptoms (worsening in symptom scores greater than the MID), whichever occurred first.

STATISTICAL ANALYSES

The sample size was calculated in the overall population based on the assumption that axitinib treatment would result in a 40% improvement in median PFS to 7 months from 5 months with sorafenib in patients with mRCC whose disease progressed after one prior systemic therapy, as described previously (15). The full analysis set included all randomized patients and was used for efficacy and PROs analyses. Median PFS was estimated using Kaplan–Meier methods, and a one-sided ($\alpha = 0.025$) log-rank test stratified by both ECOG performance status and prior therapy was used to compare the two treatment arms. Similar survival analysis methods (without stratification) were used to compare TTD between treatments. ORRs between the two treatment groups were compared using a one-sided Cochran–Mantel–Haenszel test stratified by ECOG performance status and prior therapy. All patients who received at least one dose of study medication were included in safety and treatment administration assessments. East version 5 was used to calculate the sample size; all other statistical analyses were done with SAS version 9.2.

RESULTS

PATIENT BASELINE CHARACTERISTICS AND DISPOSITION

Baseline characteristics of patients randomly assigned to axitinib ($n = 361$) and sorafenib ($n = 362$) were well balanced in the overall population and included 25 and 29 Japanese patients, respectively (Table 1). Baseline characteristics of Japanese patients were generally comparable to those of the overall population, except that a higher percentage of Japanese patients had ECOG performance status 0, favorable Memorial Sloan-Kettering Cancer Center (MSKCC) risk and prior cytokine-based therapy. There were no Japanese patients with prior temsirolimus or bevacizumab/IFN- α therapy enrolled in this study since temsirolimus was approved in Japan after the enrollment period for this study and bevacizumab/IFN- α therapy is not available in Japan.

At the time of data cutoff date of 31 August 2010, five (20%) of 25 Japanese patients in the axitinib arm discontinued study treatment either due to an AE ($n = 1$ transient ischemic attack), disease progression ($n = 3$) or death

Table 1. Baseline demographics and clinical characteristics

Characteristics	Overall population			Japanese patients			P value ^a
	Axitinib (n = 361)	Sorafenib (n = 362)	Total (n = 723)	Axitinib (n = 25)	Sorafenib (n = 29)	Total (n = 54)	
Age, median (range) (years)	61 (20–82)	61 (22–80)	61 (20–82)	62 (32–82)	63 (28–77)	62 (28–82)	0.2059 ^b
Gender, n (%)							0.5284
Male	265 (73)	258 (71)	523 (72)	16 (64)	21 (72)	37 (69)	
Female	96 (27)	104 (29)	200 (28)	9 (36)	8 (28)	17 (31)	
ECOG PS, n (%)							<0.001
0	195 (54)	200 (55)	395 (55)	23 (92)	24 (83)	47 (87)	
1	162 (45)	160 (44)	322 (45)	2 (8)	5 (17)	7 (13)	
>1	1 (<1)	0	1 (<1)	0	0	0	
Site of metastases, n (%)							
Lung	274 (76)	292 (81)	566 (78)	22 (88)	26 (90)	48 (89)	0.0580
Lymph node	209 (58)	202 (56)	411 (57)	13 (52)	10 (34)	23 (43)	0.0321
Bone	119 (33)	107 (30)	226 (31)	4 (16)	7 (24)	11 (20)	0.0923
Liver	102 (28)	103 (28)	205 (28)	1 (4)	6 (21)	7 (13)	0.0075
MSKCC risk group ^c , n (%)							<0.001
Favorable	100 (28)	101 (28)	201 (28)	14 (56)	13 (45)	27 (50)	
Intermediate	134 (37)	130 (36)	264 (37)	7 (28)	12 (41)	19 (35)	
Poor	118 (33)	120 (33)	238 (33)	1 (4)	2 (7)	3 (6)	
NA	9 (2)	11 (3)	20 (3)	3 (12)	2 (7)	5 (9)	
Prior treatment, n (%)							
Nephrectomy	327 (91)	331 (91)	658 (91)	24 (96)	28 (97)	52 (96)	0.2160
Radiotherapy	75 (21)	73 (20)	148 (20)	1 (4)	5 (17)	6 (11)	0.0811
Systemic therapy							<0.001
Sunitinib	194 (54)	195 (54)	389 (54)	5 (20)	9 (31)	14 (26)	
Cytokines	126 (35)	125 (35)	251 (35)	20 (80)	20 (69)	40 (74)	
Bevacizumab	29 (8)	30 (8)	59 (8)	0	0	0	
Temsirrolimus	12 (3)	12 (3)	24 (3)	0	0	0	

ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; NA, not available.

^aFisher's exact test comparing baseline demographics and clinical characteristics (except age) between all non-Japanese versus all Japanese patients.

^bt-test comparing baseline mean age between all non-Japanese and all Japanese patients.

