INLYTA® (axitinib)

Mace Rothenberg, MD
Senior Vice President Clinical Development and Medical Affairs, Pfizer Oncology

Oncologic Drugs Advisory Committee Meeting

December 7, 2011
FDA White Oak Campus
Silver Spring, MD

Presentation Overview

Introduction	Mace Rothenberg, MD Senior Vice President Clinical Development and Medical Affairs, Pfizer Oncology
Axitinib Background	Glen Andrews, MS Axitinib Team Leader, Pfizer Oncology
Summary of Clinical Efficacy	Brian Rini, MD Associate Professor of Medicine Cleveland Clinic, Ohio
Summary of Clinical Safety	Sinil Kim, MD Clinical Lead for Axitinib Development Program, Pfizer Oncology
Clinical Perspective on Axitinib and Benefit/Risk in Patients with RCC	Robert J Motzer, MD Attending Physician Memorial Sloan Kettering Cancer Center, New York
Concluding Remarks	Mace Rothenberg, MD Senior Vice President Clinical Development and Medical Affairs, Pfizer Oncology

Additional Expert

David Cella, PhD
Professor and Chair
Department of Medical Social Sciences
Northwestern University Feinberg School of Medicine

Patient Reported Outcomes
Consultant

Disease Background

- In 2011, more than 60,000 new cases of renal cell carcinoma (RCC) will be diagnosed in the United States (US)[1,2]
- Approximately 20% of patients present with metastatic disease
- Of those who present with local or locally advanced disease, approximately 30% of patients will relapse[3]
- As a result, approximately 13,000 Americans will die of this disease this year[1,2]

[1]Jemal A, et al. Cancer Statistics. CA Cancer J Clin 2010;60(5):277–300; [2]SEER, 2011; [3]Cohen HT and McGovern FJ. N Engl J Med 2005;353:2477-90

Therapeutic Approaches to Treatment of Clear Cell RCC

- Three distinct targets and related therapeutic approaches:
  - Immune system (cytokine-based therapy)[1,2]
  - mTOR (mammalian target of rapamycin)[3]
  - Vascular endothelial growth factor (VEGF) pathway[3]
- Inhibition of VEGF receptors forms backbone of advanced RCC therapy
  - Inactivation of Von Hippel-Lindau (VHL) tumor suppressor gene[4] leading to high levels of VEGF[5,6,7]
  - Signaling by VEGF is key to angiogenesis[8] and RCC tumors are known for their vascularity

[1]McDermott DF, et al. J Clin Oncol 2005;23(1):133–41; [2]Yang JC, et al. J Clin Oncol 2003;21:3127; [3]Motzer RJ and Bukowski RM, J Clin Oncol 24: 5601-08, 2006; [4]Gnarra JR, et al. Nature Genet. 1994;7:85-90; [5]Ilopoulos O et al. Proc Natl Acad Sci USA 1996;93:10595-9; [6]Mukopadhyay D et al. Mol Cell Biol 1997;17(9):5629-39; [7]Pal S et al. J Biol Chem 1997;272(44):27509-12; [8]Smith NR, et al. Clin Cancer Res 16(14) July 15, 2010

FDA-approved Targeted Therapies – Design of Phase 3 Studies

Patients Studied	Therapy (Approval Date)	Indication	Control	Primary Endpoint
First-line (good or intermediate risk)	**Pazopanib**[1] (Oct 2009)	Advanced RCC	Placebo	PFS
	Sunitinib[2] (Jan 2006)	Advanced RCC	IFN-α	PFS
	Bevacizumab + IFN-α[3] (Jul 2009)	Advanced RCC	IFN-α	PFS
First-line (poor risk)	**Temsirolimus**[4] (May 2007)	Advanced RCC	IFN-α	OS
Previous cytokine	**Pazopanib**[1] (Oct 2009)	Advanced RCC	Placebo	PFS
	Sorafenib[5] (Dec 2005)	Advanced RCC	Placebo	PFS
Previous TKI	**Everolimus**[6] (Mar 2009)	Advanced RCC after failure of treatment with sunitinib or sorafenib	Placebo	PFS

[1]Votrient Prescribing Information, 2011; [2]Sutent Prescribing Information, 2011; [3]Avastin Prescribing Information, 2009; [4]Torisel Prescribing Information, 2011; [5]Nexavar Prescribing Information, 2011; [6]Motzer RJ, et al. Cancer. September 15, 2010

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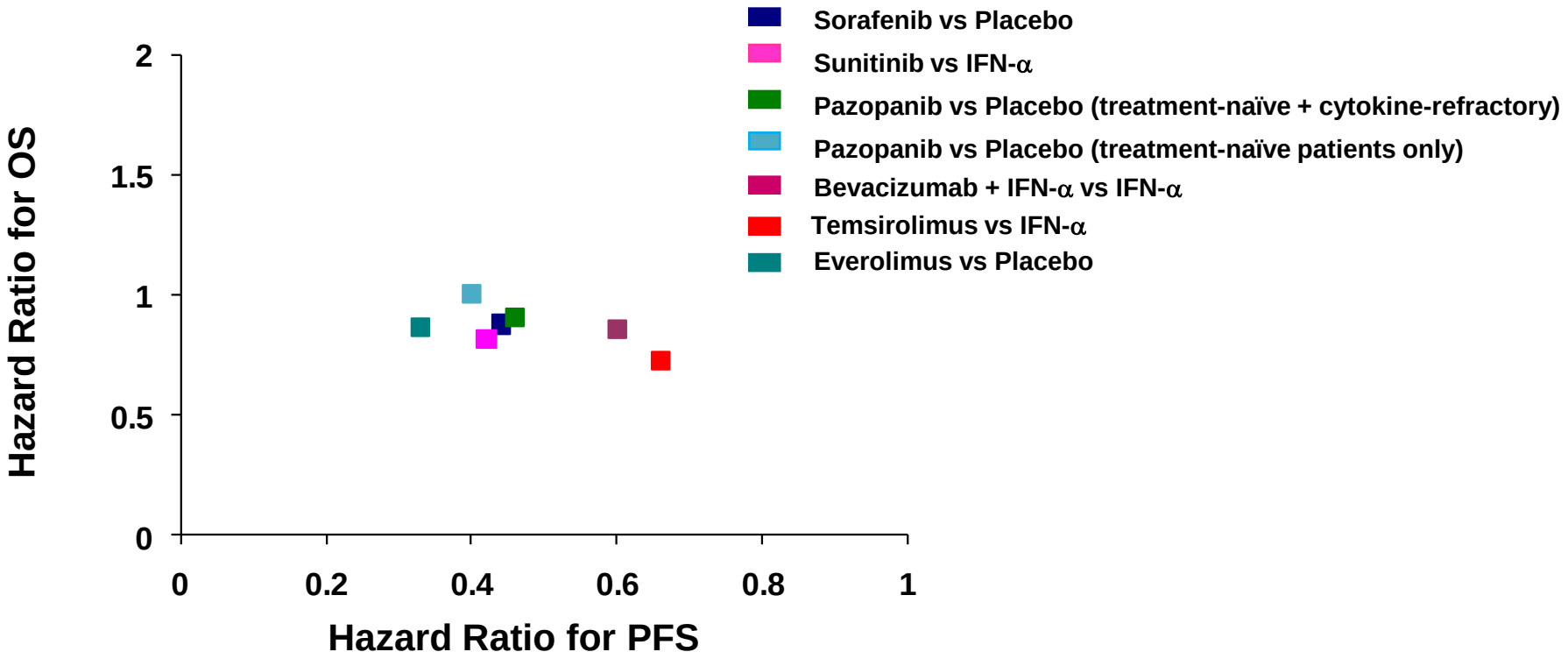
FDA-approved Therapies – Results of Phase 3 Studies

Patients studied	Therapy	Control	Median PFS (mo)	HR	P-value	OS benefit?
First-line (good or intermediate risk)	**Pazopanib**[1,2]	Placebo	11.1 vs 2.8	**0.40**	NR	**No**
	Sunitinib[3,4]	IFN-α	10.9 vs 5.1	**0.42**	<0.000001	**No**
	Bevacizumab/IFN-α[5,6]	IFN-α	10.2 vs 5.4	**0.60**	<0.0001	**No**
First-line (poor risk)	**Temsirolimus**[7]	IFN-α	5.5 vs 3.1	**0.66**	0.0001	**Yes**
Previous cytokine	**Pazopanib**[1]	Placebo	7.4 vs 4.2	**0.54**	NR	**No**
	Sorafenib[8,9]	Placebo	5.5 vs 2.8	**0.44**	<0.001	**No**
Previous TKI	**Everolimus**[10]	Placebo	4.9 vs 1.9	**0.33**	<0.001	**No**

NR: not reported; [1]Votrient Prescribing Information, 2011; [2]http://www.nice.org.uk/nicemedia/live/12032/52263/52263.pdf; [3]Sutent Prescribing Information, 2011; [4]Motzer RJ et al. J Clin Oncol, 2009; [5]Avastin Prescribing Information, 2009; [6]Escudier B et al. J Clin Oncol, 2010; [7]Torisel Prescribing Information, 2011; [8]Nexavar Prescribing Information, 2011; [9]Escudier B, et al. J Clin Oncol 2009 Jul 10;27(20):3312-8; [10]Motzer RJ, et al. Cancer 2010 Sep 15;116:4256-65.

FDA-approved Therapies - Relationship between OS and PFS Hazard Ratios



How This Relates to Today's Presentation

- Primary endpoint for axitinib study was progression-free survival (PFS) reviewed by Independent Review Committee (IRC)
  - Agreed to by FDA (Special Protocol Assessment [SPA] completed April 2008)
- Use of an active (sorafenib) control arm
  - First Phase 3 trial in 2nd-line advanced RCC to use an active VEGFR TKI comparator
  - First head to head comparison of VEGFR TKIs
  - Active control → higher hurdle for experimental arm to demonstrate superiority than if placebo or BSC were used
- Challenges in measuring effect on overall survival (OS)
  - Receipt of subsequent active therapy cannot be controlled
  - This can – and will – influence OS to an extent that is difficult to quantify

Axitinib Background

Glen Andrews, MS

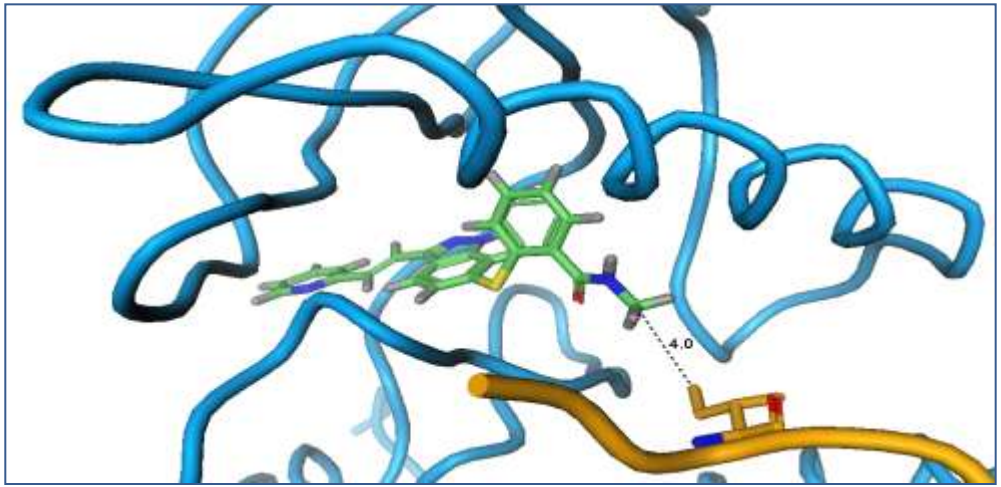
Axitinib Team Leader

Pfizer Oncology

Axitinib

- Axitinib purposefully designed for optimized fit into deep pocket of ATP site of VEGF receptor kinase domain
- Molecular characteristics aimed at achieving greater efficacy with less toxicity compared to multi-targeted tyrosine kinase inhibitors (TKIs)

