



FDA Review

NDA 202324
Inlyta™ (axitinib)

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NDA 202324

Proposed Indication:

“INLYTA is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma.”



Outline of Presentation

- Background Information
- Key Regulatory History Milestones
- Pivotal Trial A4061032 (AXIS)
- FDA Review Results
 - Efficacy
 - Safety
- Major Findings
- Question to ODAC



Main Findings with this NDA

1. PFS benefit driven by subset of patients
2. PFS difference of 2 months, no OS difference compared to sorafenib
 - Difference between experimental arm and active comparator arm, not placebo or interferon



Advanced RCC

- All newer agents indicated for the treatment of advanced RCC
 - Exception: Everolimus, indicated for the advanced RCC after failure of treatment with sunitinib or sorafenib
- Order of agents for either first-line or second-line treatment of advanced RCC is unknown



Advanced RCC Treatment

Product	RCT Design	Endpoint	Key Findings
Sorafenib	<ul style="list-style-type: none"> •Placebo control •One prior therapy 	PFS	HR: 0.44 (0.35-0.55) Median PFS 5.5 vs. 2.8 mos
Sunitinib	<ul style="list-style-type: none"> •IFN-α control •Previously untreated 	PFS	HR: 0.42 (0.32-0.54) Median PFS 10.8 vs. 5.1 mos
Temsirolimus	<ul style="list-style-type: none"> •IFN-α control •Previously untreated 	OS	HR: 0.73 (0.58-0.92) Median OS 10.9 vs. 7.3 mos
Everolimus	<ul style="list-style-type: none"> •Placebo control •Previously treated with sorafenib or sunitinib 	PFS	HR: 0.33 (0.25-0.43) Median PFS 4.9 vs. 1.9 mos
Bevacizumab+ IFN α	<ul style="list-style-type: none"> •IFNα control •Previously untreated 	PFS	HR: 0.60 (0.49-0.72) Median PFS 10.2 vs. 5.4 mos
Pazopanib	<ul style="list-style-type: none"> •Placebo control •Treatment-naïve (54%) or one prior cytokine regimen (46%) 	PFS	HR: 0.46 (0.34-0.62) Median PFS 9.2 vs. 4.2 mos



Regulatory Background

- 12/2001: IND activated
- 05/2007: EOP2 meeting
 - Phase 3 trial in second-line, advanced RCC with sorafenib as comparator arm with blinded IRC-assessed PFS proposed
 - Sponsor indicated second-line indication would be sought based on design of Phase 3 trial
- 04/2008: SPA granted with final PFS analysis endpoint



A4061032 (AXIS)

Axitinib (AG-013736) as Second Line
Therapy for Metastatic Renal Cell Cancer:
Axis Trial.



Axis Trial Design

Prior treatment:
Sunitinib or
Bevacizumab or
Temsirrolimus or
Cytokines

650 Patients with Advanced RCC

Stratification factors:
ECOG status
Prior treatment

Randomize 1:1

Axitinib
5 mg po BID

Sorafenib
400 mg po BID

Disease evaluations:
every 6 weeks x 2,
then every 8 weeks

Treatment Period
(to PD or unacceptable toxicity)

1° endpoint:
PFS by blinded IRC

Post-treatment follow-up
(to death or three years after last patient randomized)



Comparator Arm-Sorafenib

- First of targeted agents to receive approval for advanced RCC
- Received full approval in 12/2005
 - Randomized trial versus placebo
 - Patients had received one prior systemic therapy
 - 83% received cytokines
 - 17% received chemotherapy or hormonal agents
 - Median PFS 5.5 versus 2.8 months (HR 0.44)
 - ORR 2.1% versus 0
 - Crossover in majority of placebo patients to sorafenib complicates OS analysis



Comparator Arm-Sorafenib

- Selected by Pfizer
- FDA agreed to choice in SPA
- Benefit of sorafenib after sunitinib unknown
- AXIS has superiority design



Key Inclusion Criteria

- Histologically or cytologically confirmed mRCC with a component of clear cell subtype.
- Measurable disease.
- Progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.0) after 1 prior systemic first-line regimen for mRCC. The prior regimen had to have contained 1 or more of the following: sunitinib, bevacizumab + IFN- α , temsirolimus, or cytokine(s).
- ECOG performance status of 0 or 1.
- No evidence of pre-existing uncontrolled hypertension as documented by 2 baseline blood pressure (BP) readings. Patients whose hypertension was controlled by antihypertensive therapies were eligible.