^cDerived using three risk factors: serum hemoglobin (≤ 130 vs. >130 g/l for men and ≤ 115 vs. >115 g/l for women), corrected serum calcium (<2.5 vs. ≥ 2.5 mmol/l) and ECOG PS (0 vs. 1). MSKCC risk groups were defined as: favorable = 0 risk factor; intermediate = 1 risk factor or poor = 2 or 3 risk factors.

associated with disease progression ($n = 1$), compared with 20 (69%) of 29 Japanese patients in the sorafenib arm who discontinued study treatment either due to an AE ($n = 5$; 1 each for angina pectoris, periodontitis and hepatic function abnormality and 2 for erythema multiforme) or disease progression ($n = 15$). In the overall population, 221 (61%) of 361 patients in the axitinib arm and 256 (71%) of 362 patients in the sorafenib arm discontinued study treatment.

TREATMENT

Japanese patients receiving axitinib generally remained on treatment longer and received study drug on more days

compared with Japanese patients receiving sorafenib, as in the overall population (Table 2). The majority of Japanese patients had one or more dose interruptions of treatment drug (96% in the axitinib arm and 83% in the sorafenib arm), compared with overall population (77 and 80%, respectively). At least one dose reduction was reported in 32% of Japanese patients treated with axitinib, compared with 66% of Japanese patients treated with sorafenib. A similar percentage of patients had at least one dose reduction in the overall population (31% in the axitinib arm and 52% in the sorafenib arm). Three (12%) Japanese patients had their axitinib dose increased above 5 mg bid, whereas 37% of patients in the overall population received axitinib doses

Table 2. Exposure to study drugs

	Overall population		Japanese patients	
	Axitinib (<i>n</i> = 359)	Sorafenib (<i>n</i> = 355)	Axitinib (<i>n</i> = 25)	Sorafenib (<i>n</i> = 29)
Days on treatment ^a				
Median (range)	196 (1–670)	152 (1–610)	161 (23–405)	130 (11–365)
Days on drug ^b				
Median (range)	186 (1–670)	141 (1–609)	157 (23–372)	84 (9–338)
Average daily dose				
Mean (standard deviation) (mg)	10.6 (3.3)	677.9 (148.8)	9.3 (2.2)	627.6 (154.1)
Relative dose intensity				
Median (range) (%)	99 (32–194)	92 (27–100)	89 (35–151)	69 (38–100)

^aTime period starting from date of the first dose to date of the last dose or data cutoff.

^bTotal number of days in which axitinib or sorafenib was actually administered.

above 5 mg bid. Mean daily dose as well as median relative dose intensity of axitinib or sorafenib were slightly lower in Japanese patients compared with the corresponding values in the overall population (Table 2).

EFFICACY

In the overall population, IRC-assessed median PFS was significantly longer with axitinib than sorafenib treatments (Fig. 1A, Table 3) (15). In the Japanese subgroup analysis, IRC-assessed median PFS with axitinib was 12.1 months (95% CI 8.6 to not estimable) compared with 4.9 months (95% CI 2.8–6.6) with sorafenib (HR 0.390; 95% CI 0.130–1.173; $P = 0.0401$, stratified one-sided log-rank test) (Fig. 1B, Table 3). Among patients who had received previous cytokine treatment, differences between median PFS for axitinib and sorafenib were statistically significant in favor of axitinib in the Japanese subgroup, as in the overall population (Table 3). In patients with prior sunitinib treatment, axitinib demonstrated significantly longer median PFS than sorafenib in the overall population whereas the number of Japanese patients with prior sunitinib therapy was too small to compare PFS between the two arms (Table 3).

A total of 15 (60%) of 25 Japanese patients in the axitinib arm and 2 (7%) of 29 in the sorafenib arm had a $\geq 30\%$ decrease in target lesions (Fig. 2). IRC-assessed ORR was significantly higher with axitinib than that with sorafenib in Japanese patients (52.0 vs. 3.4%, respectively, $P = 0.0001$) (Fig. 3, Table 4). In the overall population, IRC-assessed ORR was 19.4 vs. 9.4%, respectively ($P = 0.0001$) (Fig. 3, Table 4) (15,42). When stratified by prior therapy, ORR for axitinib was statistically significantly higher in Japanese patients previously treated with cytokines, but the number of Japanese patients with prior sunitinib therapy was too small to compare ORR (Table 4).

PATIENT-REPORTED OUTCOMES

Nearly 100% of the eligible Japanese patients completed FKSI questionnaires, which was higher than the 90% for the overall population. In Japanese patients, the pre-defined TTD composite endpoint utilizing the FKSI-15 or FKSI-DRS in addition to death and progression, demonstrated a 47% ($P = 0.0258$) and 19% ($P = 0.2613$) respective reduction in risk for axitinib compared with sorafenib patients (Fig. 4) favoring axitinib; the corresponding risk reductions in the overall population were 17 and 16%, respectively (15).

