EUROPEAN JOURNAL OF CANCER 47 (2011) 2592–2602

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# 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

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ARTICLE INFO

*Article history:*
Available online 31 August 2011

*Keywords:*
Axitinib
Biomarker
Proteinuria
Renal cell carcinoma
VEGFR-2

ABSTRACT

*Background:* Axitinib (AG-013736) is an oral, selective and potent inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, 2 and 3. This phase II study investigated axitinib efficacy, safety and biomarkers in Japanese patients with cytokine-refractory metastatic renal cell carcinoma (mRCC).

*Patients and methods:* In an open-label, multicentre study, 64 patients received an axitinib starting dose of 5 mg twice daily.

*Results:* Objective response rate (ORR) was 50.0% and median progression-free survival (PFS) was 11.0 months per independent review committee. Common treatment-related adverse events were hypertension (84%; 70% grade $\geqslant$3), hand–foot syndrome (75%; 22% grade $\geqslant$3) and diarrhoea (64%; 5% grade $\geqslant$3). Eighteen patients (28%) developed proteinuria $\geqslant$2 g/24 h and required dose reduction or treatment interruption/discontinuation. Proteinuria was a major cause for treatment discontinuation. Baseline urine protein levels were associated with development of proteinuria $\geqslant$2 g/24 h (hazard ratio [HR] = 5.457, $P = 0.0035$ in patients with baseline proteinuria $\geqslant$1+ versus <1+). Baseline urine protein levels correlated more strongly with axitinib-related proteinuria than other baseline renal function test values or blood pressure. Patients with greater decreases in soluble VEGFR-2 concentrations had significantly higher ORR and longer PFS than those with smaller

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0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2011.07.014

decreases (ORR: 64.5% versus 37.5%, $P = 0.045$; median PFS: 12.9 months versus 9.2 months, HR = 0.42, $P = 0.01$).

*Conclusions:* Axitinib showed significant antitumour activity and was well tolerated in Japanese mRCC patients. Baseline proteinuria and soluble VEGFR-2 levels may be key indicators of axitinib-induced proteinuria and efficacy, respectively.



## 1. Introduction

Renal cell carcinoma (RCC) is the most common form of kidney cancer,[1] accounting for 2–3% of adult malignancies worldwide[2] and increasing at a rate of 2–3% per decade.[1] Approximately 30% of RCC patients have metastatic disease (mRCC) at the time of diagnosis.[1,3–5] Although the overall incidence of RCC is lower in Asian countries than in North America and Europe, it is particularly high among Japanese males.[5] In 2008, the incidence rate (per 100,000 persons at risk) for kidney cancer was 17.7, 13.6 and 2.0 in North America, Europe and Asia, respectively; the rate among Japanese males was 16.2.[6] Surgical removal of primary tumours is widely recommended,[2] but systemic therapy is needed for mRCC patients. Furthermore, mRCC is resistant to traditional cancer treatments, e.g. chemotherapy and radiation. Until recently, cytokine treatment with interferon-α (IFN-α) and/or interleukin-2 (IL-2) was the standard of care for mRCC.[4,7] However, these therapies offer modest clinical benefit.[4]

Rising rates of RCC, prevalence of metastatic cases and limited efficacy of available therapies highlight the need for novel treatment options. Pathways leading to angiogenesis, which is essential for tumour progression and metastasis, are key targets of current research. Most clear-cell RCC, which accounts for 75% of mRCC cases,[8] exhibit loss of function of the von Hippel Lindau gene.[9,10] This leads to acceleration of the vascular endothelial growth factor (VEGF) pathway and promotion of angiogenesis.[9]

Axitinib, an oral, selective and potent inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFR)-1, 2 and 3,[11] demonstrated clinical efficacy in phase II studies of various tumour types.[12–17] Single-agent axitinib is active and well tolerated as second-line treatment for mRCC.[12,15] Objective response rates (ORR) for axitinib were 44.2% and 22.6% in phase II studies of patients with cytokine-refractory[12] and sorafenib-refractory mRCC,[15] respectively, conducted in Western countries.

The present phase II study investigated the efficacy, safety and biomarkers of axitinib in Japanese patients with cytokine-refractory mRCC. This was the first study to investigate the activity and safety of axitinib for mRCC in Asian patients.

## 2. Patients and methods

### 2.1. Study design and end-points

This was an open-label, multicentre phase II study. The primary end-point was ORR. Secondary end-points included progression-free survival (PFS), duration of response (DR), safety and changes in the plasma concentrations of potential biomarkers (soluble VEGFR [sVEGFR]-1, 2, 3; VEGF and soluble stem cell factor receptor [sKIT]). Exploratory analyses evaluated the relationship between changes in plasma concentration profiles of biomarkers and efficacy end-points. Potential predictive factors of axitinib-induced proteinuria were investigated as post hoc exploratory analyses.

This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines on Good Clinical Practice, the study protocol and applicable local regulatory requirements and laws. All participants provided informed consent and agreed to comply with the study protocol, which was approved by an institutional review board at each site. The trial is registered on ClinicalTrials.gov (NCT00569946).