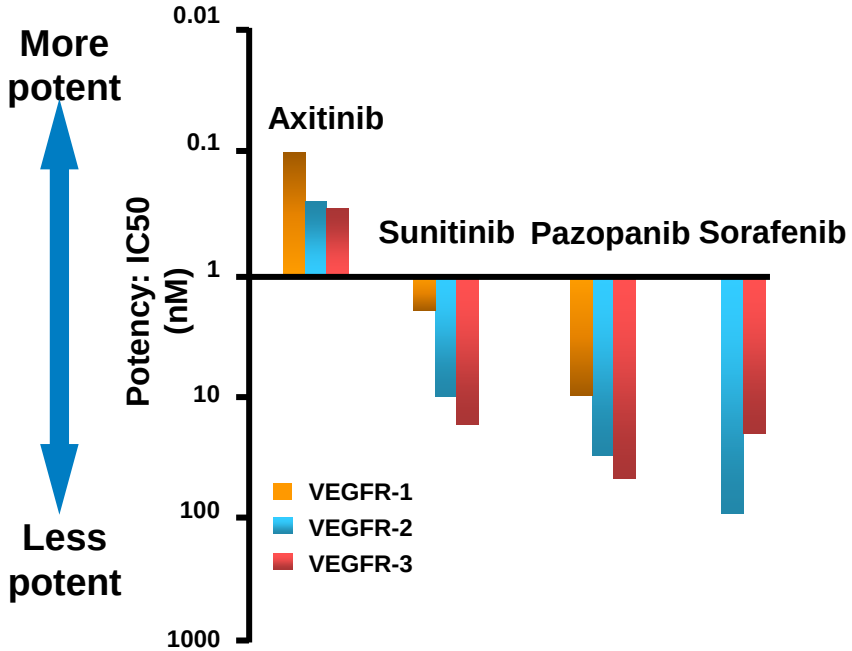
Co-crystal Structure Modeling for Axitinib Binding to JM Domain-containing VEGFR-2 Kinase[1]



[1]Solowiej J. et al, Biochemistry 2009;48:7019 and Pfizer data on file

Axitinib is More Potent and Selective than Currently-Approved VEGFR TKIs

Most Potent for VEGFR-1, -2, and -3[1]



Most Selective for VEGFR -1, -2, and -3

Target Selectivity				
	Axitinib[1]	Sorafenib[2]	Sunitinib[3]	Pazopanib[4]
VEGFR-2	+	+	+	+
PDGFR b		+	+	+
c-kit		+	+	+
FLT-3		+	+	nd
CSF-1R		nd	+	+
Raf-1	nd	+	nd	nd

VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor; c-KIT = v-kit Hardy-Zukerman 4 feline sarcoma viral oncogene homolog; FLT: FMS-like tyrosine kinase; CSF: colony-stimulating factor; Raf: v-raf-1 murine leukemia viral oncogene homolog 1; nd: not determined; +: inhibition of receptor kinase comparable (<10 times) to potency for VEGFR-2

[1] Hu-Lowe, et al. Clin Cancer Res 2008; 14:7272; [2] Wilhelm, et al. Cancer Res 2004; 64:7099; [3] Roskoski. BBRC 2007; 356: 323; [4] Kumar, et al. Mol Can Ther 2007; 6: 2012

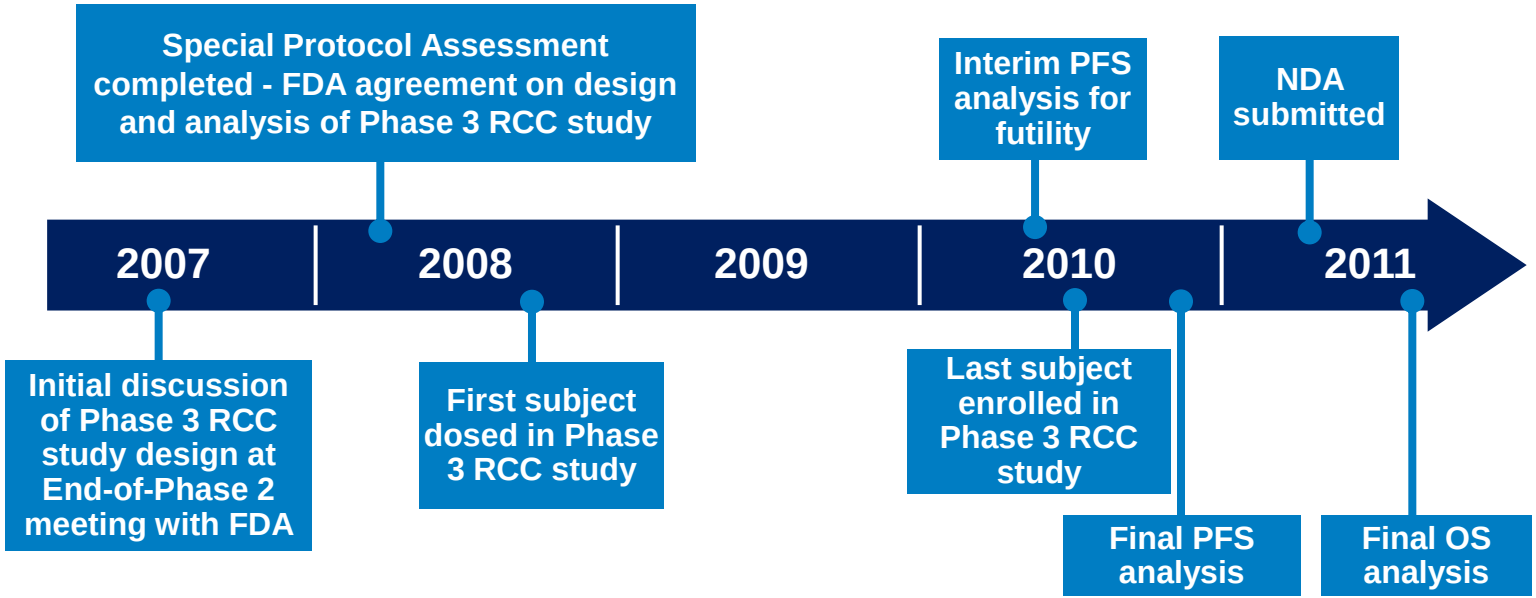
Phase 2 RCC Studies Indicated Anti-tumor Activity in Cytokine- and Sorafenib-Refractory Patients

	Cytokine-Refractory Patients		Sorafenib-Refractory Patients
Endpoint	**A4061012 N=52**	**A4061035 N=64**	**A4061023 N=62**
Response rate[1], % (95% CI)	**44.2** (30.5, 58.7)	**50.0** (37.2, 62.8)	**22.6** (12.9, 35.0)
Median PFS, months (95% CI)	13.7 (9.7, 23.0)	11.0 (9.2, 12.0)	7.4 (6.7, 11.0)
Median OS, months (95% CI)	29.9 (20.3, NE)	NA	13.6 (8.4, 18.7)

NA: not available; NE: not estimable

[1]Pfizer clinical study A4061012 and A4061023 were according to investigator and study A4061035 was according to IRC

Key Milestones in RCC Development Program



Overview of RCC Studies in Axitinib NDA

Study	Phase / Patient Population	N
A4061012 (Phase 2 supportive)	Phase 2 in cytokine-refractory patients	52
A4061035 (Phase 2 supportive)	Phase 2 in cytokine-refractory Japanese patients	64
A4061023 (Phase 2 supportive)	Phase 2 in sorafenib-refractory patients	62
A4061032 (Phase 3 pivotal)	**Randomized, open-label, Phase 3 study of axitinib vs sorafenib in patients previously treated with sunitinib-, cytokine-, bevacizumab-, or temsirolimus-containing regimen**	**723**

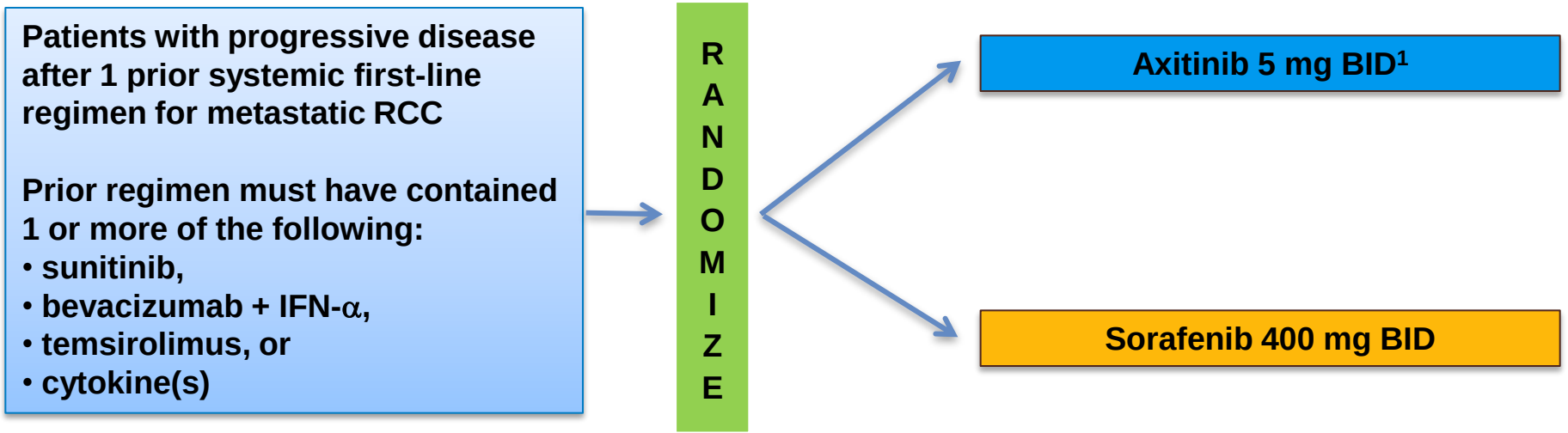
Basis for NDA

- Primary endpoint achieved
- Axitinib has greater efficacy compared with sorafenib, an approved multi-targeted TKI
- Adverse events (AEs) expected for class and manageable with generally similar overall incidence as sorafenib
- Favorable benefit/risk profile

Summary of Clinical Efficacy

Brian Rini, MD
Associate Professor of Medicine
Cleveland Clinic
Ohio

Design of Phase 3 RCC Study A4061032



1:1

Stratified: ECOG PS and prior treatment

PFS primary endpoint

BID: twice daily; ECOG PS: Eastern Cooperative Oncology Group Performance Status; [1]Stepwise dose increases from 5 mg BID to 7 mg BID and then to maximum of 10 mg BID permitted

Rationale for Phase 3 RCC Study Design

- Patient population:
  - Approach supported global study with different regional treatment choices
  - Impractical to conduct several Phase 3 studies with individual prior regimens
    - Design allowed choice of prior treatment from one of several approved agents
- Sorafenib comparator:
  - First Phase 3 study against active targeted agent
  - FDA-approved for treatment of “advanced RCC” based on Phase 3 study in refractory subjects[1]
  - Active in patients with RCC refractory to sunitinib, bevacizumab, and ≥1 prior antiangiogenic agent[2,3,4]

[1]Nexavar Prescribing Information, 2011; [2]Tamaskar I, et al. J Urol 179(1):81-6; 2008; [3]Garcia JA, et al. Cancer 2010 Dec 1;116(23):5383-90; [4]Di Lorenzo G, et al. J Clin Oncol. 2009 Sep 20;27(27):4469-7

Key Inclusion Criteria and Endpoints

- Key Eligibility
  - Metastatic clear cell RCC (measurable disease per RECIST version 1.0)
  - RECIST-defined progressive disease after one prior first-line regimen
    - Prior regimen must have contained one or more of the following: sunitinib-, bevacizumab + IFN-α, temsirolimus-, or cytokine(s)
  - ECOG performance status 0 or 1
  - Adequate blood counts and serum chemistry
- Endpoints
  - Primary: PFS (per blinded IRC)
  - Secondary: OS, objective response rate (ORR), duration of response (DR), safety, and kidney cancer specific symptoms/health status