SAFETY

Hypertension, hand–foot syndrome and diarrhea were the most common ($\geq 50\%$ of patients) all-causality AEs (all grades) in both axitinib and sorafenib arms in the Japanese subgroup (Table 5). Dysphonia, fatigue, hypothyroidism, decreased appetite, dysgeusia and weight decrease were more frequently reported by Japanese patients receiving axitinib whereas hand–foot syndrome, rash and alopecia were more common with sorafenib (Table 5). Fewer laboratory abnormalities (all grades) were associated with axitinib than sorafenib in Japanese patients (Table 5). The common all-causality grade ≥ 3 AEs in Japanese patients were hypertension, hand–foot syndrome, decreased appetite and fatigue with axitinib and hypertension, hand–foot syndrome and lipase elevation with sorafenib (Table 5).

The safety profiles of axitinib and sorafenib in Japanese patients were generally similar to those observed in the overall population, with few exceptions. Hypertension, dysphonia, hand–foot syndrome, hypothyroidism and stomatitis occurred more frequently among Japanese patients treated with either axitinib or sorafenib than in the overall population. On the other hand, incidences of nausea and asthenia were lower among Japanese patients compared with the overall population (Table 5).

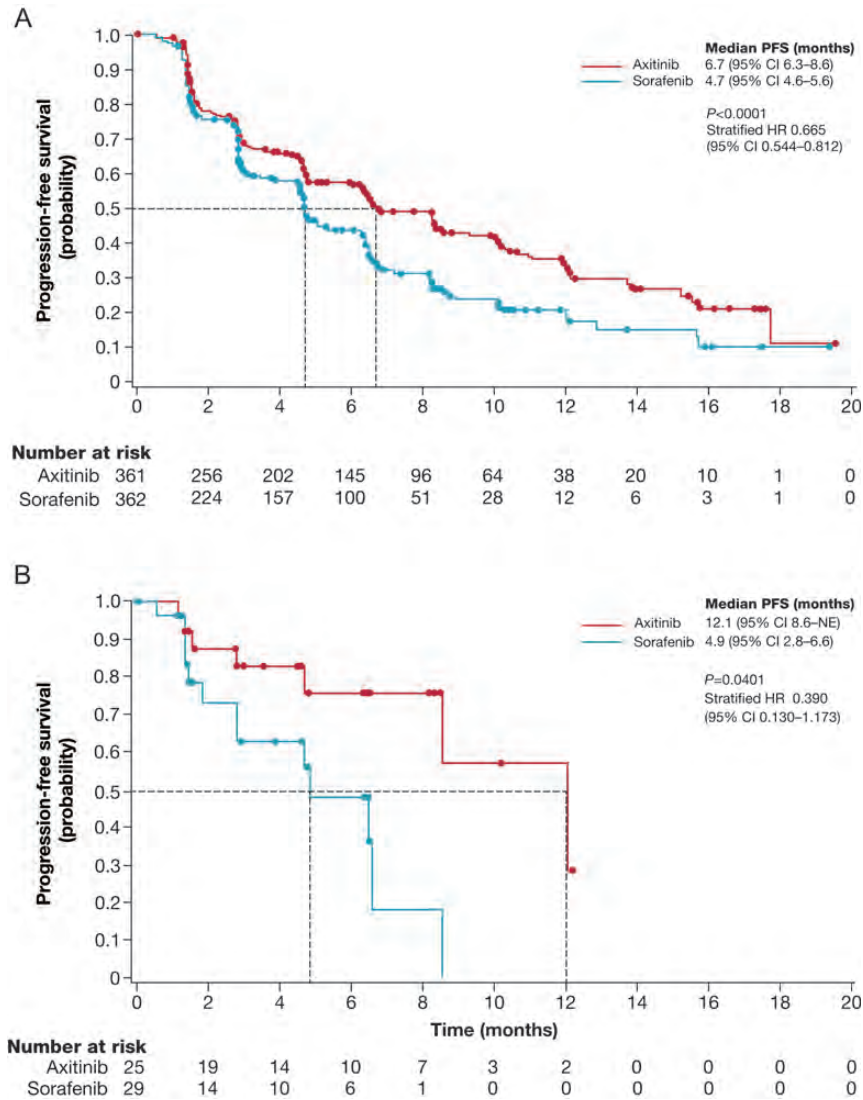


Figure 1. Kaplan–Meier plot of progression-free survival assessed by Independent Review Committee (IRC) in (A) the overall population and (B) Japanese patients [(A) was reprinted from Rini et al. (15), Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial, p 1931–9, Copyright 2011, with permission from Elsevier. All rights reserved]. P values based on one-sided log-rank test stratified by ECOG performance status and prior therapy. CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

HYPERTENSION

All-causality hypertension (all grades) was more common with axitinib than sorafenib in the overall population (40 vs. 29%, respectively), whereas it was similarly higher in both treatment arms in Japanese patients (64 vs. 62%, respectively). Incidence of grade ≥ 3 hypertension was also more common with axitinib than sorafenib in the overall population (16 vs. 11%, respectively) whereas it was similarly higher in both treatment arms in the Japanese subgroup (44 vs. 45%, respectively). In the Japanese subgroup, 36% of patients received anti-hypertensive medications before treatment with axitinib and 80% started new or increased their dose of existing anti-hypertensive medication during treatment with axitinib. In the overall population, anti-hypertensive medications were administered to 47% of patients prior to treatment with axitinib and new or increased

dose of existing anti-hypertensive medication was administered to 55% of patients after treatment with axitinib.