### 2.2. Patient population

Patients aged ⩾20 years had histologically confirmed mRCC with clear-cell component, ⩾1 target lesion defined by Response Evaluation Criteria in Solid Tumours (RECIST, version 1.0),[18] prior nephrectomy, and were refractory to first-line cytokine therapy (IFN-α and/or IL-2). Patients were required to have Eastern Cooperative Oncology Group performance status of 0 or 1; adequate bone marrow, hepatic and renal function; baseline proteinuria <2+ by urine dipstick or <2 g/24 h urine collection; and blood pressure (BP) ⩽140/90 mmHg (antihypertensive medications were permitted). Patients with clinically evident gastrointestinal disorders potentially affecting ingestion or absorption were excluded. Other exclusion criteria were active seizure disorders; evidence of brain metastases, spinal cord compression or carcinomatous meningitis; myocardial infarction, severe or unstable angina, coronary or peripheral artery bypass graft, symptomatic congestive heart failure or cerebrovascular accident ⩽12 months prior to study registration.

### 2.3. Study treatments

Axitinib was orally administered with food at a starting dose of 5 mg twice daily (BID) continuously. The axitinib dose could be increased to 7 mg BID and then to a maximum of 10 mg BID in patients with no grade >2 treatment-related adverse events (AEs) and with ⩽150/90 mmHg for ⩾2 weeks without the use of antihypertensive medication. The axitinib dose was reduced to 3 mg BID and then to 2 mg BID in patients who developed grade 3 treatment-related non-haematologic AEs and patients with two readings of systolic BP >150 mmHg or diastolic BP >100 mmHg who were receiving maximal antihypertensive therapy. The axitinib dose was interrupted in patients with grade 4 treatment-related AEs, two readings of

systolic BP >160 mmHg or diastolic BP >105 mmHg, or ⩾2 g protein/24 h and resumed at one lower dose level when AEs improved to grade ⩽2, BP was <150/100 mmHg or <2 g protein/24 h was present.

### 2.4. Assessments

Tumours were radiologically assessed prior to initiation of axitinib therapy and every 8 weeks thereafter according to RECIST, version 1.0. Tumour responses were also assessed by an independent review committee (IRC). AEs were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.[19] Urinalysis was conducted at screening and at each clinic visit; for urinary protein ⩾2+ by semiquantitative dipstick analysis, a 24-h urine collection was performed. Thyroid function tests were conducted at screening; cycle 1 days 1, 8, 15 and 22; cycles 2 and 3 day 1; day 1 of odd-numbered cycles thereafter; and at end of treatment. Blood samples for evaluation of the changes in plasma concentrations of sVEGFR-1, 2 and 3; VEGF; and sKIT were collected pre-dosing, day 1 of cycles 2–7, and at end of treatment. Plasma concentrations of proteins were measured by an enzyme-linked immunosorbent assay (Alta Analytical Laboratory; El Dorado Hills, CA, USA).

### 2.5. Statistical analysis

Sixty-three patients were required to test the null hypothesis that the true ORR was ⩽10% versus the alternative hypothesis that the true ORR was ⩾25% with a one-sided alpha level of 5% and 90% power. All patients receiving at least one dose of axitinib were included in the safety and efficacy analyses. This analysis was conducted 1 year after all patients (excluding those who discontinued treatment) initiated axitinib.

## 3. Results

### 3.1. Patient characteristics and treatment exposure

Sixty-four patients were enrolled (Table 1). Median duration of treatment with axitinib was 326 days (range, 13–696) with a mean daily dose of 7.1 mg (range, 1.6–16.4). Axitinib dosing was titrated >5 mg BID in five patients (8%), and reduced to <5 mg BID in 42 patients (66%). In all, 37 patients discontinued the study, 13 due to treatment-related AEs and 24 due to disease progression. As of the analysis cut-off date, 27 patients (42%) were still receiving axitinib.

### 3.2. Efficacy

A summary of axitinib efficacy is shown in Table 2. Thirty-two (50.0%; 95% confidence interval [CI], 37.2–62.8) and 35 (54.7%; 95% CI, 41.7–67.2) patients achieved an objective response according to IRC and investigator assessments, respectively. Median PFS was 11.0 months (95% CI, 9.2–12.0) (Fig. 1A) and 12.0 months (95% CI, 9.2–14.8) according to IRC and investigator assessments, respectively. Tumour size decreased by ⩾30% in 37 patients (58%) according to IRC assessment (Fig. 1B). Median DR ($n = 32$) was 11.5 months (95% CI, 8.3 – not estimable) by IRC assessment.

**Table 1 – Baseline patient characteristics.**

| | N = 64 |
|---|---|
| Male/female, *n* (%) | 44 (69)/20 (31) |
| Age, median (range) (year) | 63 (34–80) |
| ECOG PS 0/1, *n* (%) | 57 (89)/7 (11) |
| *Primary histology, n (%)* | |
| Clear cell | 62 (97) |
| Papillary carcinoma | 1 (2) |
| Spindle cell | 1 (2) |
| *Prior adjuvant therapy, n (%)* | |
| Yes | 10 (16) |
| No | 54 (84) |
| *MSKCC risk criteria*[a]*, n (%)* | |
| Favourable | 10 (16) |
| Intermediate | 47 (77) |
| Poor | 4 (7) |

ECOG PS, Eastern Cooperative Oncology Group performance status and MSKCC, Memorial Sloan-Kettering Cancer Center.
[a] Unknown for three patients.

**Table 2 – Summary of efficacy.**

| | IRC assessment N = 64 | Investigator assessment N = 64 |
|---|---|---|
| *Best response by RECIST, n (%)* | | |
| Partial response (PR) | 32 (50.0) | 35 (54.7) |
| Stable disease[a] (SD) | 29 (45.3) | 26 (40.6) |
| Progressive disease | 1 (1.6) | 1 (1.6) |
| Indeterminate[b] | 2 (3.1) | 2 (3.1) |
| Objective response rate (PR) | 32 (50.0) | 35 (54.7) |
| 95% CI | 37.2–62.8 | 41.7–67.2 |
| Median PFS, months | 11.0 | 12.0 |
| 95% CI | 9.2–12.0 | 9.2–14.8 |

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival and RECIST, Response Evaluation Criteria in Solid Tumours.
[a] Stable disease ⩾8 weeks.
[b] No tumour assessment after dosing due to adverse event-related discontinuation.

