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

Takeshi Ueda1,*, Hirotsugu Uemura2, Yoshihiko Tomita3, Taiji Tsukamoto4, Hiroomi Kanayama5, Nobuo Shinohara6, Jamal Tarazi7, Connie Chen8, Sinil Kim7, Seiichiro Ozono9, Seiji Naito10 and Hideyuki Akaza11

1Prostate Center and Division of Urology, Chiba Cancer Center, Chiba, 2Department of Urology, Kinki University School of Medicine, Osaka, 3Department of Urology, Yamagata University Faculty of Medicine, Yamagata, 4Department of Urology, Sapporo Medical University School of Medicine, Hokkaido, 5Department of Urology, The University of Tokushima Graduate School, Tokushima, 6Department of Urology, Hokkaido University Graduate School of Medicine, Hokkaido, Japan, 7Clinical Oncology, Pfizer, Inc., San Diego, CA, 8Global Outcomes Research, Pfizer, Inc., New York, NY, USA, 9Department of Urology, Hamamatsu University School of Medicine, Shizuoka, 10Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka and 11Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan

*For reprints and all correspondence: Takeshi Ueda, Prostate Center and Division of Urology, Chiba Cancer Center, 666-2 Nitona-cho, Chuo-ku, Chiba-shi, Chiba 260-8717, Japan. E-mail: urolccc@yahoo.co.jp

Received November 27, 2012; accepted March 24, 2013

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 versus sorafenib in patients previously treated mRCC (15). Results from AXIS demonstrated a significant improvement in progression-free survival (PFS) for axitinib versus 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 <+ by urine dipstick or <2 g/24 h urine collection; and no uncontrolled hypertension, i.e. blood pressure (BP) ≤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 ≥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, hemiceturia, 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 (α = 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
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
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 ≥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 (≥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).
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 ≥10 μIU/ml among patients who had TSH < 5 μIU/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         |
| **PFS, months**    |                    |                   |                   |
| Overall            | $n = 361$          | $n = 362$         | $n = 25$          | $n = 29$          |
| 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)|                   |
| $P$ value$^a$      | $<0.0001$          |                   |                   | 0.0401            |
| **Stratified by prior therapy** |                   |                   |                   |
| Prior cytokine therapy | $n = 126$          | $n = 125$         | $n = 20$          | $n = 20$          |
| 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)|                   |
| $P$ value$^b$      | $<0.0001$          |                   |                   | 0.0085            |
| Prior sunitinib therapy | $n = 194$          | $n = 195$         | $n = 5$           | $n = 9$           |
| 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)|                   |
| $P$ value$^b$      | 0.0107             |                   |                   | 0.5175            |

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

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

$^b$Based 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.
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 \( \geq 2^+ \) 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

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  |
| \( P \) 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  |
| \( P \) 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 | –        | –         |
| \( P \) 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.

\(^a\)Based on one-sided Cochran–Mantel–Haenszel test stratified by ECOG PS and prior therapy.

\(^b\)Based on one-sided Cochran–Mantel–Haenszel test stratified by ECOG PS.
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

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.
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 ≤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 ~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

| Table 5. Summary of common all-causality adverse events and laboratory abnormalities |
|-----------------------------------------------|-----------------|-----------|-----------------|-----------------|
|                                  | Overall population | Japanese patients |
|                                  | Axitinib (n = 359) | Sorafenib (n = 355) | Axitinib (n = 25) | Sorafenib (n = 29) |
|                                 | All grades Grade ≥3 | All grades Grade ≥3 | All grades Grade ≥3 | All grades Grade ≥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 |
| Anemia                          | 74 (21) 19 (5) | 50 (14) 9 (3) | 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, n (%)

|                                  | Overall population | Japanese patients |
|----------------------------------|--------------------|-------------------|
|                                  | Axitinib (n = 359) | Sorafenib (n = 355) | Axitinib (n = 25) | Sorafenib (n = 29) |
|                                 | All grades Grade ≥3 | All grades Grade ≥3 | All grades Grade ≥3 | All grades Grade ≥3 |
| Anemia                           | 113/320 (35) 1/320 (<1) | 165/316 (52) 12/316 (4) | 5/25 (20) 0 | 12/26 (46) 0 |
| Hemoglobin elevation             | 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.
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.