Study Endpoints

Primary

- PFS assessed by IRC
 - defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause

Secondary

- Overall Survival
- Objective Response Rate
- Duration of Response
- Safety



Response Adjudication

- An IRC adjudicated all responses included for the primary analysis
- IRC consisted of two radiologists blinded to treatment arm
- If disagreement, adjudication by third radiologist



AXIS: Patient Baseline Characteristics



Patient Demographics

	Axitinib N=361	Sorafenib N=362
Median Age, Years (Min, Max)	61 (20, 82)	61 (22, 80)
Sex (%)		
Male	265 (73.4)	258 (71.3)
Female	96 (26.6)	104 (28.7)
ECOG PS (%)		
0	192 (54)	200 (55.2)
1	162 (44.9)	160 (44.2)
Race (%)		
White	278 (77)	269 (74.3)
Black	1 (<1)	4 (1.1)
Asian	77 (21.3)	81 (22.4)
Other	5 (1.4)	13 (3.6)
MSKCC Risk Group (%)		
Favorable	158 (43.8)	148 (40.9)
Intermediate	199 (55.1)	210 (58)
Poor	4 (1.1)	4 (1.1)



Enrollment by Geographic region

	Axitinib N=361 (%)	Sorafenib N=362 (%)
North America	88 (24.4)	98 (27.1)
Europe	187 (51.8)	170 (47)
Asia	73 (20.2)	79 (21.8)
Other	13 (3.6)	15 (4.1)



Prior treatment

Treatment	Axitinib N=361 (%)	Sorafenib N=362 (%)
Sunitinib	194 (53.7)	195 (53.9)
Bevacizumab	29 (8)	30 (8.3)
Temsirolimus	12 (3.3)	12 (3.3)
Cytokine	126 (34.9)	125 (34.5)