RECIST: Response Evaluation Criteria in Solid Tumors

Statistical Analysis Plan

- Planned size
  - N = 650 powered for PFS (409 events) and OS (417 events)
- Primary PFS analysis (per IRC assessment)
  - Stratified log rank test with one-sided alpha of 0.025
  - 90% power to detect a reduction in the risk of progression or death of 29% (hazard ratio of 0.714)
- Interim analysis for futility
  - One interim analysis planned at 50% of total PFS events (per IRC assessment)

Patient Characteristics

	Axitinib, N=361	Sorafenib, N=362
Median age (range), years	61 (20, 82)	61 (22, 80)
Male/Female, %	73/27	71/29
ECOG performance status, %		
0/1	54/45	55/44
Geographic Region, %		
North America	24	27
Europe	52	47
Asia	20	22
Other	4	4
MSKCC risk group, %		
Favorable/Intermediate/Poor	28/37/33	28/36/33
Not available	2	3
Race, %		
White	77	74
Asian	21	22
Other/Black	1/0.3	2/1

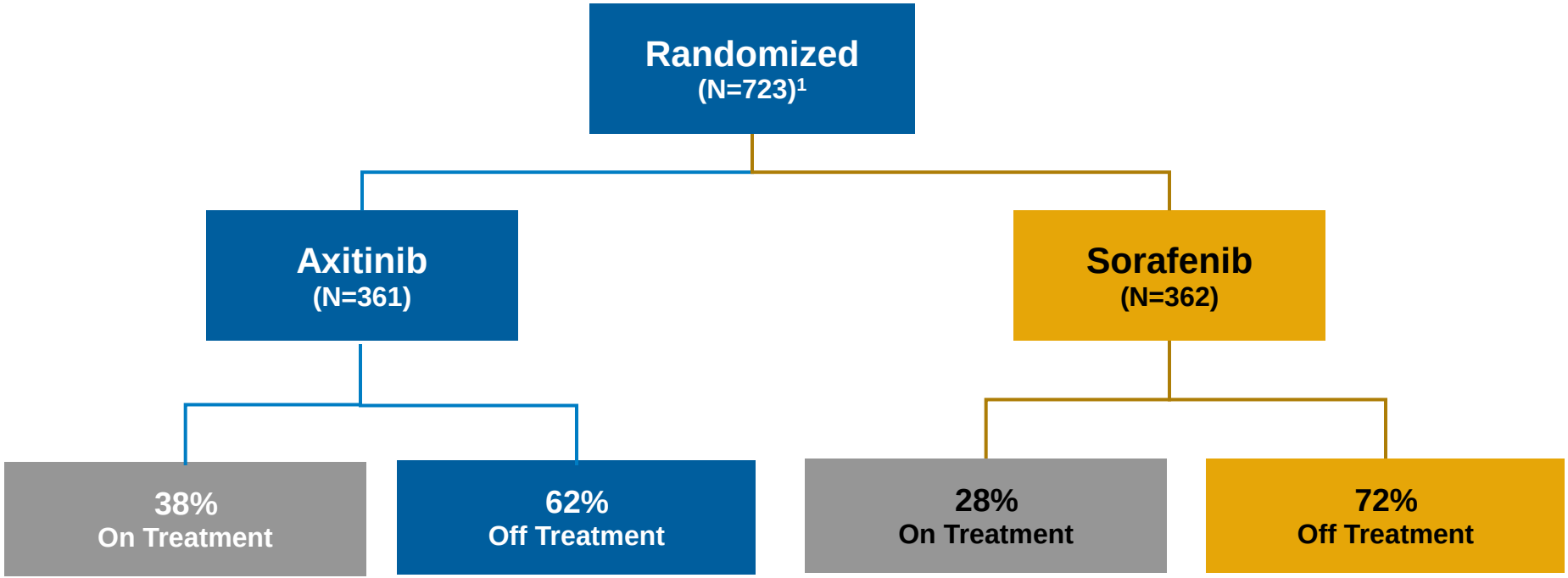
MSKCC: Memorial Sloan Kettering Cancer Center

Baseline Disease Characteristics

	Axitinib N=361	Sorafenib N=362
Prior regimen containing treatment (% of subjects)		
Sunitinib	54	54
Cytokines[1]	35	35
Bevacizumab	8	8
Temsirolimus	3	3
Metastatic site in >30% of subjects (% of subjects)		
Lung	76	81
Lymph node	58	56
Bone	33	30
Prior treatments (% of subjects)		
Surgery for nephrectomy	91	91
Radiation therapy	21	20

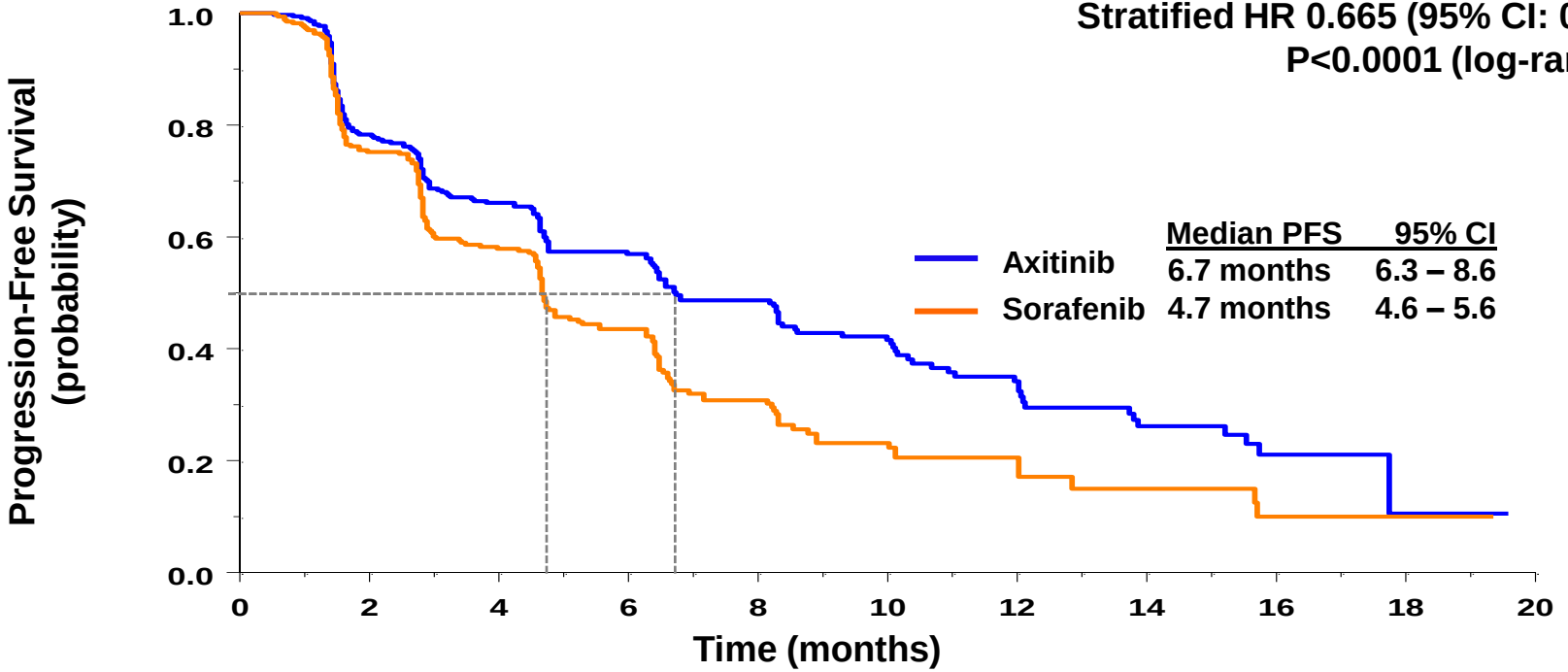
[1]In US, 21-25% patients in both arms received prior treatment with cytokines

Patient Disposition



[1]Final enrollment increased from 650 to 723 patients to accommodate patients in screening and to meet regulatory requirements for Japan

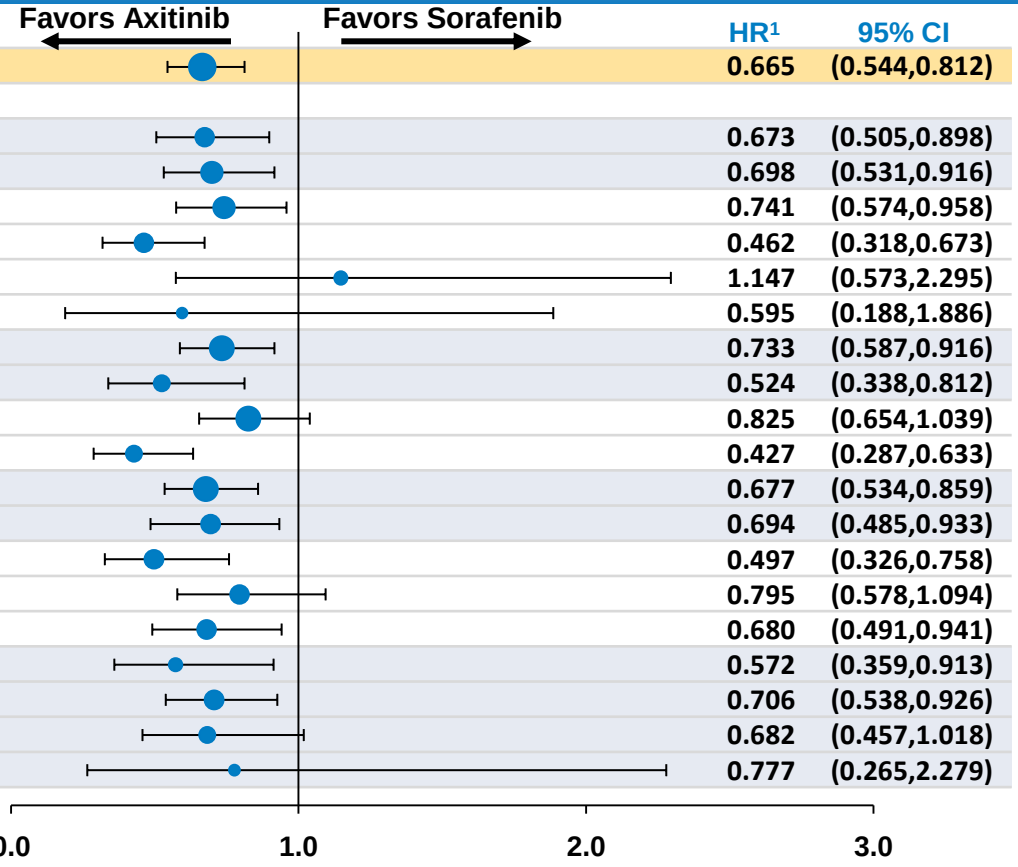
PFS in Overall Population (IRC)



Number at Risk											
Axitinib	361	256	202	145	96	64	38	20	10	1	0
Sorafenib	362	224	157	100	51	28	12	6	3	1	0

