Phase III AXIS trial of axitinib versus sorafenib in metastatic renal cell carcinoma: Updated results among cytokine-treated patients

MD Michaelson,[1] BI Rini,[2] B Escudier,[3] J Clark,[4] B Redman,[5] J Tarazi,[6] B Rosbrook,[6] S Kim,[6] RJ Motzer[7]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]The Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [3]Institut Gustave Roussy, Villejuif, France; [4]Loyola University Chicago Cardinal Bernardin Cancer Center, Maywood, IL, USA; [5]University of Michigan, Comprehensive Cancer Center, Ann Arbor, MI, USA; [6]Pfizer Oncology, San Diego, CA, USA; [7]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

INTRODUCTION

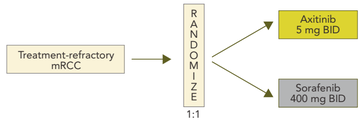
- Axitinib is a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors.[1]
- Axitinib is approved in the US for the treatment of advanced renal cell carcinoma (RCC) after failure of 1 prior systemic therapy.[2]
- In the phase III AXIS trial, axitinib improved progression-free survival (PFS) compared with sorafenib as second-line therapy in patients with metastatic RCC (mRCC).[3]
  - In patients previously treated with cytokines, median PFS (mPFS) was 12.1 months with axitinib vs 6.5 months with sorafenib.
- In a prior phase II study of axitinib for cytokine-refractory mRCC, mPFS was 13.7 months and the 5-year overall survival (OS) rate was 20.6%.[4,5]
- Here, we report updated efficacy and safety data for patients who had received prior cytokine-based regimens and participated in the AXIS trial (ClinicalTrials.gov ID NCT00678392).

METHODS

Study Design and Treatment

- The AXIS trial is a phase III, multicenter, open-label, randomized trial that enrolled 723 patients with clear cell mRCC and progressive disease after 1 prior systemic therapy.
- Patients were stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) and prior therapy and randomized 1:1 to receive axitinib or sorafenib (**Figure 1**).

Figure 1. Study design.



BID = twice daily; mRCC = metastatic renal cell carcinoma.

- Axitinib was administered at a starting dose of 5 mg twice daily (BID).
  - The dose could be titrated to 7 mg BID, and then to a maximum of 10 mg BID, in patients with no grade >2 axitinib-related toxicities for consecutive 2-week periods and blood pressure (BP) ≤150/90 mmHg without antihypertensive medication.
  - The dose was interrupted and/or reduced to 3 mg BID, and then to 2 mg BID, in patients with grade ≥3 axitinib-related adverse events (AEs), BP >150/100 mmHg with maximal antihypertensive treatment, or ≥2 g proteinuria/24 hr.
- Sorafenib was administered at a starting dose of 400 mg BID.
  - The dose was interrupted and/or reduced to 400 mg once daily, and then to 400 mg every other day, in patients with grade ≥3 sorafenib-related AEs, grade ≥2 skin toxicity that was not resolved within 7 days, more than 1 occurrence of grade ≥2 skin toxicity, or severe or persistent hypertension despite treatment with antihypertensive therapy.

Patients: Key Eligibility Criteria

- Histologically or cytologically confirmed mRCC with clear cell component.
- Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST).
- RECIST-defined progressive disease after 1 prior sunitinib-, bevacizumab + interferon-α (IFN-α)-, temsirolimus-, or cytokine-based regimen.
- ECOG PS 0 or 1.
- Adequate renal, hepatic, and hematologic organ function.
- BP ≤140/90 mmHg; antihypertensive therapies were permitted.

Assessments

- Tumor assessments were performed at baseline, Week 6, Week 12, and every 8 weeks thereafter.
- AEs were recorded throughout the study period and graded according to Common Terminology Criteria for Adverse Events (CTCAE v3.0).
- Physical examinations, laboratory assessments, and BP measurements were performed at screening, Week 2, Week 4, and every 4 weeks thereafter.

Statistical Analysis

- The primary endpoint of the study was PFS as assessed by an independent review committee.
- Secondary endpoints included OS, objective response rate, safety, and duration of response.
- The AXIS trial was 90% powered to detect an improvement in PFS from 5 months with sorafenib to 7 months with axitinib.

RESULTS

Patients

- In all, 251 patients enrolled in the AXIS trial had received prior interleukin-2 (IL-2) or IFN-α (**Table 1**).

Table 1. Demographics and baseline characteristics of patients with mRCC previously treated with cytokines.