### 3.3. Safety

The most frequently reported treatment-related non-haematologic AEs were hypertension, hand–foot syndrome, diarrhoea and dysphonia (Table 3). The most common grade ⩾3 treatment-related non-haematologic AEs were hypertension and hand–foot syndrome. Few patients experienced treatment-related haematologic AEs (Table 3). The treatment-related laboratory abnormality most frequently reported as an AE was proteinuria (Table 3). Treatment-related AEs leading to study discontinuation were proteinuria ($n = 7$; 11%), anxiety, decreased weight, polycythemia, subarachnoid haemorrhage, malaise and thyrotoxicosis ($n = 1$ each; 2%).

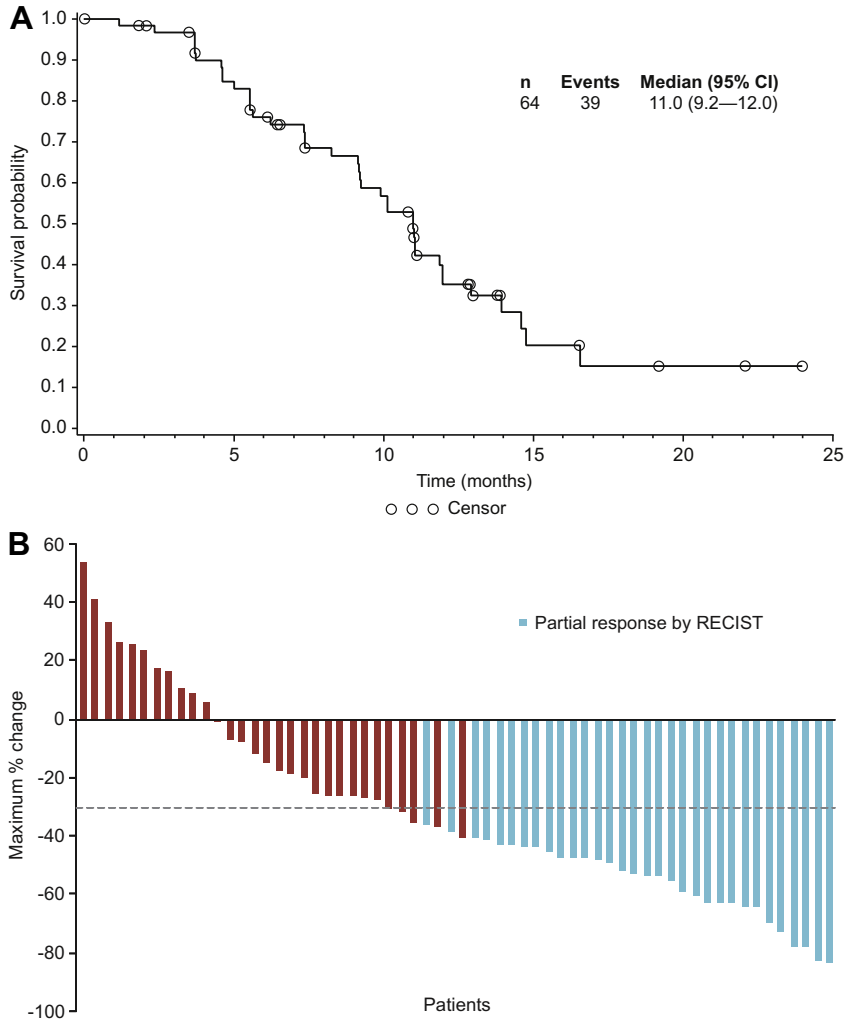


**Fig. 1 – Efficacy. (A) Kaplan–Meier plot of progression-free survival (IRC assessment) and (B) maximum percentage change in target lesion size (IRC assessment). Bars represent individual patients. IRC, independent review committee.**

### 3.4. *Proteinuria*

Eighteen patients (28%) developed proteinuria ⩾2 g/24 h, requiring dose reduction or treatment interruption/discontinuation. Median proteinuria prior to dose interruption was 2.8 g/24 h (range, 2.1–10.8). Proteinuria ⩾2 g/24 h resolved to <2 g/24 h within 3–47 days (median, 7 days) of treatment interruption. Median proteinuria was 1.0 g/24 h (range, 0.5–1.9) when axitinib treatment was resumed at a lower dose level. Seven patients discontinued treatment because proteinuria ⩾2 g/24 h was still observed at the lowest available dose (2 mg BID). Baseline urine protein levels correlated more strongly with axitinib-related proteinuria ⩾2 g than other baseline renal function-related test values or BP (Table 4). The hazard ratio [HR] for the development of axitinib-related proteinuria ⩾2 g was 5.457 (95% CI, 1.749–17.029; $P = 0.0035$) in patients with baseline proteinuria ⩾1+ compared with those with baseline proteinuria <1+. Patients with baseline proteinuria ⩾2+ had a higher risk of shorter treatment duration due to axitinib-induced proteinuria (Table 5). Time to treatment discontinuation due to proteinuria ranged from 44 to 118 days compared with 158–344 days in patients with baseline proteinuria ⩾2+ and <2+, respectively. Higher levels of baseline urine protein were associated with axitinib-induced proteinuria ⩾2 g (Table 6).