HYPOTHYROIDISM

At baseline, a similar percentage of Japanese patients in the axitinib and sorafenib arms were receiving medications such as levothyroxine for hypothyroidism (12 and 14%, respectively). However, during study treatment, more patients administered axitinib were diagnosed with hypothyroidism than those receiving sorafenib (44 and 24%, respectively) (Table 5). The diagnosis of hypothyroidism in either arm was more common among Japanese than in the overall population, although the incidence of TSH elevation to $\geq 10 \mu\text{IU/ml}$ among patients who had TSH $< 5 \mu\text{IU/ml}$ before treatment was comparable between Japanese patients and the

Table 3. IRC-assessed progression-free survival (overall or stratified by prior therapy)

	Overall population		Japanese patients	
	Axitinib	Sorafenib	Axitinib	Sorafenib
<i>PFS, months</i>				
Overall	<i>n</i> = 361	<i>n</i> = 362	<i>n</i> = 25	<i>n</i> = 29
Median PFS (95% CI)	6.7 (6.3–8.6)	4.7 (4.6–5.6)	12.1 (8.6–NE)	4.9 (2.8–6.6)
HR (95% CI)	0.665 (0.544–0.812)		0.390 (0.130–1.173)	
<i>P</i> value ^a	<0.0001		0.0401	
Stratified by prior therapy				
Prior cytokine therapy	<i>n</i> = 126	<i>n</i> = 125	<i>n</i> = 20	<i>n</i> = 20
Median PFS (95% CI)	12.1 (10.1–13.9)	6.5 (6.3–8.3)	12.1 (8.6–NE)	6.6 (4.7–8.5)
HR (95% CI)	0.464 (0.318–0.676)		0.171 (0.034–0.858)	
<i>P</i> value ^b	<0.0001		0.0085	
Prior sunitinib therapy	<i>n</i> = 194	<i>n</i> = 195	<i>n</i> = 5	<i>n</i> = 9
Median PFS (95% CI)	4.8 (4.5–6.4)	3.4 (2.8–4.7)	4.7 (1.3–4.7)	2.8 (1.4–4.9)
HR (95% CI)	0.741 (0.573–0.958)		1.033 (0.229–4.671)	
<i>P</i> value ^b	0.0107		0.5175	

IRC, Independent Review Committee; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; NE, not estimable.

^aBased on one-sided log-rank test stratified by ECOG PS and prior therapy.

^bBased on one-sided log-rank test stratified by ECOG PS.

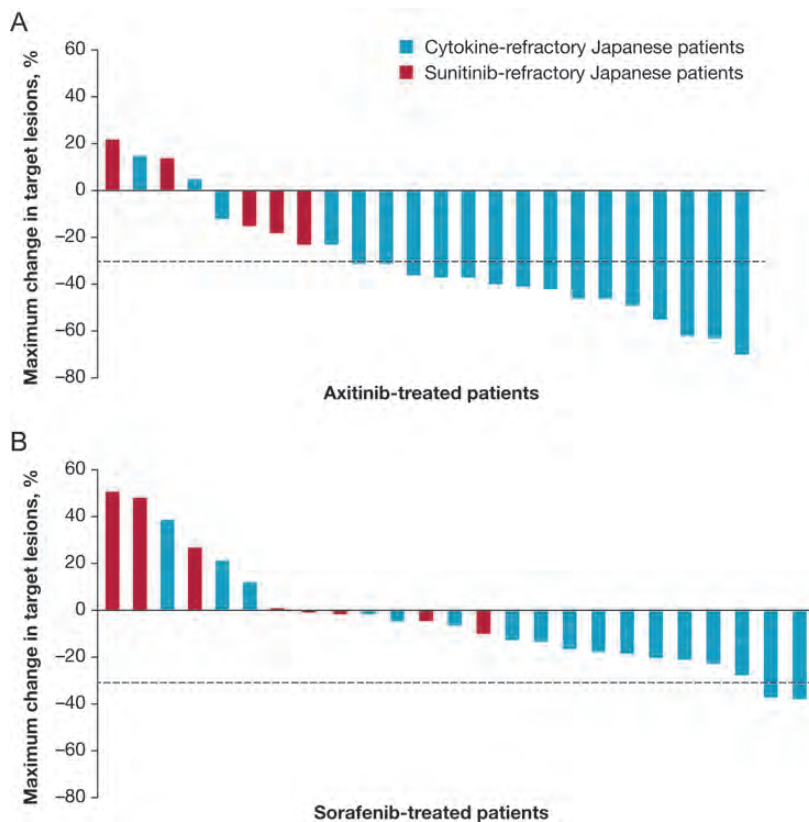


Figure 2. IRC assessed maximum percent change in target lesions in Japanese patients treated with (A) axitinib (*n* = 24; 1 indeterminate) and (B) sorafenib (*n* = 25; 4 indeterminate). Dotted lines represent 30% decrease in target lesions.