Efficacy Results

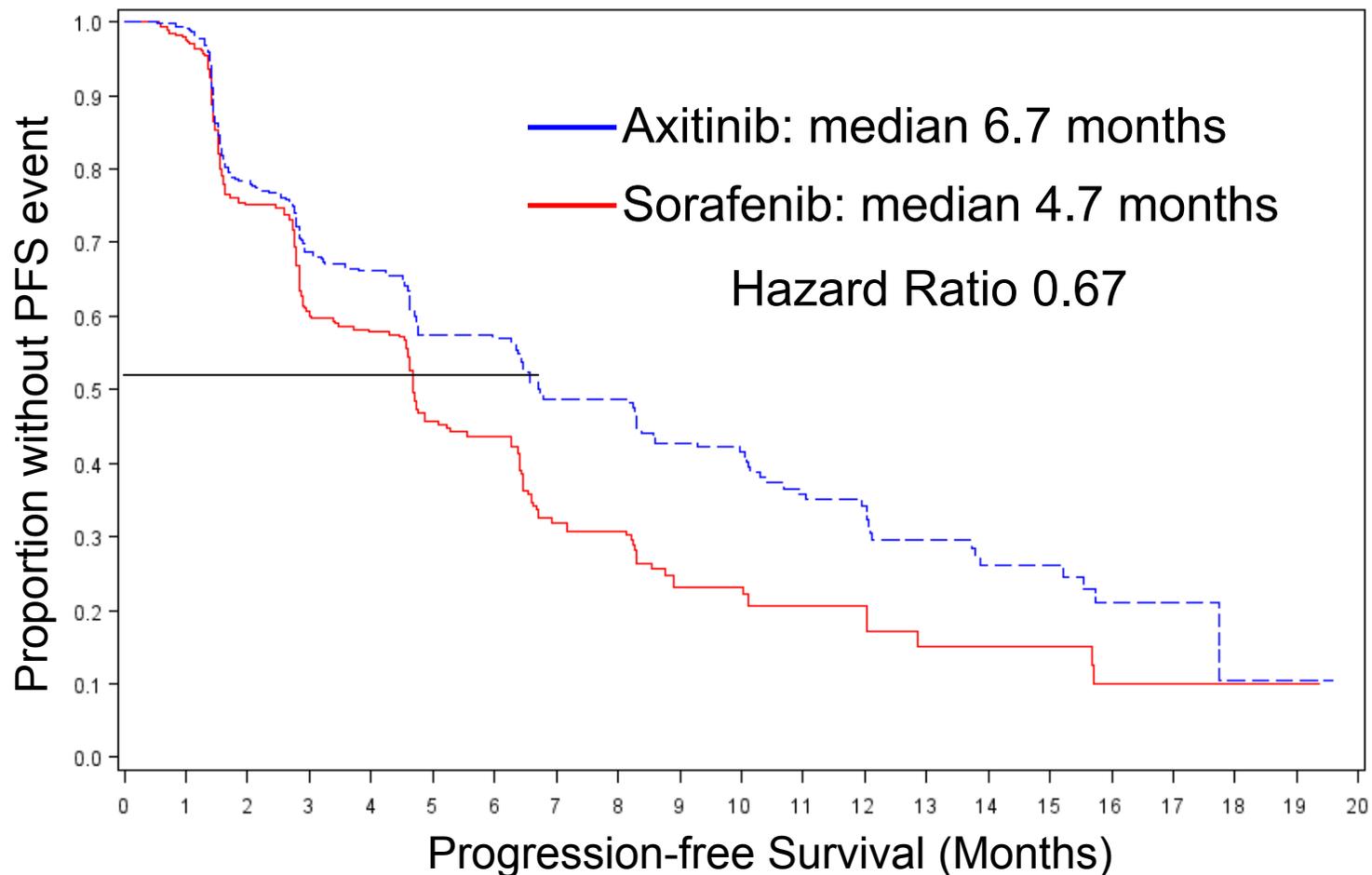


AXIS: PFS

	Axitinib (N=361)	Sorafenib (N=362)
PFS event (%)	192 (53.2)	210 (58)
Number of patients with deaths (%)	12 (3.3)	10 (2.8)
Number of patients with progression (%)	180 (49.9)	200 (55.2)
Median PFS in months (95% CI)	6.7 (6.3-8.4)	4.7 (4.6-5.6)
Hazard ratio (95% CI)	0.67 (0.54-0.81)	
P-value	<0.0001	