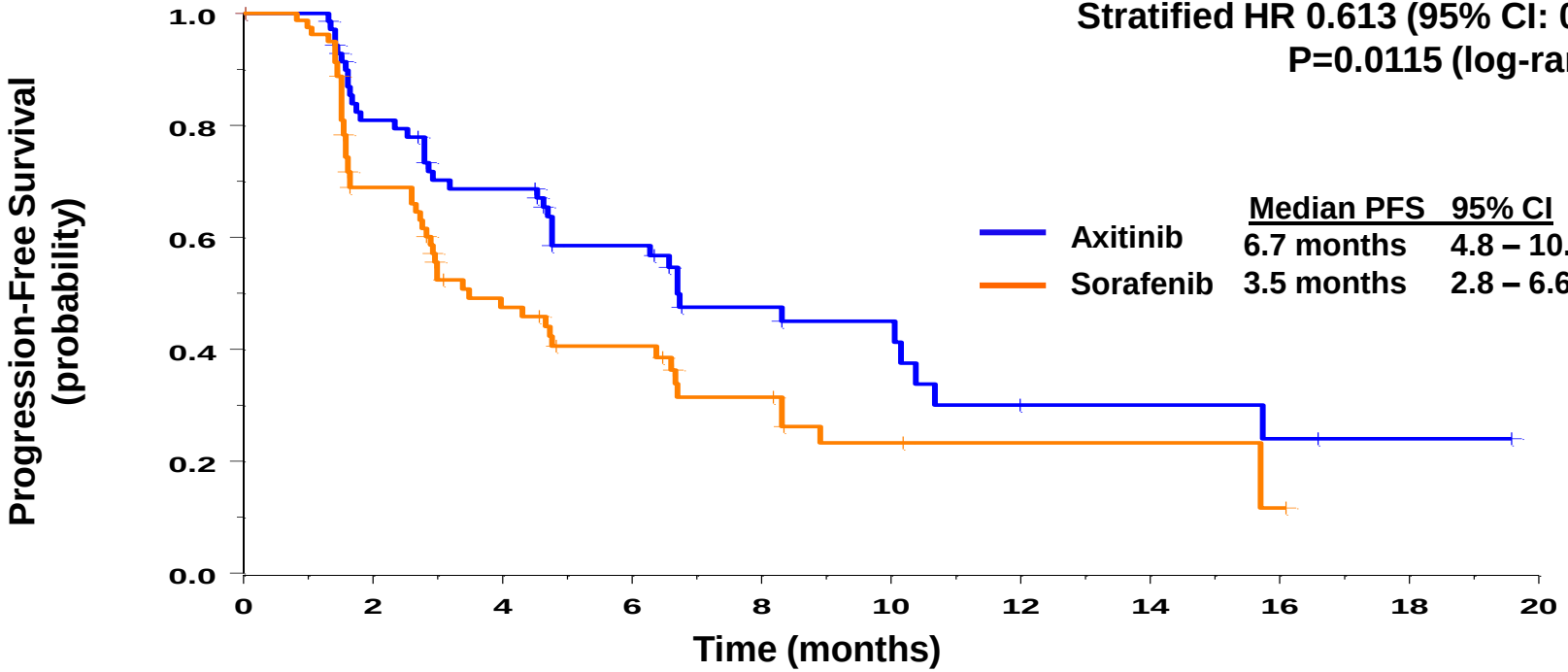
Subgroup Analysis of PFS Supports Consistent Treatment Effect

	N	HR[1]	95% CI
Overall	**723**	**0.665**	**(0.544,0.812)**
ECOG PS 1	327	0.673	(0.505,0.898)
ECOG PS 0	396	0.698	(0.531,0.916)
Sunitinib-containing Regimen	389	0.741	(0.574,0.958)
Cytokine-containing Regimen	251	0.462	(0.318,0.673)
Bevacizumab-containing Regimen	59	1.147	(0.573,2.295)
Temsirolimus-containing Regimen	24	0.595	(0.188,1.886)
White	547	0.733	(0.587,0.916)
Non-White	176	0.524	(0.338,0.812)
Male	523	0.825	(0.654,1.039)
Female	200	0.427	(0.287,0.633)
Age<65	476	0.677	(0.534,0.859)
Age >=65	247	0.694	(0.485,0.933)
MSKCC Favorable	201	0.497	(0.326,0.758)
MSKCC Intermediate	264	0.795	(0.578,1.094)
MSKCC Poor	238	0.680	(0.491,0.941)
Asia	152	0.572	(0.359,0.913)
Europe	357	0.706	(0.538,0.926)
North America	186	0.682	(0.457,1.018)
Other Regions	28	0.777	(0.265,2.279)



[1]Overall hazard ratio is adjusted for ECOG PS and prior therapy, subgroup hazard ratios unadjusted

PFS in United States Patient Population (IRC)

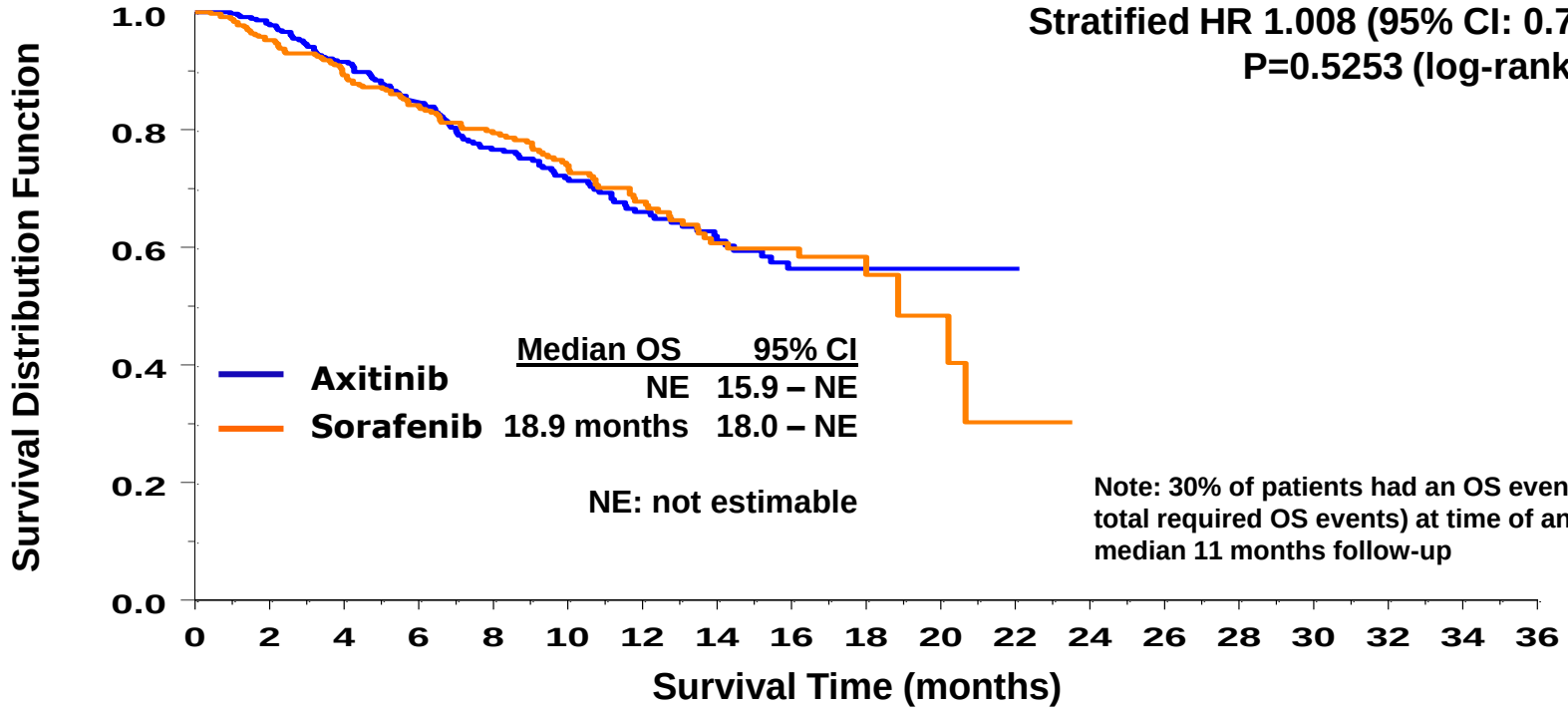


Objective Tumor Response in Overall Population

	Axitinib N=361	Sorafenib N=362	P-value[1]
Objective response, %			
Partial response	19.4	9.4	0.0001
Stable disease	49.9	54.4	
Progressive disease	21.6	21.0	
Indeterminate	6.1	11.6	
Median duration of response, months	11.0	10.6	

[1]Based on 1-sided Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior treatment

Interim OS (31 August 2010) in Overall Population

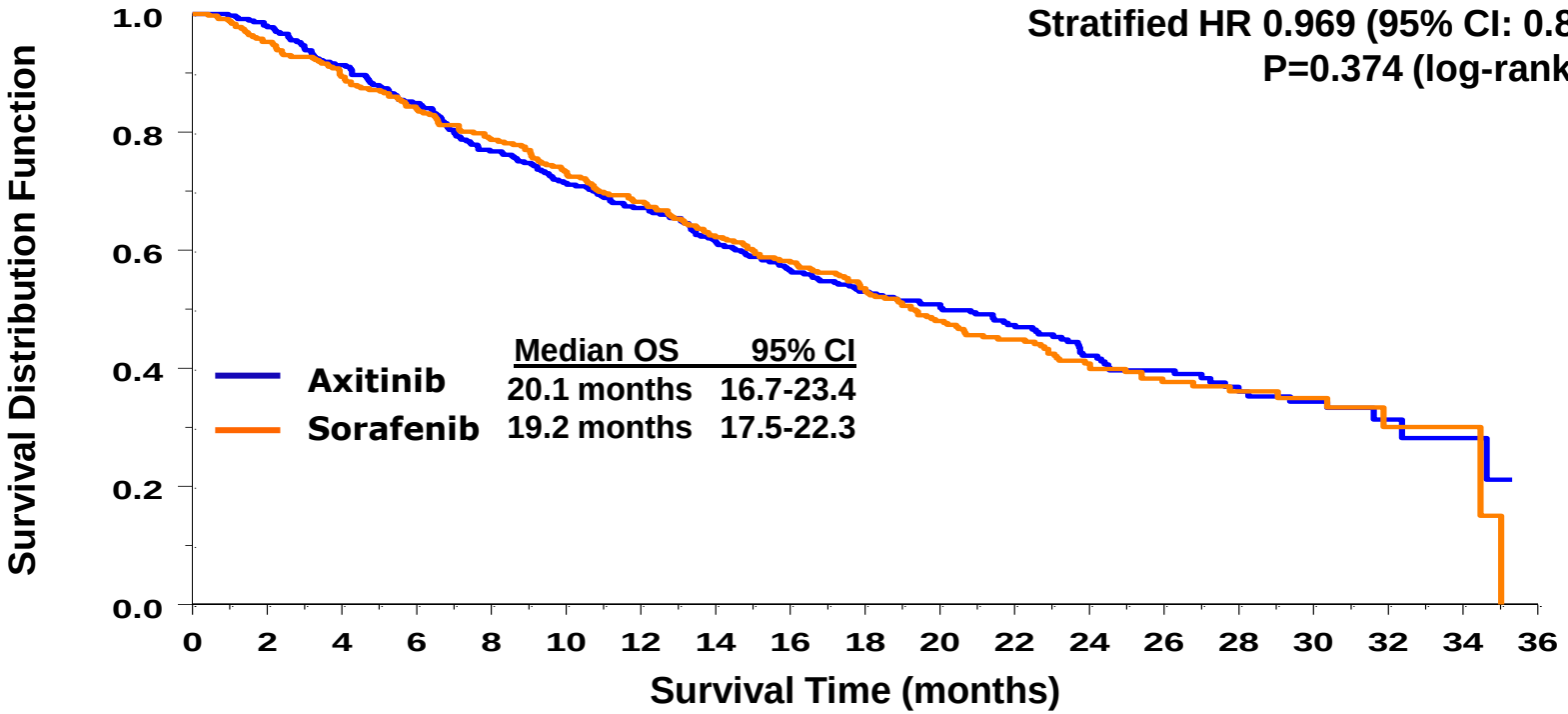


Stratified HR 1.008 (95% CI: 0.774-1.313)
P=0.5253 (log-rank, 1-sided)

Note: 30% of patients had an OS event (50% of total required OS events) at time of analysis with median 11 months follow-up

Number at Risk													
Axitinib	361	349	321	272	215	154	114	76	51	21	7	1	0
Sorafenib	362	337	311	260	213	164	114	70	44	19	7	1	0

Final OS (1 November 2011) in Overall Population



Efficacy Conclusions

- There is a statistically-significant and clinically-meaningful improvement in efficacy parameters (PFS and ORR) for axitinib compared to an active comparator (sorafenib)
- The results from the pivotal Phase 3 and supportive Phase 2 RCC studies are consistent
- The treatment benefit of axitinib was apparent across all subgroups
- The results in US patients were consistent with the entire study population