	Axitinib n=126	Sorafenib n=125
Age, y, median (range)	61 (20–82)	60 (35–79)
Gender, n (%)		
Male	95 (75.4)	87 (69.6)
Female	31 (24.6)	38 (30.4)
Race, n (%)		
White	82 (65.1)	81 (64.8)
Black	0	0
Asian	43 (34.1)	42 (33.6)
Other	1 (0.8)	2 (1.6)
ECOG PS, n (%)		
0	75 (59.5)	74 (59.2)
1	51 (40.5)	51 (40.8)
MSKCC risk group, n (%)		
Favorable	52 (41.3)	50 (40.0)
Intermediate	38 (30.2)	37 (29.6)
Poor	35 (27.8)	31 (24.8)
N/A	1 (0.8)	7 (5.6)

ECOG PS = Eastern Cooperative Oncology Group performance status; mRCC = metastatic renal cell carcinoma; MSKCC = Memorial Sloan-Kettering Cancer Center.

Efficacy

- As of June 3, 2011, mPFS (95% confidence interval [CI]) for patients previously treated with cytokines was 12.0 months (10.1, 13.9) with axitinib vs 6.6 months (6.4, 8.3) with sorafenib: HR (95% CI) 0.519 (0.375, 0.720); *P*<0.0001 (**Figure 2A**).
  - mPFS was numerically longer with axitinib vs sorafenib in patients previously treated with an IL-2 -containing regimen (**Figure 2B**) and significantly longer with axitinib vs sorafenib in those previously treated with IFN-α alone (**Figure 2C**).
- As of November 1, 2011, median OS (mOS) (95% CI) in the cytokine-treated subgroup was 29.4 months (24.5, not estimable [NE]) with axitinib vs 27.8 months (23.1, 34.5) with sorafenib: HR (95% CI) 0.813 (0.555, 1.191); *P*=0.144 (**Figure 3A**).
  - mOS was numerically longer with axitinib vs sorafenib in patients previously treated with an IL-2–containing regimen (**Figure 3B**) and numerically longer with sorafenib vs axitinib in those previously treated with IFN-α alone (**Figure 3C**).

Safety

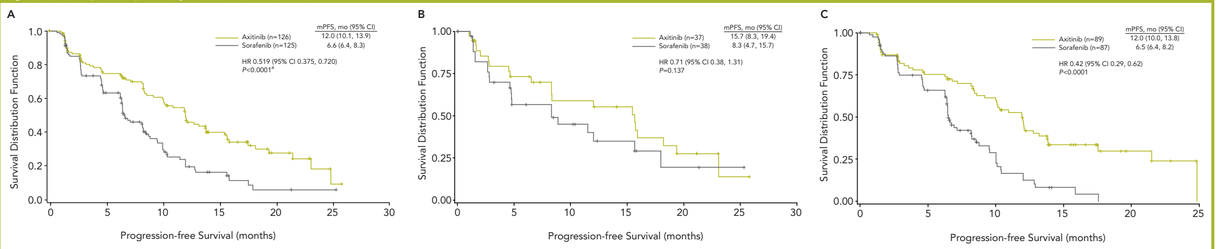
- Fatigue, dysphonia, and hypothyroidism were more common with axitinib, whereas hand–foot syndrome, alopecia, and rash were more common with sorafenib (**Table 2**).
- In all, 7 (5.6%) patients previously treated with cytokines discontinued axitinib and 9 (7.3%) discontinued sorafenib due to toxicity.
- Of patients previously treated with cytokines who discontinued treatment with axitinib or sorafenib, 46% in each arm received follow-up systemic therapy.

Table 2. Treatment-emergent, all-causality adverse events in patients with mRCC previously treated with cytokines.

	Axitinib n=126		Sorafenib n=123	
Adverse event, n (%)[a]	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Diarrhea	62 (49.2)	12 (9.5)	56 (45.5)	9 (7.3)
Hypertension	60 (47.6)	29 (23.0)	52 (42.3)	19 (15.4)
Fatigue	45 (35.7)	15 (11.9)	30 (24.4)	4 (3.3)
Dysphonia	37 (29.4)	0	15 (12.2)	0
Hand–foot syndrome	36 (28.6)	5 (4.0)	71 (57.7)	23 (18.7)
Decreased appetite	29 (23.0)	6 (4.8)	23 (18.7)	3 (2.4)
Nausea	26 (20.6)	2 (1.6)	14 (11.4)	1 (0.8)
Weight decreased	25 (19.8)	4 (3.2)	23 (18.7)	2 (1.6)
Hypothyroidism	24 (19.0)	0	7 (5.7)	0
Stomatitis	21 (16.7)	3 (2.4)	15 (12.2)	1 (0.8)
Cough	19 (15.1)	1 (0.8)	19 (15.4)	1 (0.8)
Alopecia	6 (4.8)	0	44 (35.8)	0
Rash	16 (12.7)	0	36 (29.3)	4 (3.3)
Pain in extremity	12 (9.5)	0	20 (16.3)	1 (0.8)