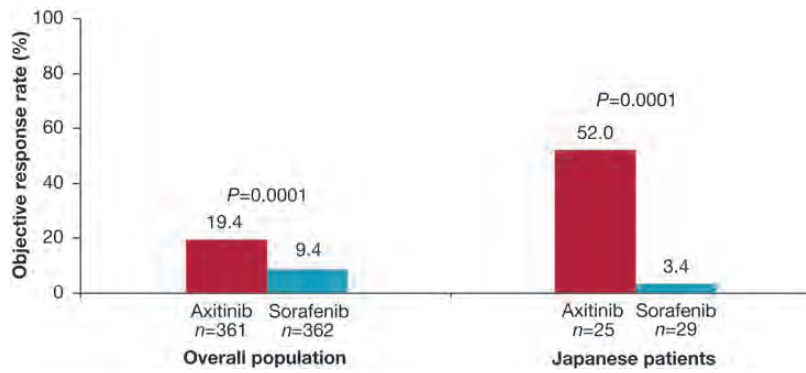


Figure 3. Objective response rate assessed by IRC. *P* values based on one-sided Cochran–Mantel–Haenszel test stratified by ECOG performance status and prior therapy.

Table 4. IRC-assessed objective tumor response (overall or stratified by prior therapy)

	Overall population		Japanese patients	
	Axitinib	Sorafenib	Axitinib	Sorafenib
Best-observed RECIST response, n (%)				
Overall	n = 361	n = 362	n = 25	n = 29
CR	0	0	0	0
PR	70 (19.4)	34 (9.4)	13 (52.0)	1 (3.4)
SD	180 (49.9)	197 (54.4)	9 (36.0)	16 (55.2)
PD	78 (21.6)	76 (21.0)	2 (8.0)	6 (20.7)
Indeterminate	22 (6.1)	42 (11.6)	1 (4.0)	4 (13.8)
ORR (CR + PR)	70 (19.4)	34 (9.4)	13 (52.0)	1 (3.4)
95% CI	15.4–23.9	6.6–12.9	31.3–72.2	0.1–17.8
<i>P</i> value ^a	0.0001		0.0001	
Stratified by prior therapy				
Prior cytokine therapy	n = 126	n = 125	n = 20	n = 20
ORR (CR + PR)	41 (32.5)	17 (13.6)	13 (65.0)	1 (5.0)
95% CI	24.5–41.5	8.1–20.9	40.8–84.6	0.1–24.9
<i>P</i> value ^b	0.0002		0.0001	
Prior sunitinib therapy	n = 194	n = 195	n = 5	n = 9
ORR (CR + PR)	22 (11.3)	15 (7.7)	0	0
95% CI	7.2–16.7	4.4–12.4	–	–
<i>P</i> value ^b	0.1085		–	

RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate.

^aBased on one-sided Cochran–Mantel–Haenszel test stratified by ECOG PS and prior therapy.

^bBased on one-sided Cochran–Mantel–Haenszel test stratified by ECOG PS.

overall population (31 vs. 32%, respectively, in the axitinib arm and 18 vs. 11%, respectively, in the sorafenib arm). As with patients in the overall population, hypothyroidism in

Japanese patients was managed with thyroid replacement therapy as the protocol recommended that hypothyroidism be treated per standard medical practice to maintain euthyroid state. In the Japanese subgroup, 12% of patients received thyroid medications before starting treatment with axitinib and 48% of patients started thyroid medications or increased the dose of existing thyroid medications during treatment with axitinib. In the overall population, the corresponding values were 19 and 26%, respectively.

PROTEINURIA

Incidences of all-causality proteinuria (all grades) were similar between axitinib- and sorafenib-treated Japanese patients (12 and 10%, respectively), which were comparable to those observed in the overall population (11 and 7%, respectively). One Japanese patient each in the axitinib and sorafenib arms had grade 3 proteinuria. No patient receiving axitinib or sorafenib developed grade 4 proteinuria in the Japanese subgroup or in the overall population. Incidence of proteinuria ≥2+ in the axitinib arm was similar between the Japanese and overall population (20 vs. 21%, respectively).