Summary of Clinical Safety

Sinil Kim, MD

Clinical Lead for Axitinib Development Program

Pfizer Oncology

Key Safety Populations

Safety Populations	N
Pooled data of axitinib monotherapy and axitinib + chemotherapy from all studies	2507
Pooled data of axitinib monotherapy from all studies	699
Pooled data of axitinib monotherapy from Phase 3 and Phase 2 RCC studies	537
Phase 3 RCC study A4061032	359
Phase 2 RCC study A4061035	64
Phase 2 RCC study A4061023	62
Phase 2 RCC study A4061012	52

Drug Exposure and Dose Delays/ Modifications

	Axitinib N=359	Sorafenib N=355
Median months on treatment (Range)	6.4 (0.03, 22.0)	5.0 (0.03, 20.0)
Dose modification or temporary delay of treatment due to AEs, %	55.4	62.0
Dose adjustments		
Patients with dose increase, %	36.8	NA
Patients with dose decrease, %	30.6	52.1
Median relative dose intensity, %	98.6	91.7

NA: not applicable

Safety Overview (as of 31 August 2010)

	Axitinib, N=359 n (%)	Sorafenib, N=355 n (%)
Adverse Events	342 (95)	347 (98)
Grade 3 AEs	181 (50)	182 (51)
Grade 4 AEs	21 (6)	36 (10)
Discontinuations due to AEs (all-causality)	33 (9)	46 (13)
Serious Adverse Events	106 (30)	110 (31)
Deaths	113 (31)	109 (31)
Deaths during treatment or within 28 days from last dose	36 (10)	24 (7)
Due to disease progression	26 (7)	17 (5)
Due to reason other than disease progression	10 (3)	7 (2)
Treatment-related deaths[1]	4 (1)	5[2] (1)

Median duration of exposure: axitinib = 6.4 mo; sorafenib = 5.0 mo

[1]Patients with a treatment-related SAE that resulted in death; [2]One of the deaths in the sorafenib arm (general physical health deterioration) occurred during follow-up.

Most Common AEs Regardless of Causality

	Axitinib, N=359, %			Sorafenib, N=355, %		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Diarrhea	55	10	<1	53	7	1
Hypertension	40	15	<1	29	11	<1
Fatigue	39	11	1	32	5	<1
Decreased appetite	34	5	<1	29	4	0
Nausea	32	2	<1	22	1	0
Dysphonia	31	0	0	14	0	0
Hand-foot syndrome	27	5	0	51	16	0
Weight decreased	25	2	0	21	1	0
Vomiting	24	3	<1	17	1	0
Asthenia	21	5	1	14	2	<1
Constipation	20	1	0	20	1	0
Hypothyroidism	19	<1	0	8	0	0
Rash	13	<1	0	32	4	0
Alopecia	4	0	0	32	0	0

Median duration of exposure: axitinib = 6.4 mo; sorafenib = 5.0 mo

Most Common AEs Regardless of Causality

	Axitinib, N=359, %			Sorafenib, N=355, %		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Diarrhea	55	10	<1	53	7	1
Hypertension	**40**	**15**	**<1**	**29**	**11**	**<1**
Fatigue	39	11	1	32	5	<1
Decreased appetite	34	5	<1	29	4	0
Nausea	32	2	<1	22	1	0
Dysphonia	**31**	**0**	**0**	**14**	**0**	**0**
Hand-foot syndrome	27	5	0	51	16	0
Weight decreased	25	2	0	21	1	0
Vomiting	24	3	<1	17	1	0
Asthenia	21	5	1	14	2	<1
Constipation	20	1	0	20	1	0
Hypothyroidism	**19**	**<1**	**0**	**8**	**0**	**0**
Rash	13	<1	0	32	4	0
Alopecia	4	0	0	32	0	0

Median duration of exposure: axitinib = 6.4 mo; sorafenib = 5.0 mo

≥ 10% difference

Most Common AEs Regardless of Causality

	Axitinib, N=359, %			Sorafenib, N=355, %		
Adverse Event	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Diarrhea	55	10	<1	53	7	1
Hypertension	40	15	<1	29	11	<1
Fatigue	39	11	1	32	5	<1
Decreased appetite	34	5	<1	29	4	0
Nausea	32	2	<1	22	1	0
Dysphonia	31	0	0	14	0	0
Hand-foot syndrome	**27**	**5**	**0**	**51**	**16**	**0**
Weight decreased	25	2	0	21	1	0
Vomiting	24	3	<1	17	1	0
Asthenia	21	5	1	14	2	<1
Constipation	20	1	0	20	1	0
Hypothyroidism	19	<1	0	8	0	0
Rash	**13**	**<1**	**0**	**32**	**4**	**0**
Alopecia	**4**	**0**	**0**	**32**	**0**	**0**

Median duration of exposure: axitinib = 6.4 mo; sorafenib = 5.0 mo

≥ 10% difference

Most Common Adverse Events Leading to Discontinuation of Treatment

Preferred Term	Axitinib, N=359, n (%)	Sorafenib, N=355, n (%)
Total	**33 (9.2)**	**46 (13.0)**
General Disorders	**15 (4.2)**	**8 (2.3)**
Asthenia/Fatigue	6 (1.7)	4 (1.1)
Disease progression	9 (2.5)	4 (1.1)
Gastrointestinal Disorders	**2 (0.6)**	**11 (3.1)**
Ascites	1 (0.3)	0
Diarrhea	0	3 (0.8)
Enterocolitis	0	1 (0.3)
Hemorrhage[1] (Duodenal ulcer, GI, Upper GI)	0	3 (0.8)
Nausea	0	2 (0.6)
Periodontitis	0	1 (0.3)
Vomiting	1 (0.3)	1 (0.3)
Skin Disorders	**1 (0.3)**	**11 (3.1)**
Erythema multiforme	0	2 (0.6)
Palmar-plantar erythrodysesthesia	1 (0.3)	4 (1.1)
Pruritus[2]	0	2 (0.6)
Rash[3]	0	3 (0.8)

Note: One (0.3%) patient discontinued axitinib treatment due to hypertension; no patients discontinued axitinib treatment due to dysphonia or hypothyroidism.; GI: gastrointestinal; [1]Duodenal ulcer hemorrhage, gastrointestinal hemorrhage, and upper gastrointestinal hemorrhage reported in one patient each. [2]Includes pruritus and pruritus generalized. [3]Includes rash and rash generalized.

Hematology Laboratory Abnormalities

	Axitinib			Sorafenib		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Anemia	**35**	**<1**	**0**	**52**	**3**	**1**
Lymphopenia	32	3	0	35	3	0
Thrombocytopenia	15	<1	0	14	0	0
Leukopenia	11	0	0	16	<1	0
Neutropenia	6	1	0	9	1	0

≥ 10% difference

Chemistry Laboratory Abnormalities and Urinalysis

	Axitinib, %			Sorafenib, %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Alk Phos increased	30	1	0	35	1	0
ALT increased	23	<1	0	22	1	1
AST increased	20	<1	0	25	1	0
Bilirubin (total)	7	<1	0	5	<1	0
Creatinine increased	**55**	**0**	**0**	**41**	**1**	**0**
Hypercalcemia[1]	6	0	0	2	0	0
Hyperglycemia	28	2	0	22	2	0
Hyperkalemia	15	3	0	10	3	0
Hypernatremia	16	1	0	12	<1	1
Hypocalcemia[1]	**39**	**1**	**1**	**59**	**1**	**1**
Hypoglycemia	10	<1	0	8	<1	0
Hyponatremia	13	3	<1	11	2	<1
Hypophosphatemia	**13**	**2**	**0**	**50**	**16**	**0**
Lipase increased	**27**	**4**	**1**	**46**	**12**	**2**
Urine protein	53	3	NA	51	2	NA

Alk Phos: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate transaminase; [1]levels adjusted for albumin; NA: not applicable

≥10% difference

Chemistry Laboratory Abnormalities and Urinalysis

	Axitinib, %			Sorafenib, %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Alk Phos increased	**30**	**1**	**0**	**35**	**1**	**0**
ALT increased	**23**	**<1**	**0**	**22**	**1**	**1**
AST increased	**20**	**<1**	**0**	**25**	**1**	**0**
Bilirubin (total)	**7**	**<1**	**0**	**5**	**<1**	**0**
Creatinine increased	55	0	0	41	1	0
Hypercalcemia[1]	6	0	0	2	0	0
Hyperglycemia	28	2	0	22	2	0
Hyperkalemia	15	3	0	10	3	0
Hypernatremia	16	1	0	12	<1	1
Hypocalcemia[1]	39	1	1	59	1	1
Hypoglycemia	10	<1	0	8	<1	0
Hyponatremia	13	3	<1	11	2	<1
Hypophosphatemia	13	2	0	50	16	0
Lipase increased	27	4	1	46	12	2
Urine protein	53	3	NA	51	2	NA

Alk Phos: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate transaminase; [1]levels adjusted for albumin; NA: not applicable

Selected Adverse Events (All-Causality) ≥ Grade 3

Adverse Event	Axitinib, N=359			Sorafenib, N=355		
	Grade 3 n(%)	Grade 4 n(%)	Grade 5 n(%)	Grade 3 n(%)	Grade 4 n(%)	Grade 5 n(%)
VTEs	4 (1.1)	5 (1.4)	1 (0.3)[a]	0	2 (0.6)	0
Hemorrhage	4 (1.1)	1 (0.3)	1 (0.3)[b]	11 (3.1)	0	3 (0.8)[c]
ATEs	4 (1.1)[d]	0	0	1 (0.3)[e]	1 (0.3)[f]	0
GI perforation	1 (0.3)	0	0	0	0	0
RPLS	1 (0.3)	0	0	0	0	0
Hypothyroidism	1 (0.3)	0	0	0	0	0

[a]Pulmonary embolism (not considered related to axitinib); [b]Gastric hemorrhage; [c]Duodenal ulcer hemorrhage, gastrointestinal hemorrhage ,and retroperitoneal hemorrhage; [d]Transient ischemic attack (3) and retinal artery occlusion (1); [e]Myocardial infarction; [f]ischemic stroke

Safety Summary

- Most common AEs expected for class
  - Incidence of hypertension, dysphonia, and hypothyroidism more frequent for axitinib than sorafenib
  - Incidence of hand-foot syndrome, rash, and alopecia less frequent compared to sorafenib
  - Grade 3+ thromboembolic events, hemorrhage, gastrointestinal perforation, RPLS, and hypothyroidism uncommon
  - Grade 3-4 laboratory abnormalities uncommon
- Most AEs manageable with low rate of treatment discontinuation

Clinical Perspective on Axitinib and Benefit/Risk in Patients with RCC

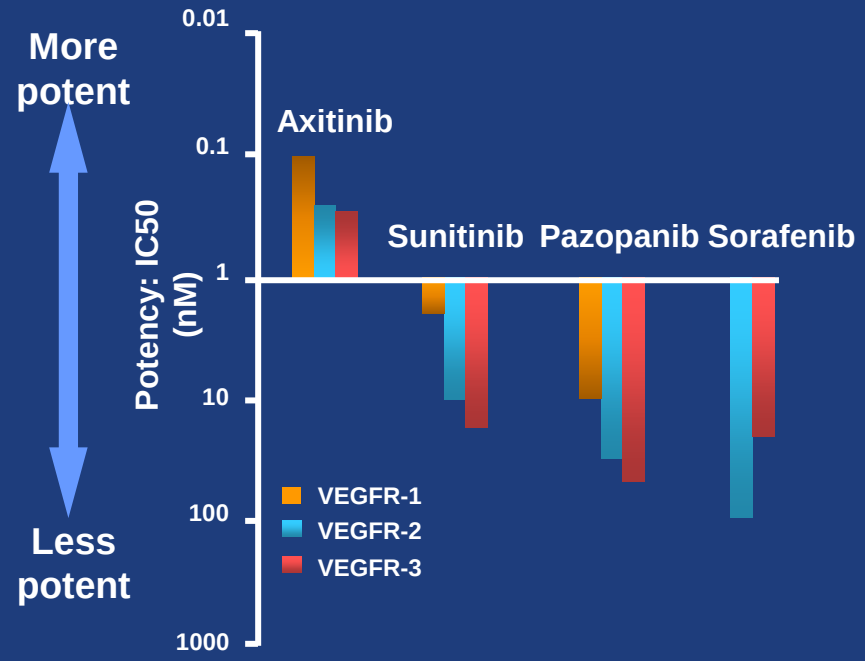
Robert J Motzer, MD
Attending Physician
Memorial Sloan Kettering Cancer Center
New York