AXIS: Kaplan-Meier Curve for PFS





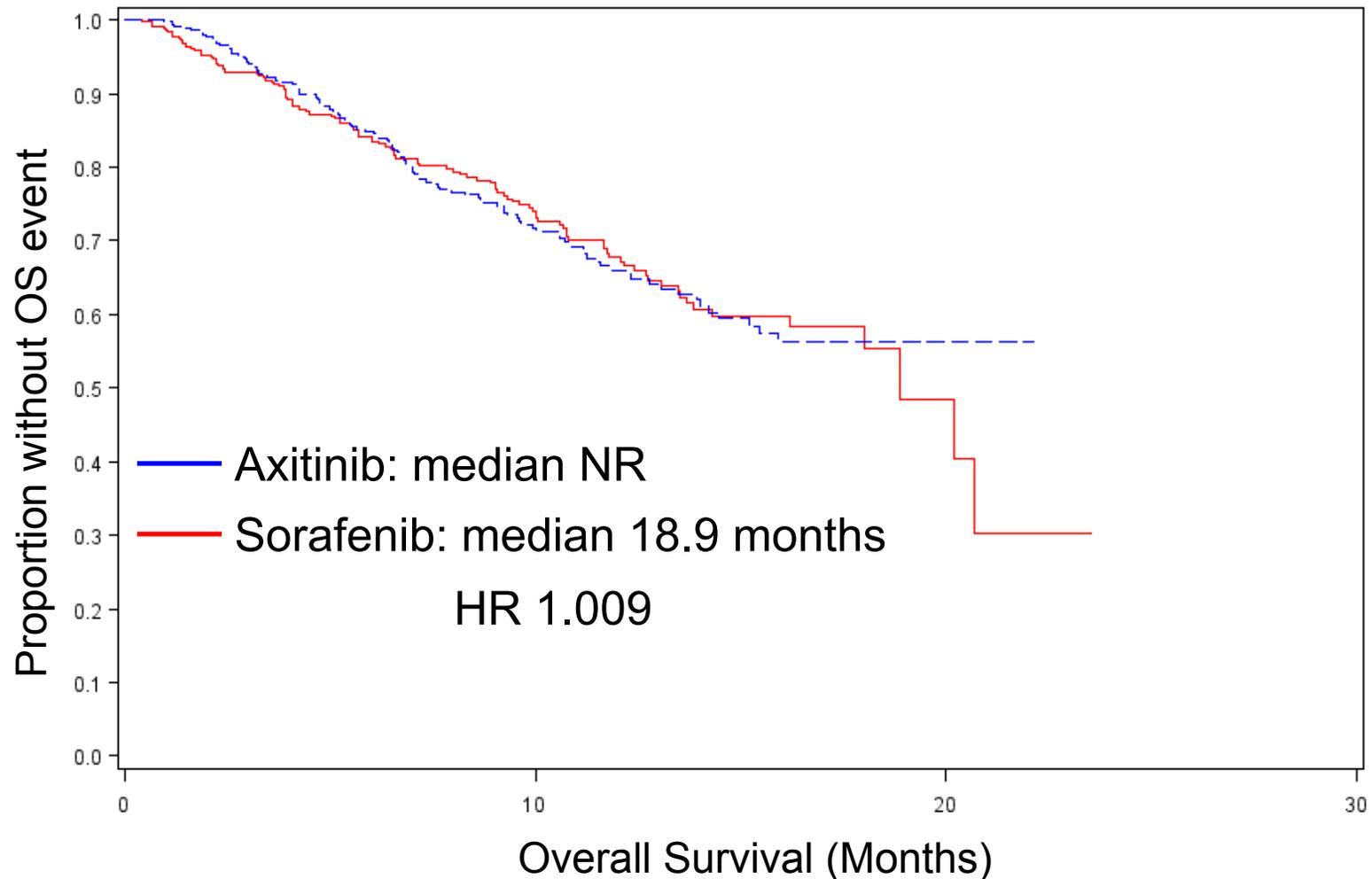
Overall Survival

	Axitinib N=361	Sorafenib N=362
Deaths (%)	113 (31.2)	110 (30.4)
Median (months)	NR* (15.9, NR)	18.9 (18, NR)
HR	1.009 (0.77-1.31)	
p-value	0.53	

*Not reached



Axis: Kaplan-Meier Curve for OS





Safety Results



Safety

- Common AEs: diarrhea, hypertension, fatigue, decreased appetite, nausea, palmar-plantar erythrodysesthesia syndrome, dysphonia
- Serious AEs: arterial and venous thrombotic events, gastrointestinal perforation, bleeding events, hypothyroidism, proteinuria, hypertensive crisis and reversible posterior leukoencephalopathy syndrome



Safety Findings: Axitinib > Sorafenib

	Axitinib N=359		Sorafenib N=355	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Diarrhea	197 (54.6)	38 (10.6)	192 (54.1)	26 (7.3)
Vomiting	86 (23.8)	12 (3.3)	63 (17.7)	3 (0.8)
Dyspepsia	36 (10)	0	9 (2.5)	0
Fatigue	146 (40.7)	56 (15.6)	104 (29.3)	18 (5.1)
Asthenia	75 (20.9)	19 (5.6)	51 (14.4)	9 (2.5)
Hypertension	146 (40.7)	56 (15.6)	104 (29.3)	39 (11)
Dysphonia	114 (31.6)	0	50 (14.1)	0
Hypothyroidism	69 (19.2)	1 (0.3)	30 (8.5)	0