DISCUSSION

The globally conducted AXIS trial has established clinical benefit and superiority of axitinib compared with sorafenib in patients with previously treated mRCC in the overall population (15). The current analysis demonstrated that in the Japanese subgroup, axitinib treatment resulted in a longer PFS and higher ORR compared with sorafenib, consistent with the results obtained in the overall population. Furthermore, median PFS and ORR achieved in axitinib-treated Japanese patients were longer and higher than those achieved in the overall population treated with axitinib. The higher percentage of the patients with ECOG performance status 0 and favorable MSKCC risk, as well as lower incidence of hepatic metastasis in the Japanese subgroup might have accounted for better efficacy compared with the overall population (43,44). In addition, the majority (80%) of

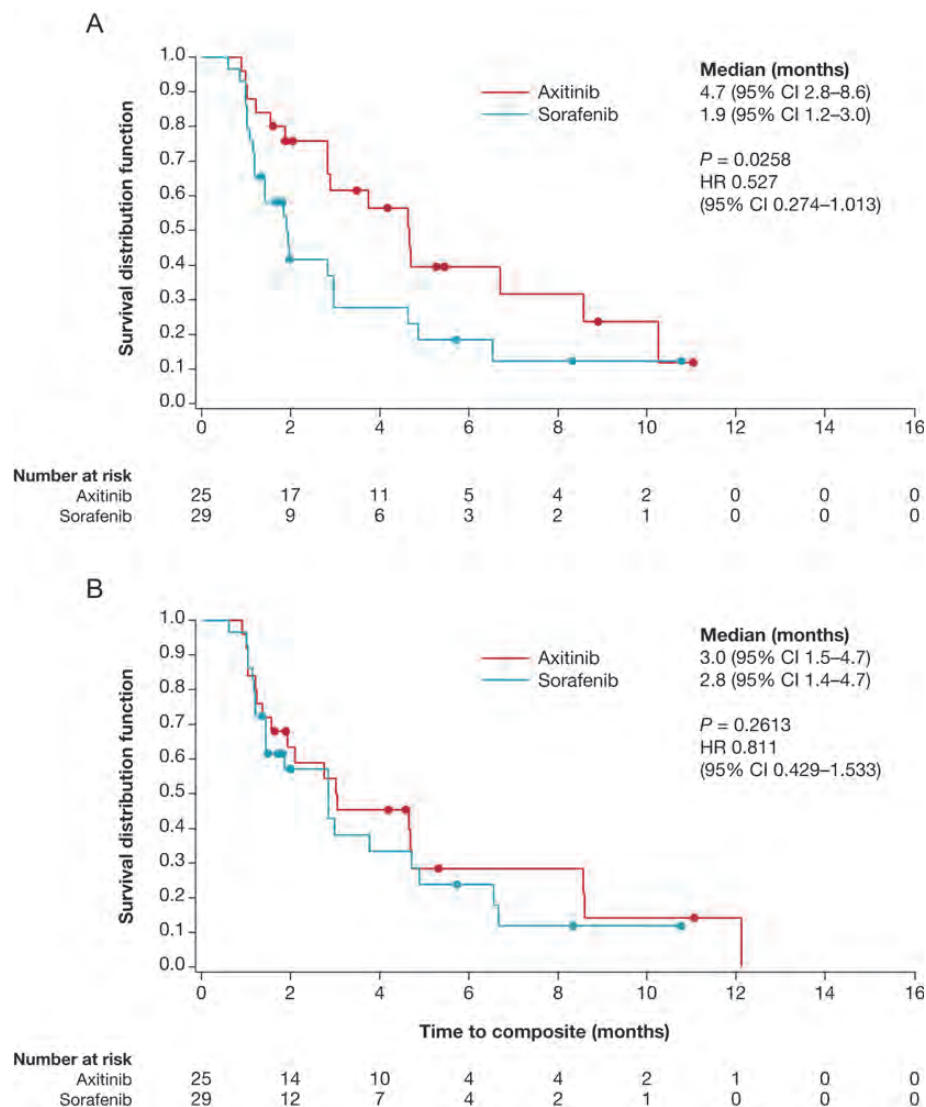


Figure 4. Kaplan–Meier analysis of time to deterioration (TTD) composite endpoint in Japanese patients. Composite endpoint of TTD was defined as time between the date of randomization to date of first occurrence of progression of disease, death or deterioration of symptoms, as measured by (A) FKSI-15 and (B) FKSI-DRS. P values based on one-sided log-rank test.

Japanese patients treated with axitinib had prior cytokine therapy, whereas in the overall population, 62% of patients treated with axitinib had prior sunitinib or bevacizumab/IFN- α therapy, both of which have the similar mode of action as axitinib.

While cross-study comparisons are difficult due to methodological differences, median PFS and ORR in cytokine-pretreated Japanese patients who received axitinib in this study were comparable to those observed in the previous Phase II study of axitinib in cytokine-pretreated Japanese patients conducted in Japan (median PFS, 11.0 months; ORR, 50.0%) (9). On the other hand, values for PFS and ORR were slightly lower in Japanese patients treated with sorafenib in this study compared with those reported in a Phase II study of sorafenib in Japanese RCC patients (median PFS, 7.4 months; ORR, 12.4%) (45). One possible reason for the differences may be the fact that 9 of 29

patients in the sorafenib arm of the AXIS trial were previously treated with sunitinib whereas none of patients enrolled in the previous sorafenib Phase II study received prior sunitinib. In addition, only investigator-assessed PFS was available in the previous sorafenib Phase II study (45).