Acknowledgements

We acknowledge the following investigators and investigational sites that also participated in this study: Y. Horikawa (Akita University School of Medicine, Akita, Japan), S. Takahashi (Nihon University School of Medicine, Tokyo, Japan), H. Fujimoto (National Cancer Center Hospital, Tokyo, Japan), M. Eto (Kumamoto University, Graduate School of Medical Sciences, Kumamoto, Japan), K. Tanabe (Tokyo Women’s Medical University, Tokyo, Japan), M. Oya (Keio University School of Medicine, Tokyo, Japan), J. Miyazaki (University of Tsukuba, Ibaraki, Japan), H. Nakazawa (Tokyo Women’s Medical University Medical Center East, Tokyo, Japan), M. Niwakawa (Shizuoka Cancer Center Hospital, Shizuoka, Japan), H. Matsuyama (Yamaguchi University, Graduate School of Medicine, Yamaguchi, Japan). We thank Paul Bycott, Brad Rosbrook and Helen Bhattacharyya of Pfizer, Inc. (San Diego, CA, USA) for assistance with statistical analyses. Medical writing support was provided by Mariko Nagashima, PhD, of UBC Scientific Solutions, Southport, CT, USA, and was funded by Pfizer, Inc.

Funding

This work was funded by Pfizer, Inc.

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.

Keiji Imai, Yoshiko Uneyama: Pfizer Japan, Inc., Tokyo, Japan.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10. 2010. http://globocan.iarc.fr (7 December 2011, date last accessed).

2. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev* 2008;34:193–205.

3. Mathew A, Devesa SS, Fraumeni JF, Jr, Chow WH. Global increases in kidney cancer incidence, 1973–1992. *Eur J Cancer Prev* 2002;11:171–8.

4. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review (CSR), 1975–2009, National Cancer Institute (based on November 2010 SEER data submission). Bethesda, MD: National Cancer Institute (NCI) 2010. http://seer.cancer.gov/csr/1975_2009_pops09 (16 May 2012, date last accessed).

5. American Cancer Society. Cancer Facts and Figures 2011. Atlanta, GA: American Cancer Society 2011. http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-029771. pdf (7 December 2011, date last accessed).

6. Ljungberg B, Cowan NC, Haabury DC, et al. EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol* 2010;58:398–406.

7. Campbell SC, Novick AC, Beldegrun A, et al. Guideline for management of the clinical T1 renal mass. *J Urol* 2009;182:1271–9.

8. Fujioka T, Obara W. Committee for establishment of the clinical T1 renal mass. *J Urol* 2009;182:1271–9.

9. Fujitaka T, Obara W. Committee for establishment of the clinical practice guideline for the management of renal cell carcinoma and the Japanese urological association. Evidence-based clinical practice guideline for renal cell carcinoma: the Japanese Urological Association 2011 update. *Int J Urol* 2012;19:496–503.

10. Tomita Y, Uemura H, Fujimoto H, et al. Key predictive factors of axitinib (AG-013736)-induced proteinuria and efficacy: a phase II study in Japanese patients with cytokine-refractory metastatic renal cell carcinoma. *Eur J Cancer* 2011;47:2592–602.

11. Copping C, Porzolt F, Awa A, Kumpf J, Oldman A, Wilt T. Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev 2005;1:CD004125.*

12. Escudier B, Eisen T, Standler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–34.

13. Motzer RJ, Hussin TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon α in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584–90.

14. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28:1061–8.

15. 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;378:1931–9.

16. Ueda T, Imamura Y, Kato Y, et al. Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). *Jpn J Clin Oncol* 2013;43(6) 627

17. 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;378:1931–9.

18. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271–81.

19. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2009;372:449–56.

20. 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;14:7272–83.

21. Choueiri TK. Axitinib, a novel anti-angiogenic drug with promising activity in various solid tumors. *Curr Opin Investig Drugs* 2008;9:658–71.

22. Kelly RJ, Rixe O. Axitinib—a selective inhibitor of the vascular endothelial growth factor (VEGF) receptor. *Target Oncol* 2009;4:297–305.

23. Goldstein R, Pickering L, Larkin J. Does axitinib (AG-013736) have a future role in metastatic renal cell carcinoma and other malignancies? *Expert Rev Anticancer Ther* 2010;10:1545–57.

24. Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. *Drugs R D* 2011;11:113–26.

25. 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;8:975–84.