### 3.5. *Thyroid function*

Fifty-six patients (88%) experienced increases and/or transient decreases in thyroid-stimulating hormone (TSH) levels beyond the normal range during axitinib treatment (Fig. 2A and B). Twenty (31%) and 14 patients (22%) had transient increases in levels of free triiodothyronine (T3) and free thyroxine (T4), respectively (Fig. 2C and D, respectively). Thirty-two patients (50%) received thyroid hormone replacement therapy during the study.

### 3.6. *Changes in soluble plasma protein concentrations and correlation with clinical activity*

Overall, levels of VEGF increased while levels of sVEGFR-1, 2 and 3 decreased during therapy (Fig. 3A and B). Small de-

**Table 3 – Safety findings.**

| | All grades *n* (%) | Grades 3/4[a] *n* (%) |
|---|---|---|
| *Treatment-related non-haematologic AEs*[b] | | |
| Hypertension | 54 (84) | 45 (70) |
| Hand–foot syndrome | 48 (75) | 14 (22) |
| Diarrhoea | 41 (64) | 3 (5) |
| Dysphonia | 34 (53) | 0 (0) |
| Fatigue | 31 (48) | 3 (5) |
| Hypothyroidism | 31 (48) | 0 (0) |
| Decreased appetite | 23 (36) | 3 (5) |
| Weight decreased | 19 (30) | 2 (3) |
| Nausea | 16 (25) | 0 (0) |
| Headache | 15 (23) | 0 (0) |
| Stomatitis | 15 (23) | 0 (0) |
| Epistaxis | 14 (22) | 0 (0) |
| Rash | 13 (20) | 0 (0) |
| Arthralgia | 12 (19) | 2 (3) |
| Dysgeusia | 12 (19) | 0 (0) |
| Vomiting | 10 (16) | 0 (0) |
| Malaise | 8 (13) | 4 (6) |
| Abdominal pain | 8 (13) | 0 (0) |
| Chest pain | 7 (11) | 0 (0) |
| Constipation | 7 (11) | 0 (0) |
| Cough | 7 (11) | 0 (0) |
| *Treatment-related haematologic laboratory AEs*[c] | | |
| Thrombocytopenia | 7 (11) | 1 (2) |
| Neutropenia | 4 (6) | 1 (2) |
| Haemoglobin decreased | 3 (5) | 0 (0) |
| Anaemia | 2 (3) | 1 (2) |
| Lymphopaenia | 2 (3) | 1 (2) |
| Polycythaemia | 2 (3) | 0 (0) |
| Leucopoenia | 2 (3) | 0 (0) |
| *Treatment-related laboratory test AEs*[b] | | |
| Proteinuria[d] | 37 (58) | 6 (9) |
| TSH increased | 20 (31) | 0 (0) |
| ALT increased | 15 (23) | 2 (3) |
| AST increased | 15 (23) | 1 (2) |
| ALP increased | 11 (17) | 0 (0) |
| LDH increased | 8 (13) | 0 (0) |

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase and TSH, thyroid-stimulating hormone.

[a] No grade 5 AEs (deaths) were reported.

[b] Reported in $\geqslant$10% of patients.

[c] Reported in $\geqslant$3% of patients.

[d] Includes proteinuria, protein urine, and protein urine present.

creases in sKIT plasma concentrations were observed. Patients with a percent change in sVEGFR-2 levels <median (greater reduction) demonstrated significantly higher ORR compared with those with a percent change $\geqslant$median (smaller reduction) (64.5% [95% CI, 45.4–80.8] versus 37.5% [95% CI, 21.1–56.3]; $P = 0.045$) (Fig. 3C). Similarly, patients with a greater reduction in sVEGFR-2 levels demonstrated significantly longer median PFS compared with those with a smaller reduction (12.9 months [95% CI, 9.3–16.6] versus 9.2 months [95% CI, 7.4–11.0]; HR 0.42 [95% CI, 0.21–0.83], $P = 0.01$) (Fig. 3D).

## 4. Discussion

In this study, axitinib was well tolerated and demonstrated significant clinical activity as second-line treatment for Japanese patients with cytokine-refractory mRCC. Moreover, tumour shrinkage was observed in the majority of patients. This clinical benefit is encouraging and warrants further investigation of axitinib in this population. Final analysis of efficacy data from this study, including overall survival, is awaited.

Common treatment-related AEs were hypertension, hand–foot syndrome, diarrhoea, and dysphonia, toxicities frequently associated with VEGF pathway inhibitors.[12,13,15,16,20–23] Other than hypertension, most AEs were grade $\leqslant$2. Hypertension was the most commonly reported AE (84% of patients) and was manageable with antihypertensive medication, which was administered to 94% of patients. The incidence of proteinuria and hand–foot syndrome was higher in this study than in the Western study of axitinib for cytokine-refractory mRCC (58% versus 8%, and 75% versus 8%, respectively).[12] In contrast,

**Table 4 – Proteinuria ⩾2 g/24 h and baseline renal function-related test values or blood pressure.**

| Baseline laboratory tests | HR (95% CI)[a] | P value[b] |
|---|---|---|
| Urine protein | 5.457 (1.749–17.029)[c] | 0.0035 |
| Creatinine | 1.446 (1.010–2.069) | 0.0439 |
| eGFR | 0.647 (0.423–0.987) | 0.0435 |
| eCcr | 0.781 (0.599–1.020) | 0.0693 |
| BUN | 1.368 (0.809–2.314) | 0.2425 |
| Albumin | 0.830 (0.649–1.062) | 0.1378 |
| Systolic BP | 1.593 (0.915–2.774) | 0.0998 |
| Diastolic BP | 0.822 (0.631–1.071) | 0.1470 |

BP, blood pressure; BUN, blood urea nitrogen; CI, confidence interval; eCcr, estimated creatinine clearance; eGFR, estimated glomerular filtration rate and HR, hazard ratio.