It should be noted that the median days on drug and relative dose intensity in the sorafenib arm in Japanese patients were shorter and lower, respectively, compared with the overall population (84 vs. 141 days, 69 vs. 92%, respectively). The mean percentage of the total number of sorafenib dose interruption was almost twice as high in Japanese patients as in the overall population (20.5 vs. 10.6%, respectively), which likely resulted in shorter days on drug and a lower relative dose intensity in Japanese patients treated with sorafenib. Furthermore, this also could have affected the efficacy of sorafenib in Japanese patients, as seen in a lower ORR in Japanese patients compared with the overall

Table 5. Summary of common all-causality adverse events and laboratory abnormalities

AE, n (%)	Overall population				Japanese patients			
	Axitinib (n = 359)		Sorafenib (n = 355)		Axitinib (n = 25)		Sorafenib (n = 29)	
	All grades	Grade \geq 3	All grades	Grade \geq 3	All grades	Grade \geq 3	All grades	Grade \geq 3
Diarrhea	197 (55)	38 (11)	189 (53)	26 (7)	14 (56)	1 (4)	15 (52)	2 (7)
Hypertension	145 (40)	56 (16)	103 (29)	39 (11)	16 (64)	11 (44)	18 (62)	13 (45)
Fatigue	140 (39)	41 (11)	112 (32)	18 (5)	11 (44)	3 (12)	7 (24)	0
Decreased appetite	123 (34)	18 (5)	101 (28)	13 (4)	8 (32)	4 (16)	3 (10)	2 (7)
Nausea	116 (32)	9 (3)	77 (22)	4 (1)	2 (8)	0	2 (7)	0
Dysphonia	111 (31)	0	48 (14)	0	17 (68)	0	8 (28)	0
Hand-foot syndrome	98 (27)	18 (5)	181 (51)	57 (16)	16 (64)	4 (16)	25 (86)	7 (24)
Weight decrease	89 (25)	8 (2)	74 (21)	5 (1)	6 (24)	0	1 (3)	0
Vomiting	85 (24)	12 (3)	61 (17)	3 (1)	4 (16)	0	3 (10)	0
Asthenia	74 (21)	19 (5)	50 (14)	9 (3)	0	0	0	0
Constipation	73 (20)	4 (1)	72 (20)	3 (1)	4 (16)	0	7 (24)	0
Hypothyroidism	69 (19)	1 (<1)	29 (8)	0	11 (44)	0	7 (24)	0
Stomatitis	54 (15)	5 (1)	44 (12)	1 (<1)	9 (36)	0	5 (17)	0
Dysgeusia	38 (11)	0	29 (8)	0	7 (28)	0	2 (7)	0
Rash	45 (13)	1 (<1)	112 (32)	14 (4)	4 (16)	0	13 (45)	2 (7)
Alopecia	14 (4)	0	115 (32)	0	2 (8)	0	11 (38)	0
Laboratory abnormalities ^a , n (%)								
Anemia	113/320 (35)	1/320 (<1)	165/316 (52)	12/316 (4)	5/25 (20)	0	12/26 (46)	0
Hemoglobin elevation ^b	31/320 (10)	NA	3/316 (1)	NA	2/25 (8)	NA	0	NA
Neutropenia	19/316 (6)	2/316 (1)	26/308 (8)	2/308 (1)	4/24 (17)	0	8/25 (32)	0
Thrombocytopenia	48/312 (15)	1/312 (<1)	44/310 (14)	0	6/25 (24)	0	7/26 (27)	0
Lymphopenia	106/317 (33)	10/317 (3)	111/309 (36)	11/309 (4)	5/25 (20)	0	10/26 (38)	1/26 (4)
Creatinine elevation	185/336 (55)	0	131/318 (41)	1/318 (<1)	12/25 (48)	0	9/26 (35)	0
Hypocalcemia	132/336 (39)	4/336 (1)	188/319 (59)	5/319 (2)	13/25 (52)	0	16/26 (62)	0
Lipase elevation	91/338 (27)	16/338 (5)	148/319 (46)	47/319 (15)	9/25 (36)	2/25 (8)	17/26 (65)	3/26 (12)

^aThe number of patients for each laboratory abnormality differed depending on the availability of baseline and at least one on-study test result.

^bDefined as hemoglobin value above the upper limit of normal.

population, respectively (3.4 vs. 9.4%), although median PFS was similar (4.9 vs. 4.7 months).

The dose-uptitration rate was lower in Japanese patients treated with axitinib compared with the overall population (12 vs. 37%, respectively). In this study, axitinib dose could be increased in patients who met dose-titration criteria: no treatment-related AEs above grade 2 according to the NCI-CTCAE v3.0 for a consecutive 2-week period; BP \leq 150/90 mmHg; and not taking any anti-hypertensive medication. The percentage of Japanese patients who experienced at least one systolic BP $>$ 150 mmHg or diastolic BP $>$ 90 mmHg during the first 2 weeks of starting axitinib was 44%, which was \sim 2-fold higher than the overall population (21%), and likely led to the difference in dose-titration rate

between Japanese patients and the overall population (the percentage of patients who had AEs above grade 2 or received anti-hypertensive medications were similar between Japanese patients and the overall population [4 vs. 6% and 64 vs. 59%, respectively]).