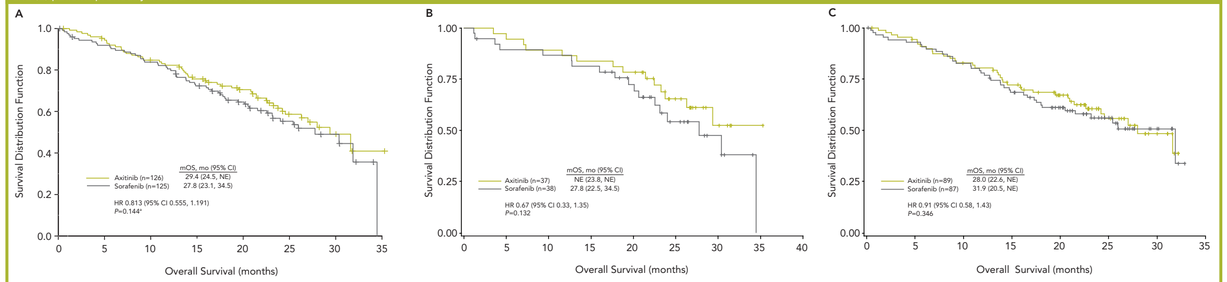
[a]Reported in ≥15% of patients in either treatment arm as of August 31, 2010.
mRCC = metastatic renal cell carcinoma.

Figure 2. Kaplan-Meier estimates of progression-free survival (IRC assessment) in patients with mRCC previously treated with cytokines. (A) All patients previously treated with cytokines, (B) patients previously treated with an IL-2–containing regimen, and (C) patients previously treated with IFN-α alone.



[a]Based on 1-sided stratified log-rank test.
CI = confidence interval; HR = hazard ratio; IFN-α = interferon-alpha; IL-2=interleukin-2; IRC = Independent Review Committee; mPFS = median progression-free survival; mRCC = metastatic renal cell carcinoma.

Figure 3. Kaplan-Meier estimates of overall survival in patients with mRCC previously treated with cytokines. (A) All patients previously treated with cytokines, (B) patients previously treated with an IL-2–containing regimen, and (C) patients previously treated with IFN-α alone.



[a]Based on 1-sided stratified log-rank test.
CI = confidence interval; HR = hazard ratio; IFN-α = interferon-alpha; IL-2 = interleukin-2; mOS = median overall survival; mRCC = metastatic renal cell carcinoma; NE = not estimable.

Table 3. Cross-trial comparison of tyrosine kinase inhibitors in patients with mRCC previously treated with cytokines.

Agent	n[a]	Study details	mPFS, mo	mOS, mo
Axitinib	126	Phase III (vs sorafenib)	12.0	29.4
	52	Phase II[4,5]	13.7	29.9
Sunitinib	105	Phase II[6]	8.3	NR
	107	Phase II[7]	8.2	19.8
Sorafenib	384 (mPFS), 451 (mOS)	Phase III (vs placebo)[8,9] 83% patients received prior cytokines	5.5	17.8
	125	Phase III (vs axitinib)	6.6	27.8
Pazopanib	202	Phase III (vs placebo)[10]	7.4	NR

[a]Number of patients evaluable for efficacy measures.
mOS = median overall survival; mPFS = median progression-free survival; mRCC = metastatic renal cell carcinoma; NR = not reported.

CONCLUSIONS

- Axitinib showed mPFS of 1 year and mOS of 2.5 years in patients previously treated with a cytokine-based regimen.
- An OS benefit with axitinib was not demonstrated, despite numerically longer mOS with axitinib compared with sorafenib in patients with mRCC previously treated with cytokines.
  - The lack of OS benefit may be due to subsequent active treatment received by patients.
- Axitinib efficacy compares favorably with historical results of other tyrosine kinase inhibitors in patients with mRCC previously treated with cytokines (**Table 3**).

ACKNOWLEDGMENTS

This study was sponsored by Pfizer Inc. Medical writing support was provided by Joanna Bloom, PhD, of UBC Scientific Solutions and was funded by Pfizer Inc.

REFERENCES

1. Hu-Lowe DD, et al. *Clin Cancer Res* 2008;14:7272-83. 2. Inlyta® (axitinib) package insert. Pfizer, Inc; 2012. 3. Rini BI, et al. *Lancet*. 2011; 378:1931-9. 4. Rixe O, et al. *Lancet Oncol* 2007;8:975-84. 5. Motzer RJ, et al. *J Clin Oncol* 2011;29s: abstr 4547. 6. Motzer RJ, et al. *JAMA* 2006;295:2516-24. 7. Escudier B, et al. *J Clin Oncol* 2009;27:4068-75. 8. Escudier B, et al. *N Engl J Med* 2007;356:125-34. 9. Escudier B, et al. *J Clin Oncol* 2009;27:3312-8. 10. Sternberg CN, et al. *J Clin Oncol* 2010;28:1061-8.

Presented at the 48th Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, June 1–5, 2012