Improvements in RCC Therapy Still Required

- Landscape of RCC has been altered by the emergence of targeted agents
- TKIs with activity against VEGFRs have emerged to form the backbone of advanced RCC therapy
- Further improvement in patient therapeutic outcome is needed
  - Improved efficacy over currently-approved therapies
  - Fewer toxicities troublesome to patients

Axitinib is More Potent and Selective than Currently-Approved VEGFR TKIs

Most Potent for VEGFR-1, -2, and -3[1]



Most Selective for VEGFR -1, -2, and -3

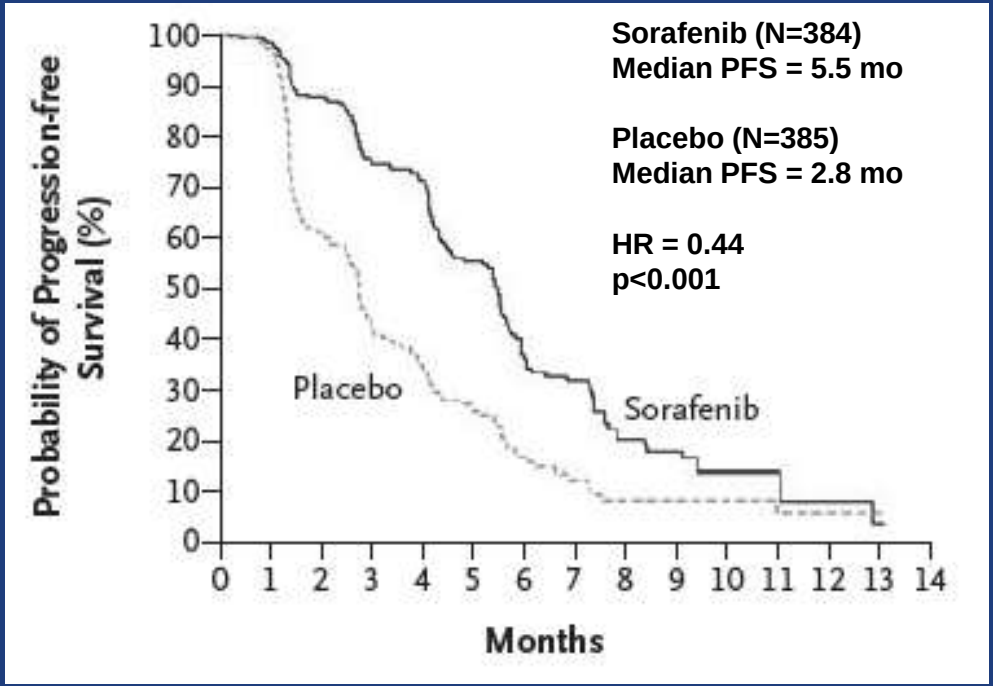
Target Selectivity				
	Axitinib[1]	Sorafenib[2]	Sunitinib[3]	Pazopanib[4]
VEGFR-2	+	+	+	+
PDGFR b		+	+	+
c-kit		+	+	+
FLT-3		+	+	nd
CSF-1R		nd	+	+
Raf-1	nd	+	nd	nd

VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor; c-KIT = v-kit Hardy-Zukerman 4 feline sarcoma viral oncogene homolog; FLT: FMS-like tyrosine kinase; CSF: colony-stimulating factor; Raf: v-raf-1 murine leukemia viral oncogene homolog 1; nd: not determined; **+**: inhibition of receptor kinase comparable (<10 times) to potency for VEGFR-2

[1] Hu-Lowe, et al. Clin Cancer Res 2008; 14:7272; [2] Wilhelm, et al. Cancer Res 2004; 64:7099; [3] Roskoski. BBRC 2007; 356: 323; [4] Kumar, et al. Mol Can Ther 2007; 6: 2012

Sorafenib Active in Cytokine-Refractory Patients

- US
  - FDA-approved (December 2005) based on Phase 3 study mainly in cytokine-refractory patients[1]
  - First TKI approved in US for “advanced RCC”
- Global
  - Widely-approved and used globally



[1]Escudier B, et al. N Eng J Med. 2007; 356: 125-34.

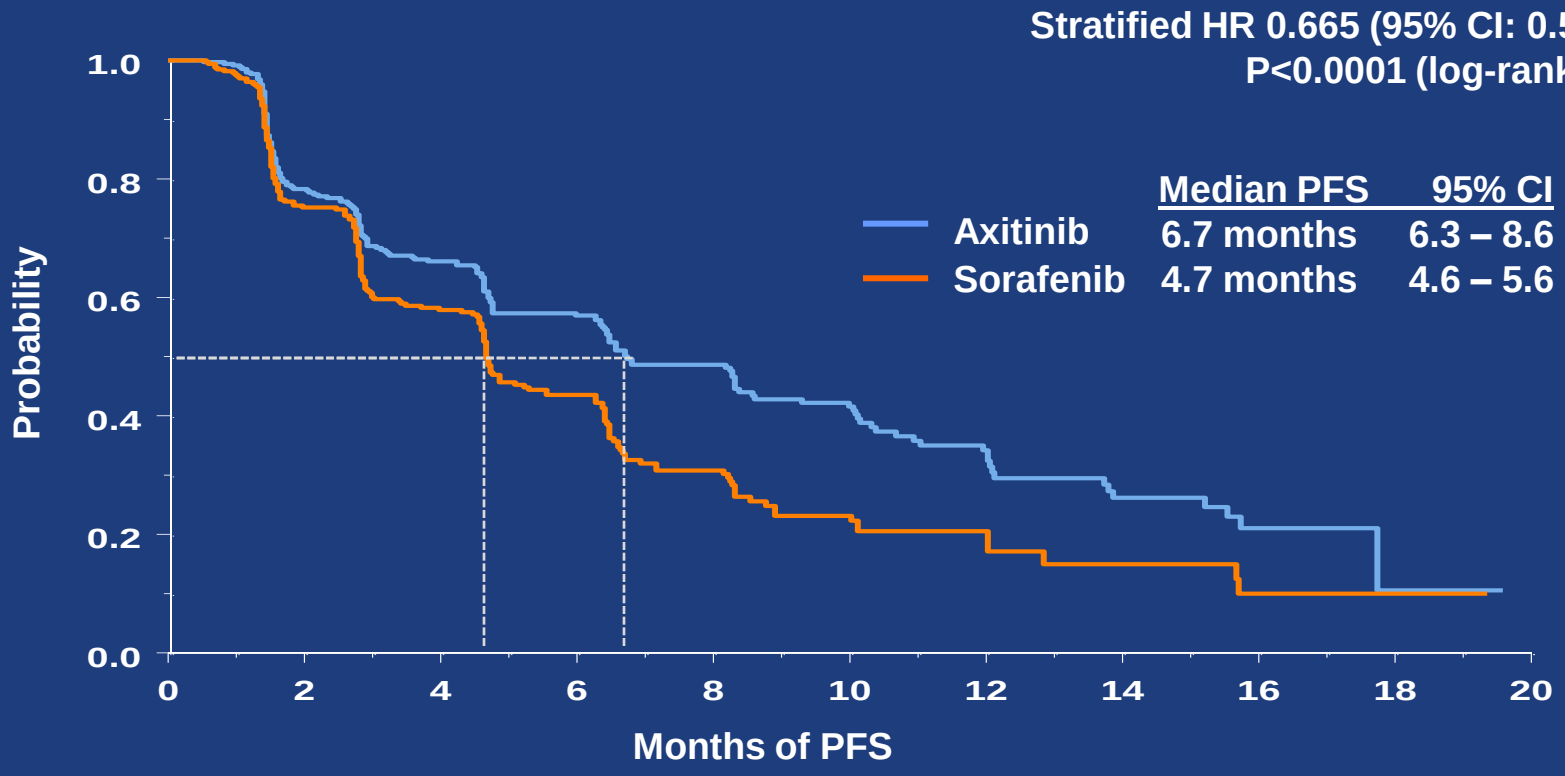
Sorafenib Active in TKI-Refractory Patients

Agent	Population	N	PFS (mo)	OS (mo)
Sorafenib[1]	Sunitinib-refractory	52	3.8	8
Sorafenib[2]	Sunitinib-refractory	27	4.4	16
	Bevacizumab-refractory	20	3.7	

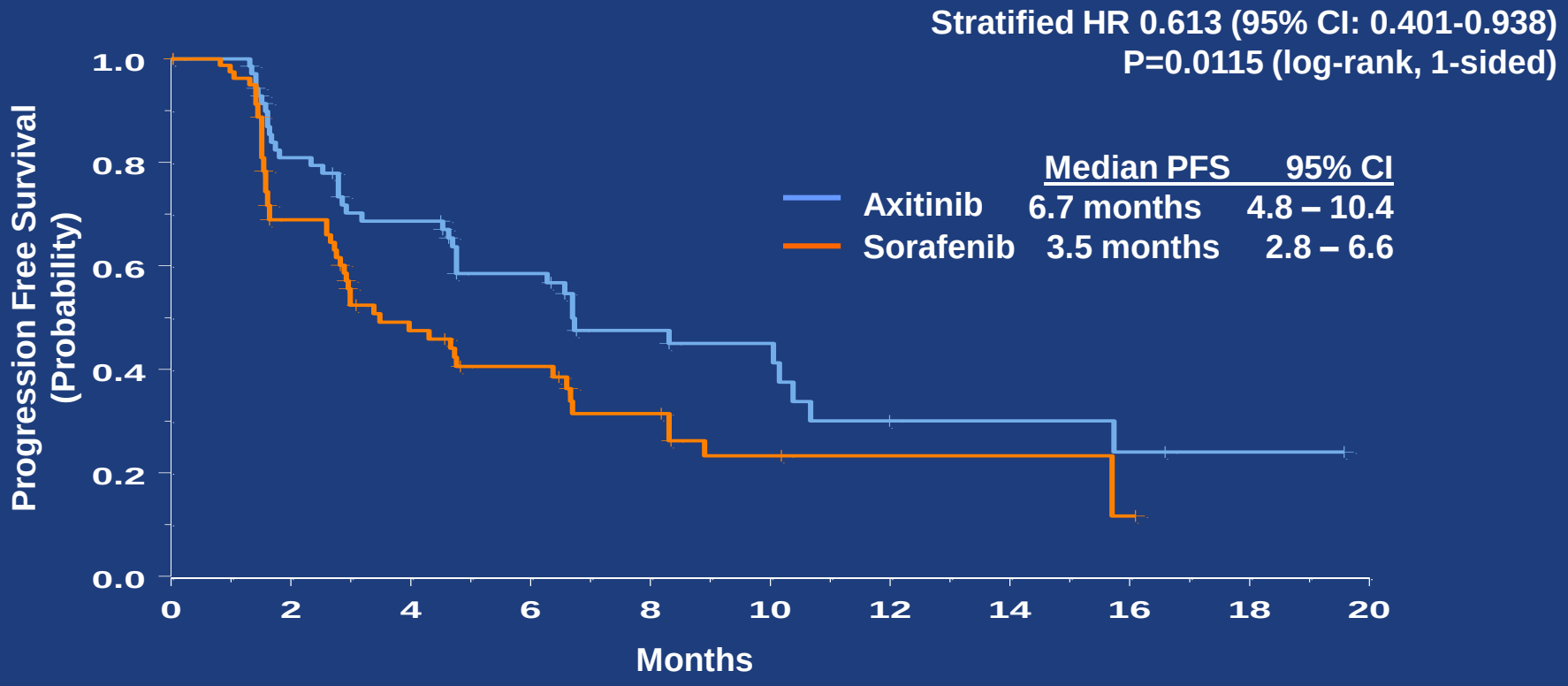
[1]Di Lorenzo, et al. J Clin Oncol. 27:4469-4474, 2009; [2]Garcia, et al. Cancer 116(23):5383-90, 2010; [3]Tumor burden reduction ≥5% observed in 30% of patients (43% of patients had stable disease)