[a] Crude HR for one-level increment by Cox proportional hazard model. One increment: creatinine 0.2, eGFR 10, eCcr 10, BUN 10, albumin 0.2, systolic BP 10, diastolic BP 5.

[b] Wald-type test.

[c] HR for urine protein ⩾1+ versus <1+ (<1+ is reference).

**Table 5 – Characteristics of patients discontinuing due to proteinuria.**

| Age (year) | Gender | Time to discontinuation due to proteinuria (days) | Baseline urine protein (mg/24 h) | Axitinib dose level | Urine protein/24 h (g) | Creatinine (mg/dL) | Best response by IRC |
|---|---|---|---|---|---|---|---|
| 61 | F | 44 | 2+ (935) | 5 mg BID | 10.8 | 1.0 | Indeterminate[a] |
| | | | | 2 mg BID[b] | 4.8 | 1.0 | |
| 54 | F | 113 | 2+ (460) | 5 mg BID | 4.5 | 1.56 | SD |
| | | | | 3 mg BID[b] | 3.4 | 1.58 | |
| | | | | 2 mg BID[b] | 2.3 | 1.58 | |
| 72 | M | 118 | 2+ (920) | 5 mg BID | 2.7 | 1.49 | SD |
| | | | | 3 mg BID[b] | 3.0 | 1.47 | |
| | | | | 2 mg BID[b] | 2.9 | 1.55 | |
| 70 | M | 158 | – | 3 mg BID[c] | 3.3 | 1.02 | SD |
| | | | | 2 mg BID[b] | 4.3 | 1.18 | |
| 79 | M | 173 | ± | 5 mg BID | 2.7 | 1.67 | SD |
| | | | | 3 mg BID[b] | 1.8 | 1.56 | |
| | | | | 2 mg BID[b] | 2.1 | 1.68 | |
| 74 | M | 225 | – | 5 mg BID | 2.2 | 1.1 | PR |
| | | | | 3 mg BID[b] | 3.0 | 1.2 | |
| | | | | 2 mg BID[b] | 2.3 | 1.3 | |
| 65 | M | 344 | – | 3 mg BID[c] | 2.7 | 0.85 | PR |
| | | | | 2 mg BID[b] | 2.6 | 0.92 | |

Shaded area: baseline urine protein of 2+.

BID, twice daily; F, female; IRC, independent review committee; M, male; PR, partial response and SD, stable disease.

[a] No tumour assessment after dosing due to discontinuation from study.

[b] The dose was reduced due to proteinuria.

[c] The dose was reduced from 5 mg BID to 3 mg BID due to hypertension prior to development of proteinuria ⩾2 g/24 h.

**Table 6 – Proteinuria ⩾2 g/24 h and baseline urine protein.**

| Baseline urine protein (*n*) | Proteinuria <2 g during treatment, *n* (%) | Proteinuria ⩾2 g during treatment, *n* (%) |
|---|---|---|
| – (51) | 40 (78) | 11 (22) |
| ± (7) | 4 (57) | 3 (43) |
| 1+ (2) | 1 (50) | 1 (50) |
| 2+ (4) | 1 (25) | 3 (75) |
| P value[a] | 0.013 | |

[a] Cochran-Armitage exact test.