In the overall population, the OS was similar between the axitinib arm and sorafenib arm (46). The OS events occurred in less than 50% of Japanese subgroup at the final analysis of OS. The OS in Japanese subgroup has not been matured yet and will be evaluated when additional OS events have occurred.

A treatment goal in a metastatic disease where there is no cure as of yet is to delay symptom worsening. It is also important for an improvement in PFS not to be offset by a

worsening in symptoms or toxicity. In the AXIS trial, kidney cancer-specific symptoms and QOL of patients were compared between the axitinib and sorafenib arms in a pre-specified composite endpoint, including death, progression or worsening of symptoms and QOL. Importantly, results demonstrated the PFS advantage of axitinib over sorafenib was maintained in Japanese patients when time to symptom deterioration was included with the overall efficacy assessment, consistent with the overall population (15) and indicated that axitinib provides extended symptom and disease control for these patients.

AEs observed in Japanese patients as well as in the overall population receiving axitinib were those expected for this class of drugs, which include diarrhea, hypertension and fatigue. Axitinib was generally well tolerated in Japanese patients and its safety profile was comparable to that in the overall population, with the exceptions of hypertension, dysphonia, hand–foot syndrome, hypothyroidism and stomatitis, which occurred more frequently in Japanese patients. Hypertension and hypothyroidism in Japanese patients were generally managed with use of anti-hypertensive and thyroid medications, respectively, as in the overall population. Both anti-hypertensive and thyroid medications were more frequently administered to Japanese patients during axitinib treatment compared with the overall population. Other AEs with higher incidences in Japanese patients were mostly managed with axitinib dose interruption and/or reduction, as evidenced by the fact that no Japanese patients in the axitinib arm discontinued study treatment due to these AEs.

It is unclear as to the cause(s) for slight differences in AEs reported by Japanese patients and the overall population. A follow-up analysis to further investigate differences and similarities in AEs between Japanese patients and the overall population is warranted. It is noteworthy that no major differences in axitinib plasma pharmacokinetics have been observed between Japanese and Caucasians in Phase I pharmacokinetic studies of axitinib in healthy volunteers and in patients with advanced solid tumors, including mRCC (47–49). Furthermore, a population pharmacokinetic analysis and a fixed effects meta-analysis of datasets pooled from a large number of axitinib clinical studies in healthy volunteers showed that none of the several common genetic polymorphisms in cytochrome P450 (CYP) 3A4/5, CYP2C19 or uridine diphosphate glucuronosyltransferase 1A1, which are known to metabolize axitinib, were significant predictors of variability in axitinib plasma pharmacokinetics (50,51). Factors such as age, gender and body weight did not significantly affect axitinib systemic clearance either. Other factors are responsible for inter-individual variability observed in axitinib plasma pharmacokinetics, which in turn, may impact AEs. The differences in AEs observed may be contributed by differences in genetics as well as in meticulousness of AE tracking.

In conclusion, the current analysis indicated that axitinib is efficacious and well tolerated in Japanese patients with mRCC, whose disease progressed after one prior systemic

treatment. Primary endpoint of the study, IRC-assessed PFS, was achieved in Japanese patients, as in the overall population. Secondary endpoints, which included ORR and PROs, supported the finding that axitinib improved efficacy over sorafenib in Japanese patients. While nature and incidence of AEs observed in Japanese patients were generally similar to those reported in the overall population, there were some notable differences. AEs more frequently reported by Japanese patients treated with axitinib included hypertension and hypothyroidism, which were effectively managed with anti-hypertensive medications and/or axitinib dose reduction/interruption and thyroid medications, respectively. Thus, axitinib provides a new targeted therapy option for Japanese patients with advanced RCC following prior systemic therapy.

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Conflict of interest statement

T.U. has received speaker honoraria from Pfizer and Bayer. H.U. has served as a consultant for Pfizer, and received speaker honoraria and research funding from Pfizer and Bayer. Y.T. has served as a consultant for Pfizer and Bayer and received speaker honoraria and research funding from Pfizer and Bayer. T.T. has received speaker honoraria from Pfizer and Bayer. H.K. has served as a consultant for Pfizer and Bayer and received speaker honoraria from Pfizer and Bayer. N.S. has served as a consultant for Pfizer and received

speaker honoraria from Pfizer. S.O. has received speaker honoraria and research funding from Pfizer and Bayer. S.N. has served as a consultant for Pfizer and received speaker honoraria from Pfizer and Bayer. H.A. has served as a consultant for Pfizer and Bayer and received speaker honoraria from Pfizer and Bayer. J.T., C.C., S.K., K.I. and Y.U. are employees of Pfizer and own stock in Pfizer.

Appendix

The following authors have contributed equally to the current study, in addition to the authors listed in the author field.

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