26. Cohen EE, Rosen LS, Vokes EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol* 2008;26:4708–13.

27. Rini BI, Wilden G, Hudes G, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:4462–8.

28. Schiller JH, Larson T, Ou SH, et al. Efficacy and safety of axitinib in patients with advanced non-small-cell lung cancer: results from a phase II study. *J Clin Oncol* 2009;27:3836–41.

29. Fruehauf JP, Lutzky J, McDermott DF, et al. Multicenter, phase II study of axitinib, a selective second-generation inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, in patients with metastatic melanoma. *Clin Cancer Res* 2011;17:7462–9.

30. Lindblad P. Epidemiology of renal cell carcinoma. *Scand J Surg* 2004;93:88–96.

31. Stafford HS, Saltzstein SL, Shimasaki S, Sanders C, Downs TM, Sadler GR. Racial/ethnic and gender disparities in renal cell carcinoma incidence and survival. *J Urol* 2008;179:1704–8.

32. Maruko K, Kanayama H, Miyao N, et al. Prevalence of renal cell carcinoma: a nation-wide survey in Japan, 2002. *Int J Urol* 2007;14:479–82.

33. Sekine I, Yamamoto N, Nishio K, Saijo N. Emerging ethnic differences in lung cancer therapy. *Br J Cancer* 2008;99:1757–62.

34. Naito S, Tomita Y, Rha SY, et al. Kidney Cancer Working Group report. *Jpn J Clin Oncol* 2010;40(Suppl. 1):51–6.

35. Rini BI, Grunwald V, Fishman MN, et al. Axitinib for first-line metastatic renal cell carcinoma (mRCC): Overall efficacy and pharmacokinetic (PK) analyses from a randomized phase II study. *J Clin Oncol* 2012;30, No. 15 (May 20 Suppl; abst 4503).

36. Nexavar® (sorafenib) prescribing information. New Jersey: Bayer Healthcare Pharmaceuticals Inc 2005. http://labeling.bayerhealthcare. com/html/products/pi/Nexavar_PI.pdf (27 June 2012, date last accessed).

37. Cella D, Yount S, Du H, et al. Development and validation of the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). *J Support Oncol* 2006;4:191–9.

38. Cella D, Yount S, Brueker PS, et al. Development and validation of a scale to measure disease-related symptoms of kidney cancer. *Value Health* 2007;10:285–93.
39. Bonomi AE, Cella DF, Hahn EA, et al. Multilingual translation of the Functional Assessment of Cancer Therapy (FACT) quality of life measurement system. *Qual Life Res* 1996;5:309–20.

40. Eremenco SL, Cella D, Arnold BJ. A comprehensive method for the translation and cross-cultural validation of health status questionnaires. *Eval Health Prof* 2005;28:212–32.

41. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value Health* 2005;8:94–104.

42. Inlyta (axitinib) tablets prescribing information. New York, NY: Pfizer Inc 2012. http://labeling.pfizer.com/ShowLabeling.aspx?id=759 (30 August 2012, date last accessed).

43. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010;116:4256–65.

44. Naito S, Yamamoto N, Takayama T, et al. Prognosis of Japanese metastatic renal cell carcinoma patients in the cytokine era: a cooperative group report of 1463 patients. *Eur Urol* 2010;57:317–25.

45. Akaza H, Tsukamoto T, Murai M, Nakajima K, Naito S. Phase II study to investigate the efficacy, safety, and pharmacokinetics of sorafenib in Japanese patients with advanced renal cell carcinoma. *Jpn J Clin Oncol* 2007;37:755–62.

46. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib vs Sorafenib for advanced renal cell carcinoma: phase III overall survival results and analysis of prognostic factors. *Ann Oncol* 2012;23:ix262. (Suppl 9; abstr 793PD).

47. 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;65:563–70.

48. 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;101:963–8.

49. Fujiwara Y, Kiyota N, Chayahara N, et al. Management of axitinib (AG-013736)-induced fatigue and thyroid dysfunction, and predictive biomarkers of axitinib exposure: results from phase I studies in Japanese patients. *Invest New Drugs* 2012;30:1055–64.

50. 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;68:645–55.

51. Garrett M, Houk BE, Myrand SP, Hee B, Mota J, Pithavala YK. A population pharmacokinetic (PK) analysis to evaluate the potential effect of the UGT1A1*28 genotype on the PK of AG-013736, an anti-angiogenic agent. *Clin Pharmacol Ther* 2007;81:S21 (Suppl 1; abstr PI-28).