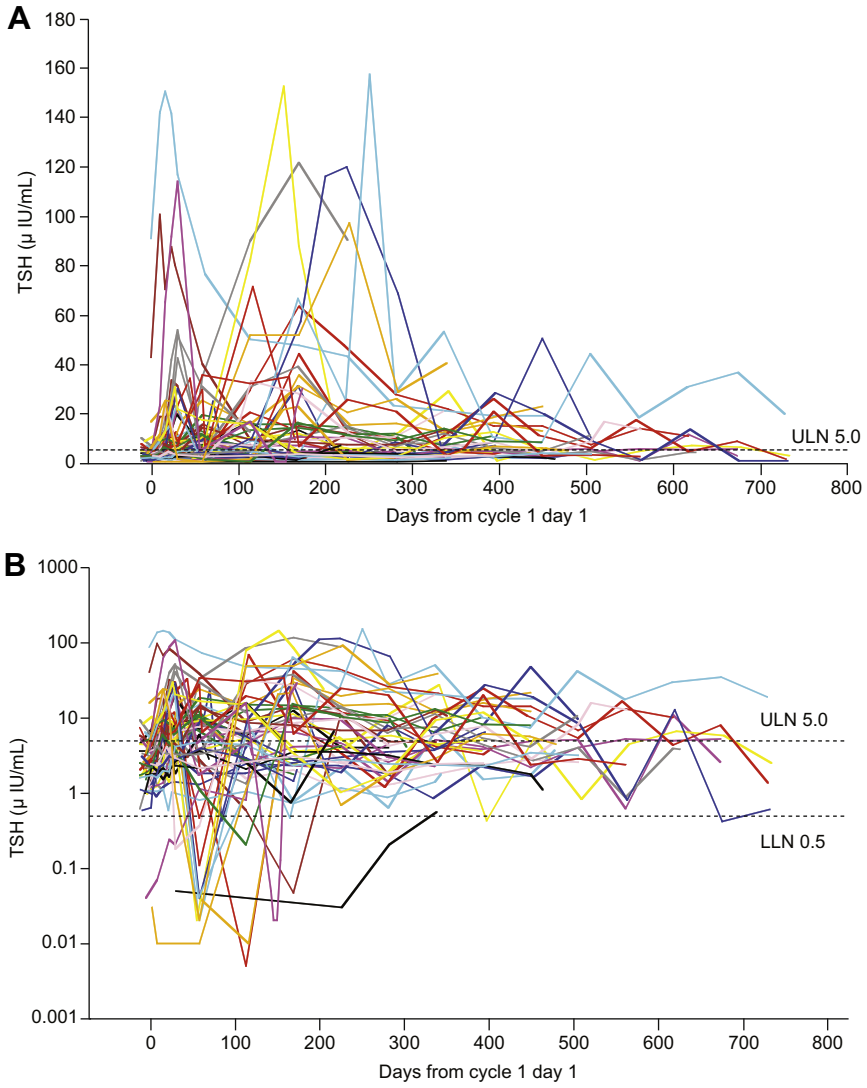


**Fig. 2 – Thyroid function test levels over time. (A) Thyroid-stimulating hormone absolute values, and (B) log scale, (C) free triiodothyronine (absolute values) and (D) free thyroxine (absolute values). Lines represent individual patients. LLN, lower limit of normal range; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine and ULN, upper limit of normal range.**

the incidence of dry skin was higher in the Western study (33% versus 5%).[12] Axitinib dose reductions were required in more Japanese patients (66%) than Western patients (29%) with cytokine-refractory mRCC.[12] It is unclear why the incidence of proteinuria and hand–foot syndrome was higher in Japanese patients compared with Western patients. Higher rates of AEs, including hand–foot syndrome and haematologic abnormalities, were also reported in Asian patients with RCC treated with sunitinib[24–27] or sorafenib[28] compared with Western patients.

Proteinuria is a widely reported side effect of antiangiogenic therapies.[29] In this study, proteinuria occurred in 58% of patients, with 28% developing proteinuria $\geqslant$2 g/24 h and requiring dose interruption or reduction. All patients developing proteinuria $\geqslant$2 g/24 h restarted axitinib at a lower dose level after proteinuria was resolved <2 g/24 h. However, 11% of patients were ultimately discontinued due to proteinuria $\geqslant$2 g/24 h with the lowest available dose (2 mg BID). These results underscore the importance of monitoring patients receiving angiogenesis inhibitors, including axitinib, for proteinuria. Control of proteinuria during antiangiogenic therapy may require dose reductions or treatment discontinuation, and patients should be referred to nephrologists when appropriate.[29] An understanding of the predictive factors leading to proteinuria in patients receiving angiogenesis inhibitors will be important for managing this AE. Here, higher baseline protein levels correlated with the development of axitinib-induced proteinuria and were associated with early discontinuation due to proteinuria. Thus, evaluation of urine protein levels at baseline may be important for selecting patients for axitinib therapy. In this study, the axitinib dose was interrupted/reduced or discontinued according to predefined dose-modification criteria for proteinuria, which has been used across axitinib clinical studies. In clinical practice, periodic interruption of axitinib treatment when indicated may help limit proteinuria to a low grade; axitinib treatment may be resumed,