OS: overall survival; PFS: Progression-free Survival

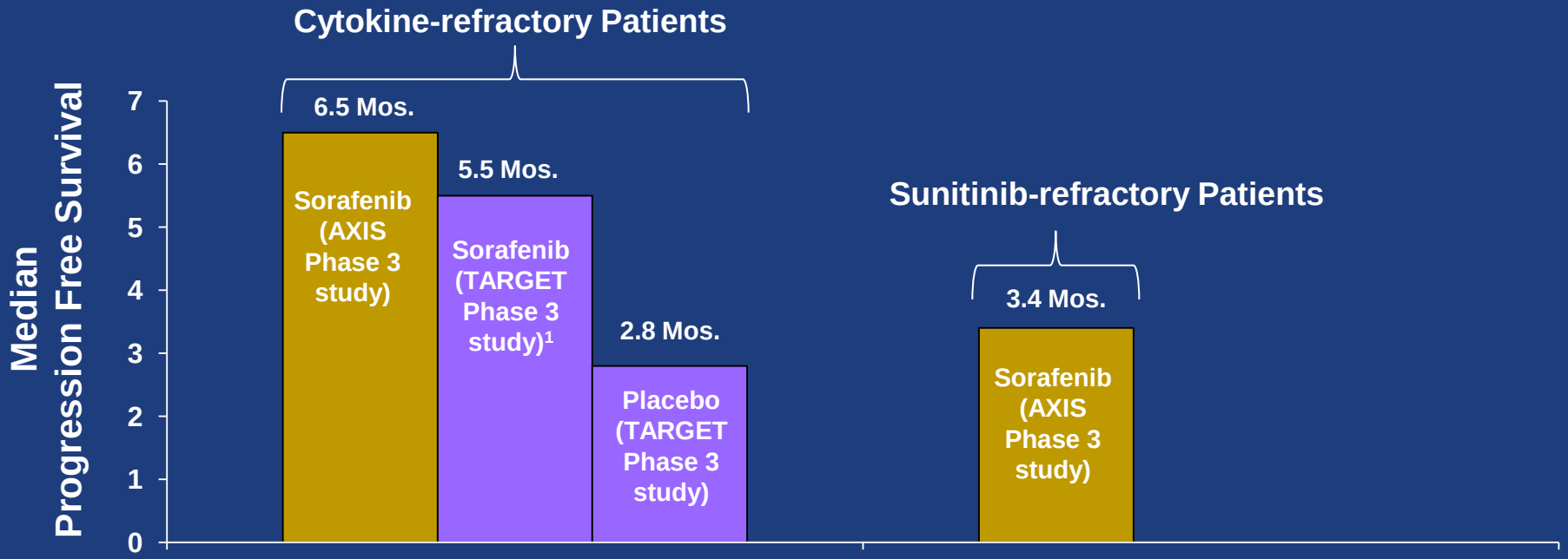
Axitinib Demonstrated Greater Efficacy Compared with Approved VEGFR TKI Sorafenib



PFS in United States Patient Population (IRC)



Sorafenib Active in Cytokine- and Sunitinib-Refractory Patients in Axitinib Phase 3 Study



[1]Nexavar Prescribing Information , 2011

Axitinib Phase 3 Study: Median PFS in Subgroups

Prior Treatment Regimen	Axitinib (N=361) months	Sorafenib (N=362) months	Hazard Ratio (95% CI)
Cytokines (n=251)	**12.1**	**6.5**	**0.46** (0.32, 0.68)
Sunitinib (n=389)	**4.8**	**3.4**	**0.74** (0.57, 0.96)
Bevacizumab (n=59)	**4.2**	**4.7**	**1.15** (0.57, 2.32)
Temsirolimus (n=24)	**10.1**	**5.3**	**0.51** (0.14, 1.87)

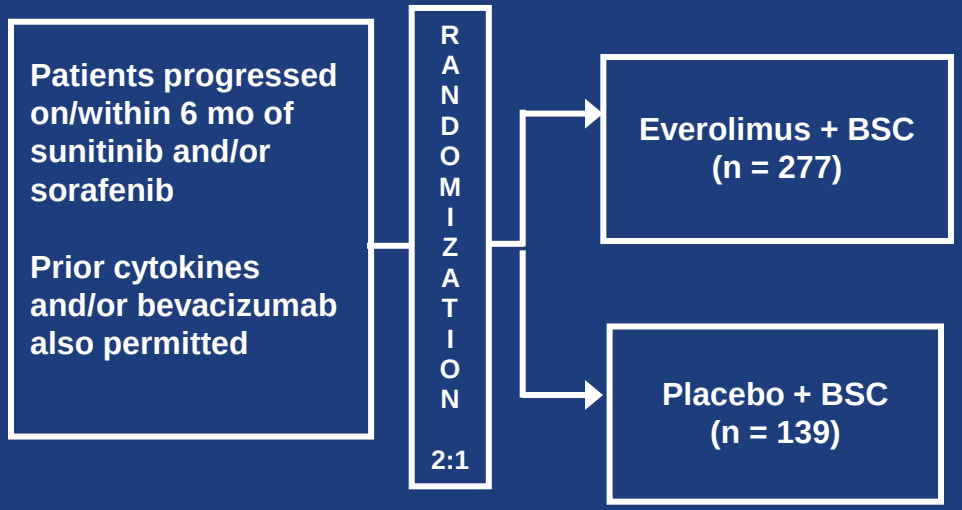
[1]One-sided log-rank test stratified by ECOG performance status

Median PFS in Cytokine-Refractory Patients

Therapy	Data Source	Comparator	Median PFS (mo)	P-value
Axitinib[1]	Phase 3 trial (n=251)	Sorafenib	**12.1** vs 6.5	<0.0001
Sunitinib[2]	Phase 2 trial (N=106)	None	8.8	NA
Pazopanib[3]	Phase 3 trial (n=202)	Placebo	7.4 vs 4.2	NR[4]
Sorafenib[5]	Phase 3 trial (N=769)	Placebo	5.5 vs 2.8	<0.001

NA: not applicable; NR: not reported; [1]Pfizer Clinical Study A4061032; [2]Motzer RJ, et al. J Urol 178 November 2007; [3]Votrient Prescribing Information, 2011; [4]p<0.001 for overall ITT population; [5]Escudier B, et al. N Eng J Med 2007; 356: 12-134 (mainly cytokine-refractory patients)

Everolimus Phase 3 Study (RECORD-1) - Design and Prior Therapy



Prior Treatment	Everolimus (n=277) %	Placebo (n=139) %
VEGFR-TKI therapy		
Sunitinib	45	43
Sorafenib	29	31
Both	26	26
Other systemic therapy		
Immunotherapy	65	67
Chemotherapy	13	16

Motzer RJ et al. Cancer 2010;116:4256–65.

79% patients received 2 or more prior therapies

Everolimus and Axitinib Phase 3 Studies

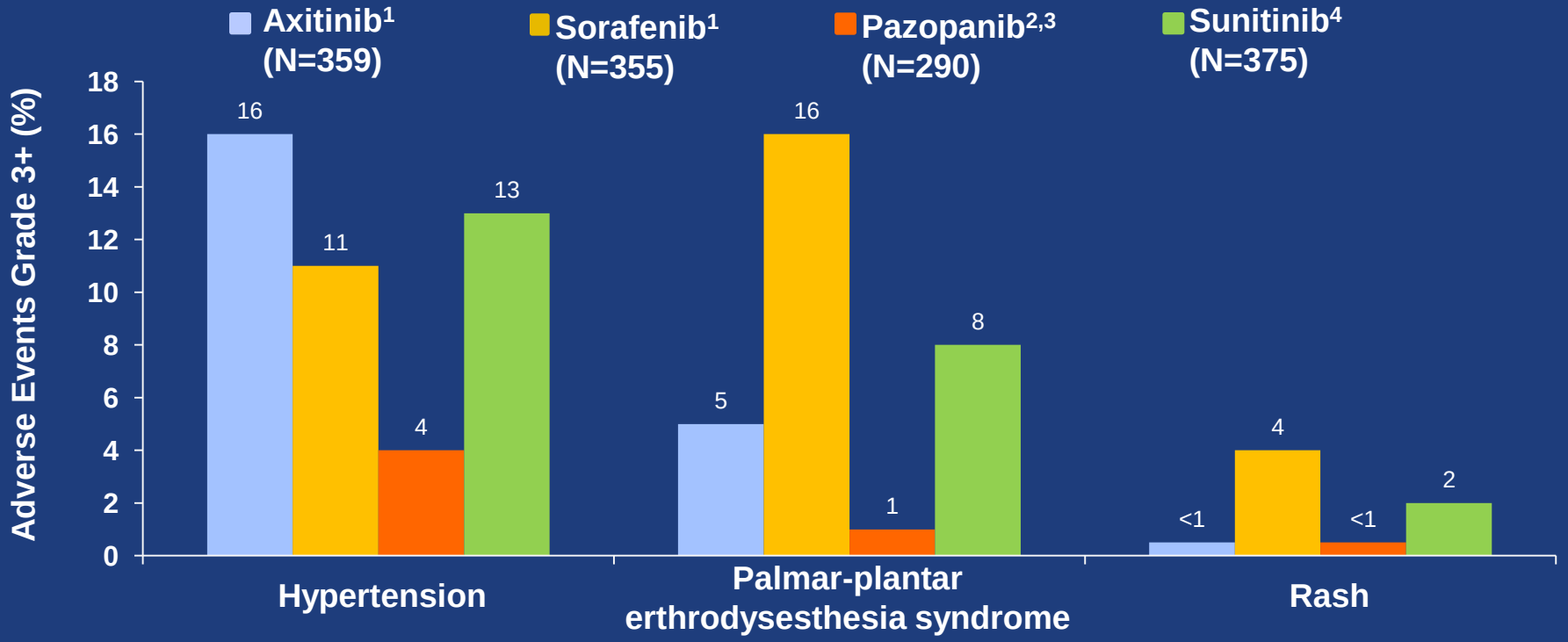
Therapy	Control	Patients	Median PFS[1] (mo)	Hazard ratio
Everolimus[1]	Placebo	All (n=416)	4.9 vs 1.9	0.33
		Sunitinib-pretreated (n=184)	3.9 vs 1.8	0.34
Axitinib[2]	Sorafenib	All (n=723)	6.7 vs 4.7	0.67
		Sunitinib-pretreated (n=389)	4.8 vs 3.4	0.74