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Vomiting	86 (23.8)	12 (3.3)	63 (17.7)	3 (0.8)
Dyspepsia	36 (10)	0	9 (2.5)	0
Fatigue	146 (40.4)	41 (11.4)	114 (32.1)	18 (5.1)
Asthenia	75 (20.8)	19 (5.6)	51 (14.4)	9 (2.5)
Hypertension	146 (40.7)	56 (15.6)	104 (29.3)	39 (11)
Dysphonia	114 (31.8)	0	50 (14.1)	0
Hypothyroidism	69 (19.2)	1 (0.3)	30 (8.5)	0



Safety Findings: Sorafenib > Axitinib

	Axitinib N=361		Sorafenib N=362	
	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
Palmar-plantar erythrodysesthesia	98 (27.1)	18 (5)	181 (51)	57 (16.1)
Rash	45 (12.5)	1 (0.3)	112 (30.9)	14 (3.9)
Pruritus	24 (6.6)	0	44 (12.2)	0
Alopecia	14 (3.9)	0	117 (32.3)	0
Erythema	9 (2.5)	0	36 (9.9)	1 (0.3)
Anemia	17 (4.7)	4 (1.1)	44 (12.2)	14 (3.9)



Safety Findings: Sorafenib > Axitinib

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	Gr 1-4 (%)	Gr 3-4 (%)	Gr 1-4 (%)	Gr 3-4 (%)
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Anemia	17 (4.7)	4 (1.1)	44 (12.2)	14 (3.9)



Main Findings with this NDA

1. PFS benefit driven by subset of patients
2. PFS difference of 2 months, no OS difference compared to sorafenib
 - Difference between experimental arm and active comparator arm, not placebo or interferon



Findings

1. PFS benefit driven by subset of patients
 - Efficacy results driven by subset of patients treated previously with cytokines; this population not prevalent in U.S. with currently available therapy



Prior Treatment in U.S. and Europe

Treatment	North America N=186	Europe N=357	Total N=723
Prior Sunitinib (%)	126 (67.7)	180 (50.4)	389 (53.8)
Prior Cytokine (%)	37 (19.9)	125 (34.5)	251 (34.7)