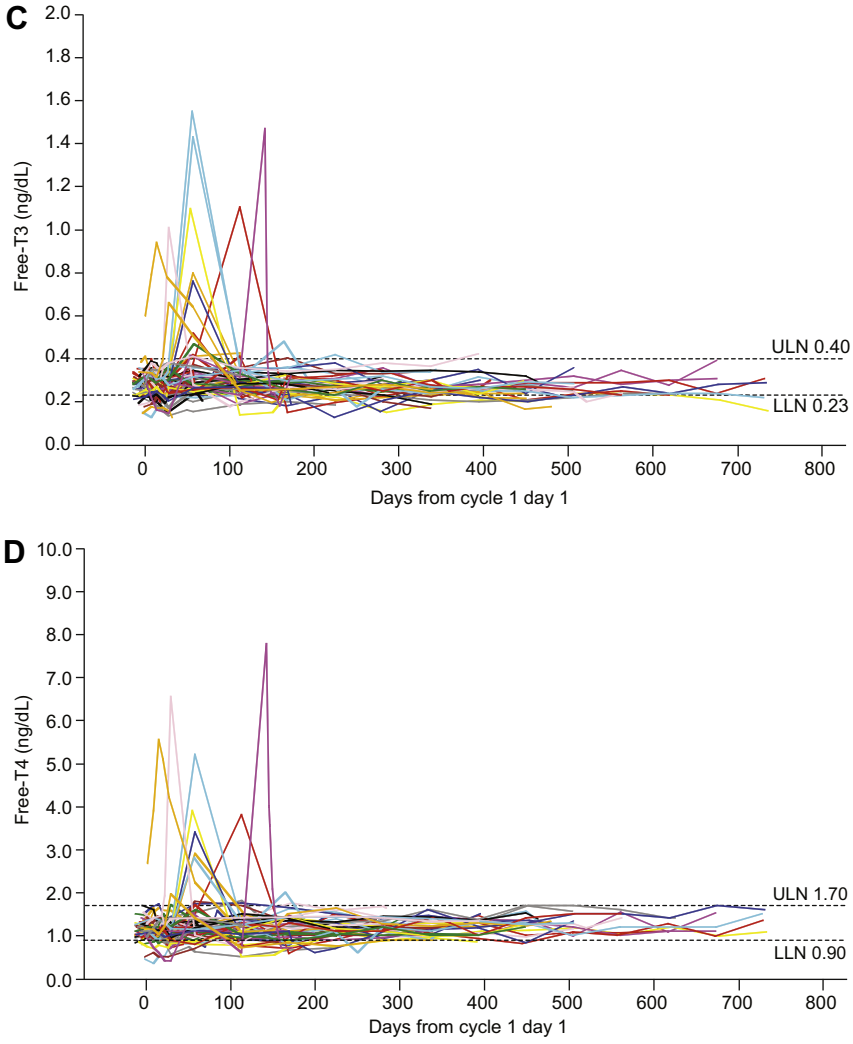


**Fig 2.** *(continued)*

especially when patients experience disease progression while off treatment. Proteinuria frequently correlates with the development of hypertension in patients receiving antiangiogenic therapies;[29] however, no clear correlation between development of proteinuria and change in BP during axitinib treatment was observed here. This may be related to multiple mechanisms of VEGFR inhibition leading to hypertension. In addition, 28 patients (44%) received antihypertensive medication prior to axitinib treatment initiation, and the majority of patients ($n$ = 54; 84%) received antihypertensive medication during the first 28 days of axitinib treatment to manage BP. This might have obscured the potential to assess the correlation between development of proteinuria and elevated BP.

Abnormalities in TSH levels were frequently reported (88% of patients). Inhibitors of VEGFR may impair thyroid function by blocking VEGF binding to normal thyroid cells and impeding thyroid blood flow.[30,31] Based on data from this and prior studies, monitoring of thyroid function is recommended during axitinib treatment. Hypothyroidism and associated symptoms may be managed by proactive administration of thyroid hormone replacement therapy.[30–34]

Agents targeting the VEGF pathway have changed the treatment paradigm for mRCC, and ongoing research is aimed at identifying biomarkers that predict their clinical benefit. Numerous candidate biomarkers have been evaluated, but a validated predictive biomarker has not yet been identified.[35] Prior studies of VEGF and sVEGFRs as biomarkers of response to angiogenesis inhibitors have yielded inconsistent results, illustrating the need for dynamic evaluation of these proteins during treatment.[35] In this study, greater reductions in sVEGFR-2 plasma concentrations during therapy were associated with higher ORR and longer PFS. Thus, sVEGFR-2 may be a useful pharmacodynamic marker of clinical outcome with axitinib.

Although there was no comparator in this study, axitinib demonstrated significant efficacy for mRCC in Japanese patients and was well tolerated in this population. Although the incidence of some AEs (e.g. proteinuria and hand–foot syndrome) was higher in Japanese compared to Western mRCC patients receiving axitinib, careful monitoring and management may help to control these toxicities if they arise during therapy. Moreover, preliminary findings suggest that baseline proteinuria and sVEGFR-2 levels may be key indicators for