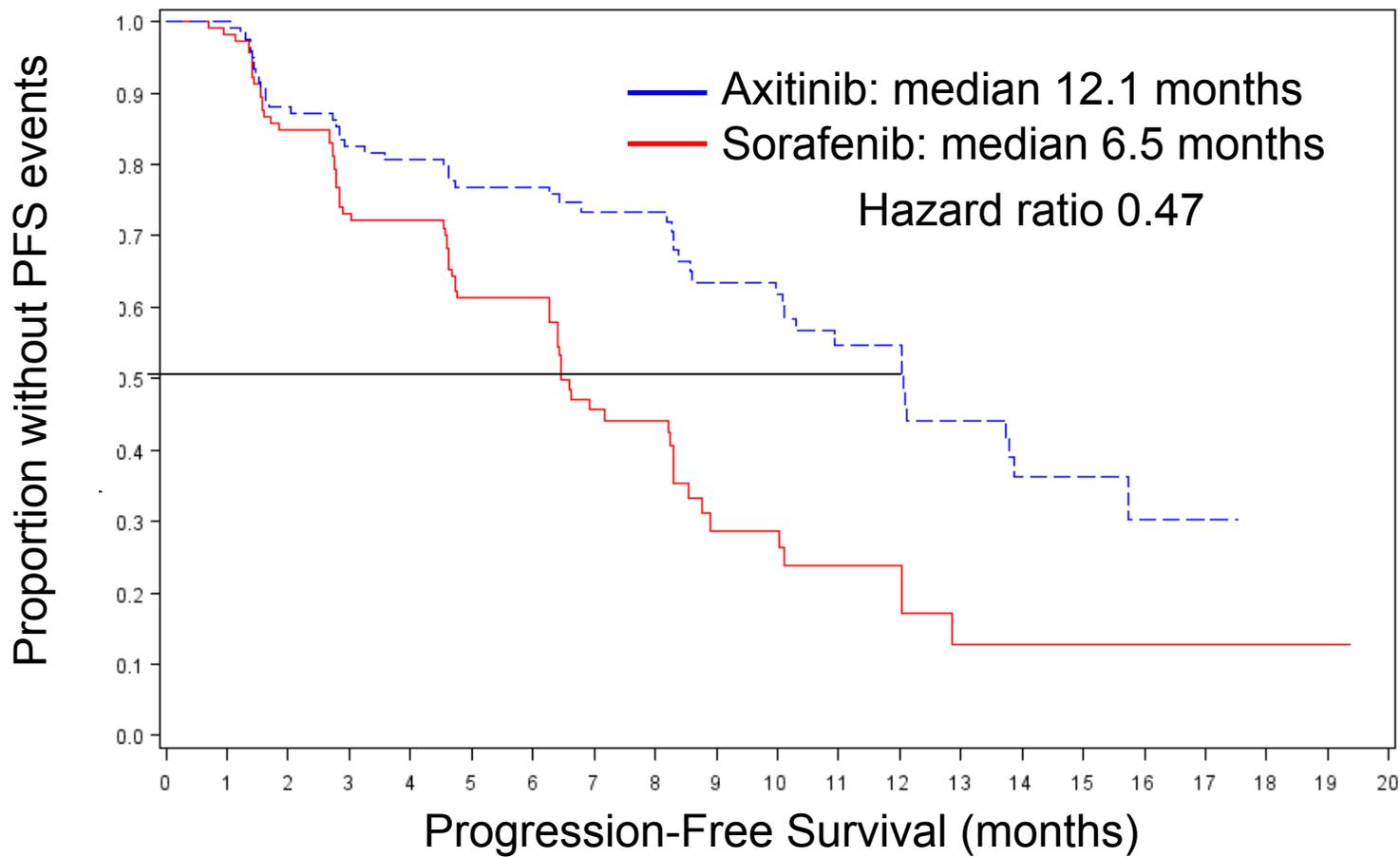


PFS-Prior Cytokine Population

	Axitinib N=126	Sorafenib N=125
PFS events (%)	50 (39.7)	69 (55.2)
Median PFS in months (95% CI)	12.1 (10.1-13.9)	6.5 (6.3-8.3)
Hazard ratio (95% CI)	0.47 (0.32-0.68)	



PFS in Patients Previously Treated with Cytokines



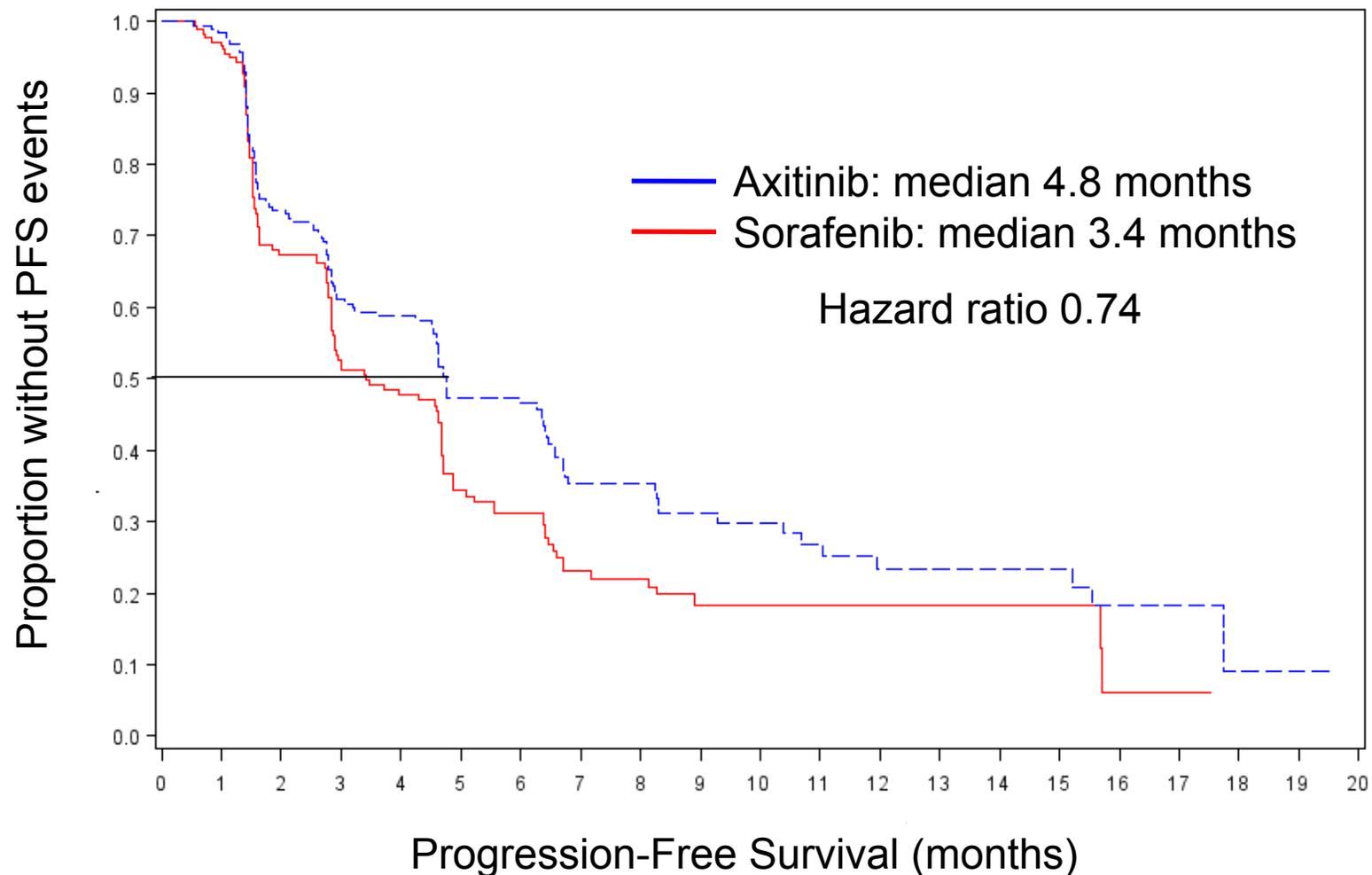


PFS: Prior Sunitinib Population

	Axitinib N=194	Sorafenib N=195
PFS events (%)	117 (60.3)	120 (61.5)
Median PFS in months (95% CI)	4.8 (4.5-6.4)	3.4 (2.8-4.7)
Hazard ratio (95% CI)	0.74 (0.57-0.96)	



PFS in Patients Previously Treated with Sunitinib





OS by Prior Treatment

	Axitinib N=361	Sorafenib N=362	HR
Median OS (months)	NR*	18.9	1.009
Prior Cytokines	NR*	NR*	0.74
Prior Sunitinib	15.2	18	1.007

*Not reached



Response Rate by Prior Treatment

	Axitinib N=361	Sorafenib N=362	RR
ORR (%)	70 (19.4)	34 (9.4)	2.06
Prior Cytokines (%)	41 (32.5)	17 (13.6)	2.39
Prior Sunitinib (%)	22 (11.3)	15 (7.7)	1.48



Findings

2. PFS difference of 2 months, no OS difference compared to sorafenib
 - Regulatory history of advanced RCC: full approval given for PFS when few agents available
 - Numerous options for treatment today
 - Best choice for first-line and second-line therapy unclear
 - Only temsirolimus has shown OS benefit vs placebo in first-line population
 - Magnitude of PFS in this setting



Subsequent Therapy

Subsequent Therapy	Axitinib N=223 %	Sorafenib N=263 %
Any subsequent therapy	45.3	50.6
Everolimus	24.7	27.8
Sorafenib	13	6.8
Temsirolimus	6.3	9.9
Bevacizumab	4.5	7.2
Sunitinib	4.5	11.4
Pazopanib	3.6	3.4



Regulatory Considerations

- Summary of results
 - Median PFS difference 2 months in overall population
 - Median PFS difference is 1.4 months in patients previously treated with sunitinib
- Application is being considered for regular approval
- PFS with sufficient magnitude has been accepted as clinical benefit for regular approval in this indication
- Unlike accelerated approval, applicant does not need to demonstrate improvement over available therapy
- Comparator sorafenib in AXIS trial is an approved therapy; magnitude of benefit for sorafenib in this setting (following sunitinib) has not been established in prospective, randomized trial