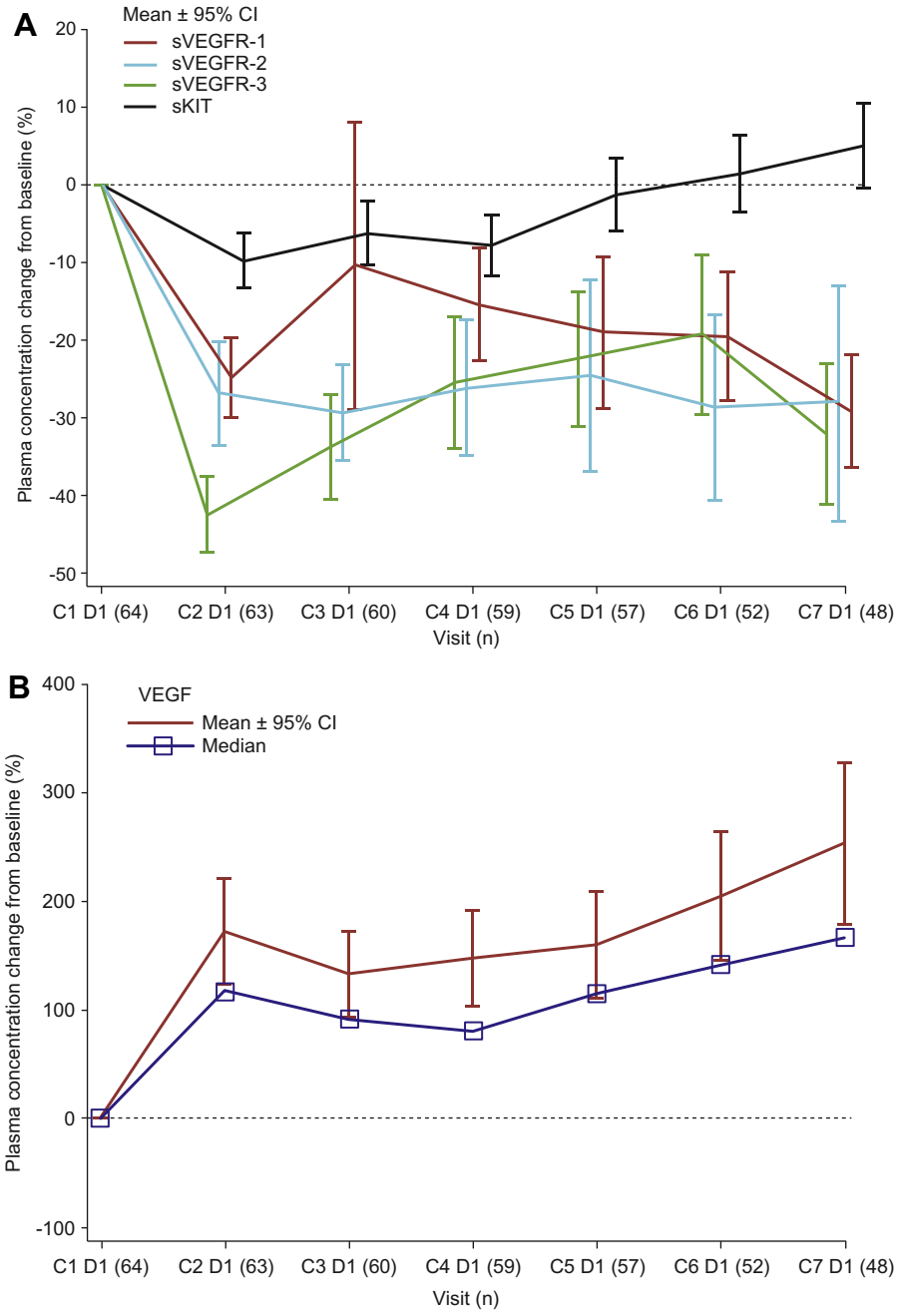


**Fig. 3 – Correlation of changes in soluble plasma protein concentrations with efficacy. Plasma concentrations of potential biomarkers (mean percent change from baseline [95% confidence interval]) for (A) sVEGFR-1, 2, 3, and sKIT, and (B) VEGF. (C) Objective response rate (IRC assessment) and (D) Kaplan–Meier plots of progression-free survival (IRC assessment) by sVEGFR-2 percent change from baseline to cycle 2 day 1. IRC, independent review committee; sKIT, soluble stem cell factor receptor; sVEGFR, soluble vascular endothelial growth factor receptor and VEGF, vascular endothelial growth factor.**

axitinib-induced proteinuria and efficacy, respectively. These data support further investigation of axitinib in mRCC in larger clinical studies. Axitinib is currently in phase III development in RCC.

## Japan Axitinib Phase II Study Group

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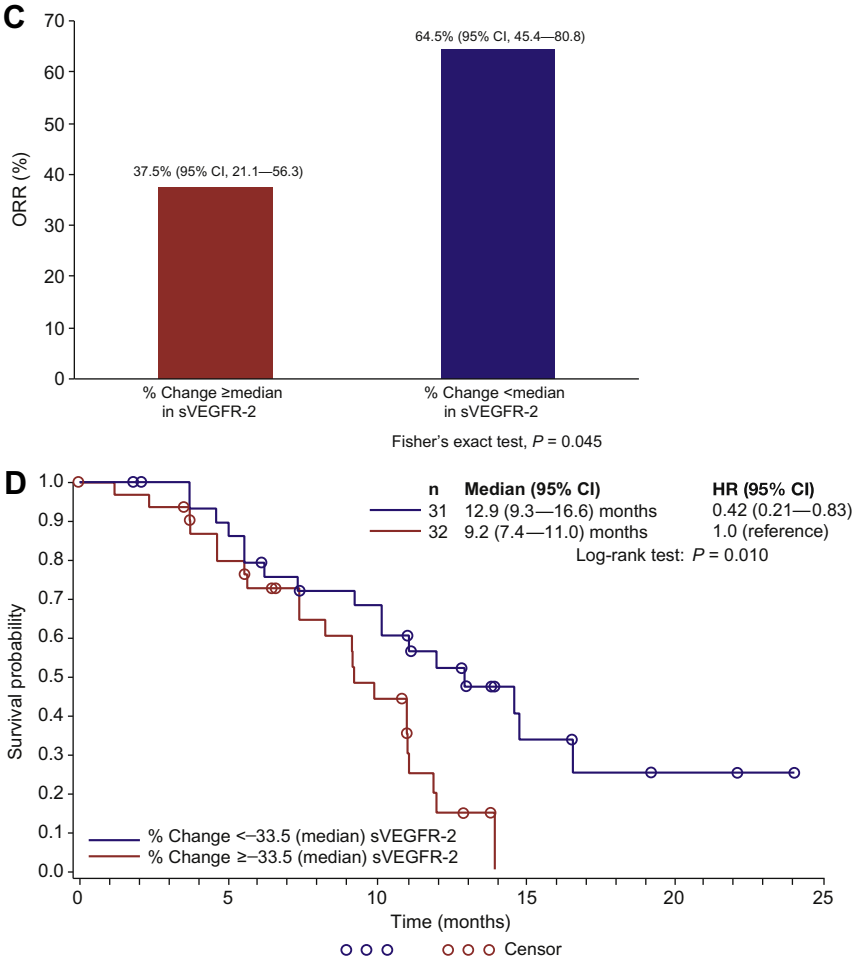


**Fig 3.** *(continued)*

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## Conflict of interest statement

Y. Tomita, H. Uemura, H. Kanayama, N. Shinohara and S. Ozono have received speaker honoraria from Pfizer. H. Fujimoto has nothing to disclose. H. Nakazawa, S. Naito and H. Akaza have received speaker honoraria, and consultant or advisory fees from Pfizer. K. Imai and Y. Umeyama are employees of Pfizer and own stock in Pfizer.

## Acknowledgements

We thank the patients and families who participated in this study, the physicians who referred them and the study coordinators. Editorial support was provided by Joanna Bloom, PhD, of UBC Scientific Solutions and was funded by Pfizer Inc. We would like to thank Gamal ElSawah, MD, Pfizer Medical Affairs, for his review of the manuscript. This study was sponsored by Pfizer Japan Inc., Tokyo, Japan. Pfizer Japan Inc. involved in the study design, interpretation of data and the writing of the manuscript. Also Pfizer Japan Inc. conducted data collection and analysis.

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