[1]Afinitor NDA 22-334 CDER review; [2]Pfizer Clinical Study A4061032

Axitinib Phase 3 Study: Most Common All Grade AEs Regardless of Causality

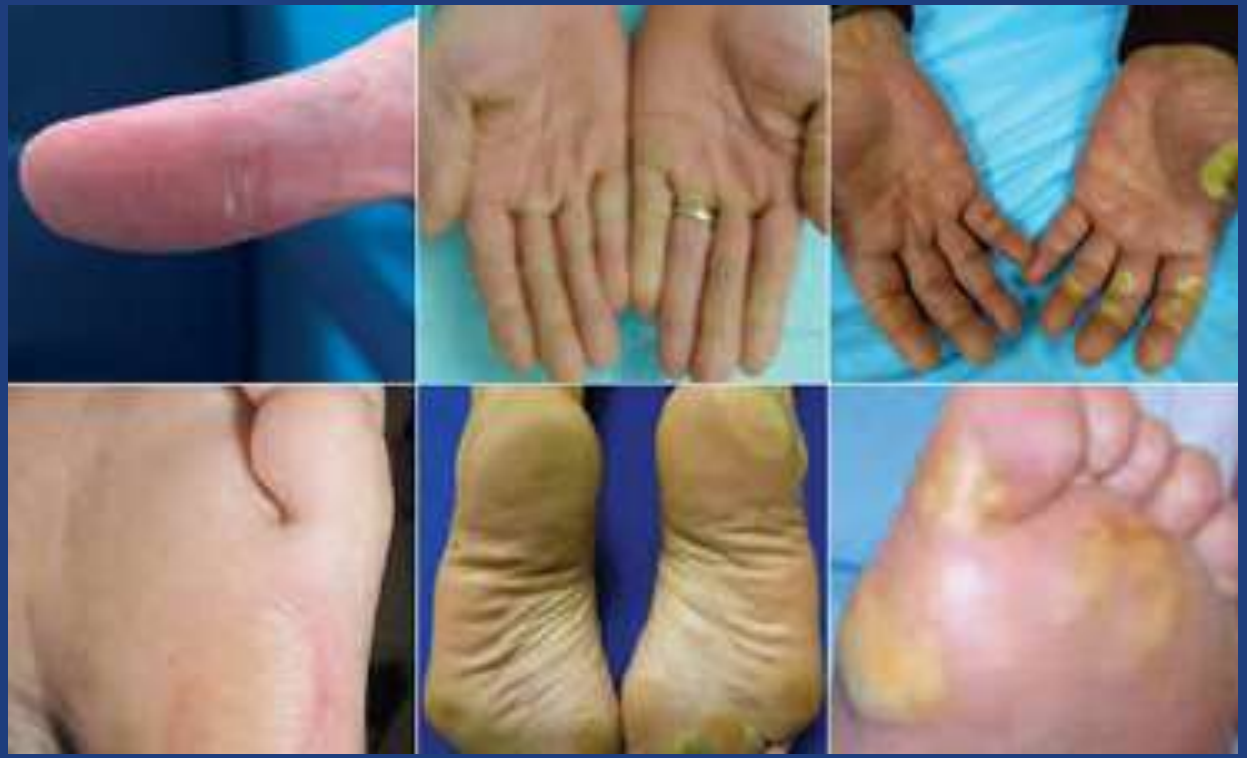
Adverse Event	Axitinib, % N=359	Sorafenib, % N=355
Diarrhea	55	53
Hypertension	40	29
Fatigue	39	32
Decreased appetite	34	29
Nausea	32	22
Dysphonia	31	14
Hand-foot syndrome	27	51
Weight decreased	25	21
Vomiting	24	17
Asthenia	21	14
Constipation	20	20
Rash	13	32
Alopecia	4	32

Hypertension and Skin Reactions Across VEGFR TKIs



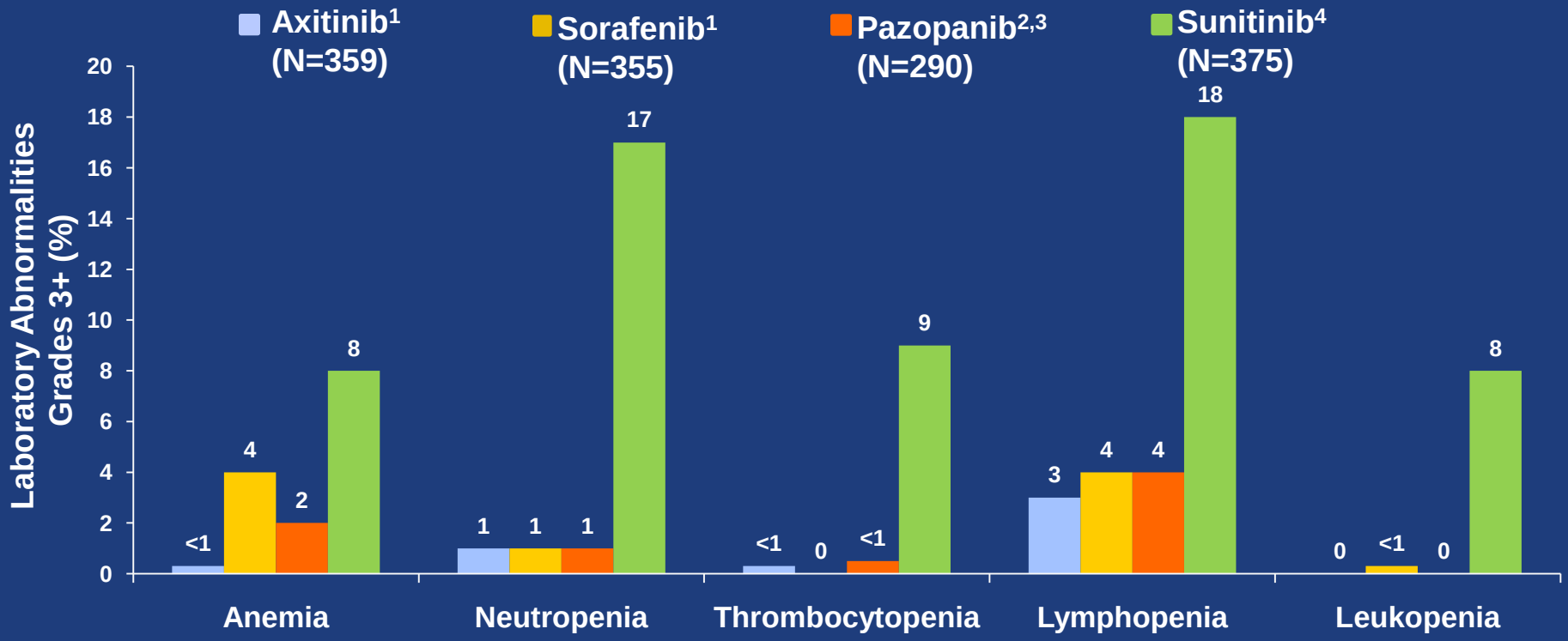
[1]Pfizer Clinical Study A4061032; [2]Votrient Prescribing Information, 2011; [3]CDER Medical Review (all-causality frequency) [4]Sutent Prescribing Information, 2011 (all-causality frequency)

Skin Reactions



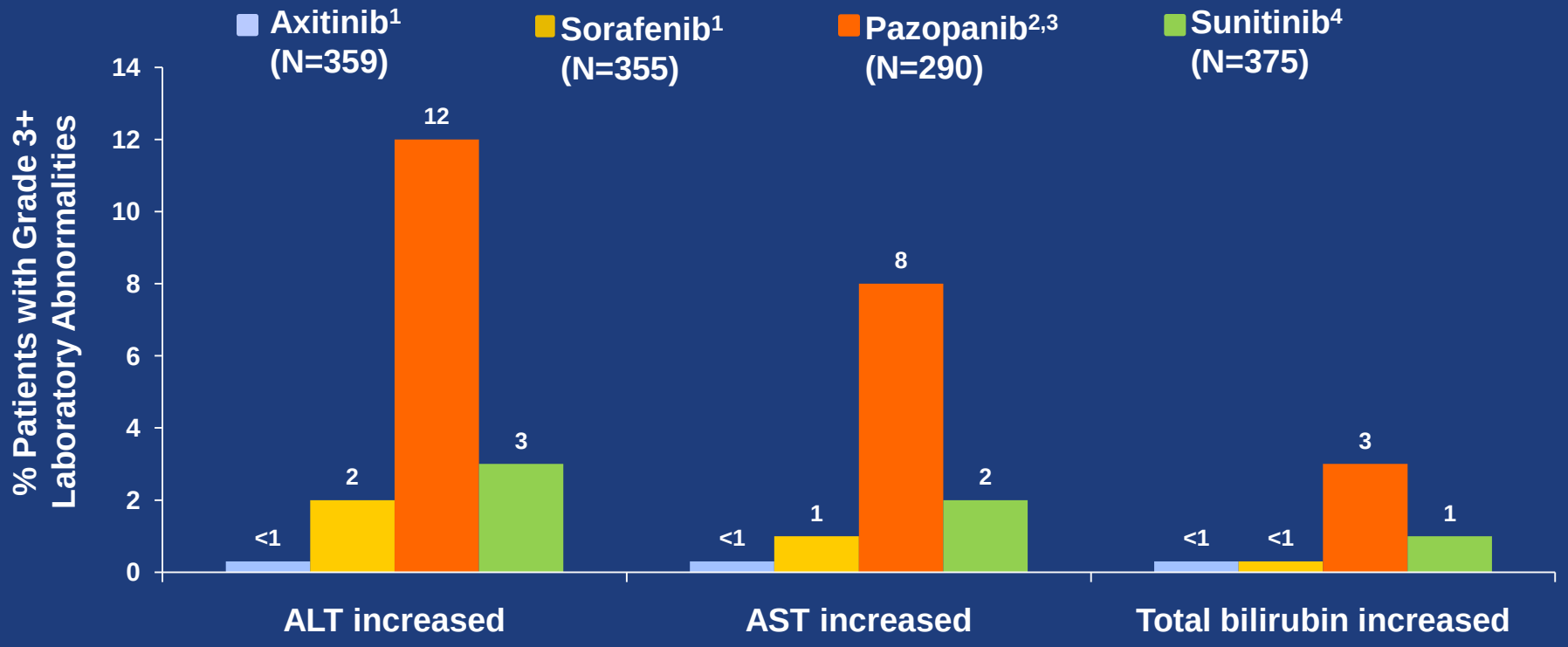
http://www.nexavar-us.com/scripts/pages/en/hcc/common-side-effects/skin-reactions/

Myelosuppression Across VEGFR TKIs



[1]Pfizer Clinical Study A4061032; [2]Votrient Prescribing Information, 2011; [3]Votrient NDA CDER Medical Review; [4]Sutent Prescribing Information, 2011

Liver Function Test Abnormalities Across VEGFR TKIs



ALT: alanine aminotransferase, AST: aspartate aminotransferase; [1]Pfizer Clinical Study A4061032; [2]Votrient Prescribing Information, 2011; [3]Votrient CDER Medical Review; [4]Sutent Prescribing Information, 2011

Current NCCN Guidelines for Clear Cell RCC

Treatment	NCCN Recommendation Category[1]	
	Subsequent Therapy Following Cytokines	Subsequent Therapy Following TKI
Sorafenib	1	2A
Sunitinib	1	2A
Temsirolimus	2A	2B
Everolimus	NA	1
Bevacizumab + IFN-α	2A	2B
Pazopanib	1	3

NA: not available; NCCN: National Comprehensive Cancer Network; [1] NCCN guidelines, Kidney Cancer, 2011 (version 2.2011); [2] Investigational agent

Recommendation based on:

- Category 1: high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus
- Category 2A: lower-level evidence and there is uniform NCCN consensus
- Category 2B: lower-level evidence and there is no uniform NCCN consensus (but no major disagreement)
- Category 3: any level of evidence but reflects major disagreement

Proposed Treatment Paradigm for Axitinib as Part of Future NCCN Guidelines for Clear Cell RCC

Treatment	NCCN Recommendation Category[1]	
	Subsequent Therapy Following Cytokines	Subsequent Therapy Following TKI
Axitinib[2]	**1**	**1**
Sorafenib	1	2A
Sunitinib	1	2A
Temsirolimus	2A	2B
Everolimus	NA	1
Bevacizumab + IFN-α	2A	2B
Pazopanib	1	3

NA: not available; NCCN: National Comprehensive Cancer Network; [1] NCCN guidelines, Kidney Cancer, 2011 (version 2.2011); [2] Investigational agent

Recommendation based on:

- Category 1: high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus
- Category 2A: lower-level evidence and there is uniform NCCN consensus
- Category 2B: lower-level evidence and there is no uniform NCCN consensus (but no major disagreement)
- Category 3: any level of evidence but reflects major disagreement

Summary

- Axitinib has superior efficacy compared to sorafenib
- Axitinib has advantages with a lower incidence of some important toxicities compared to approved VEGFR TKIs
- The benefit/risk evaluation is favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy

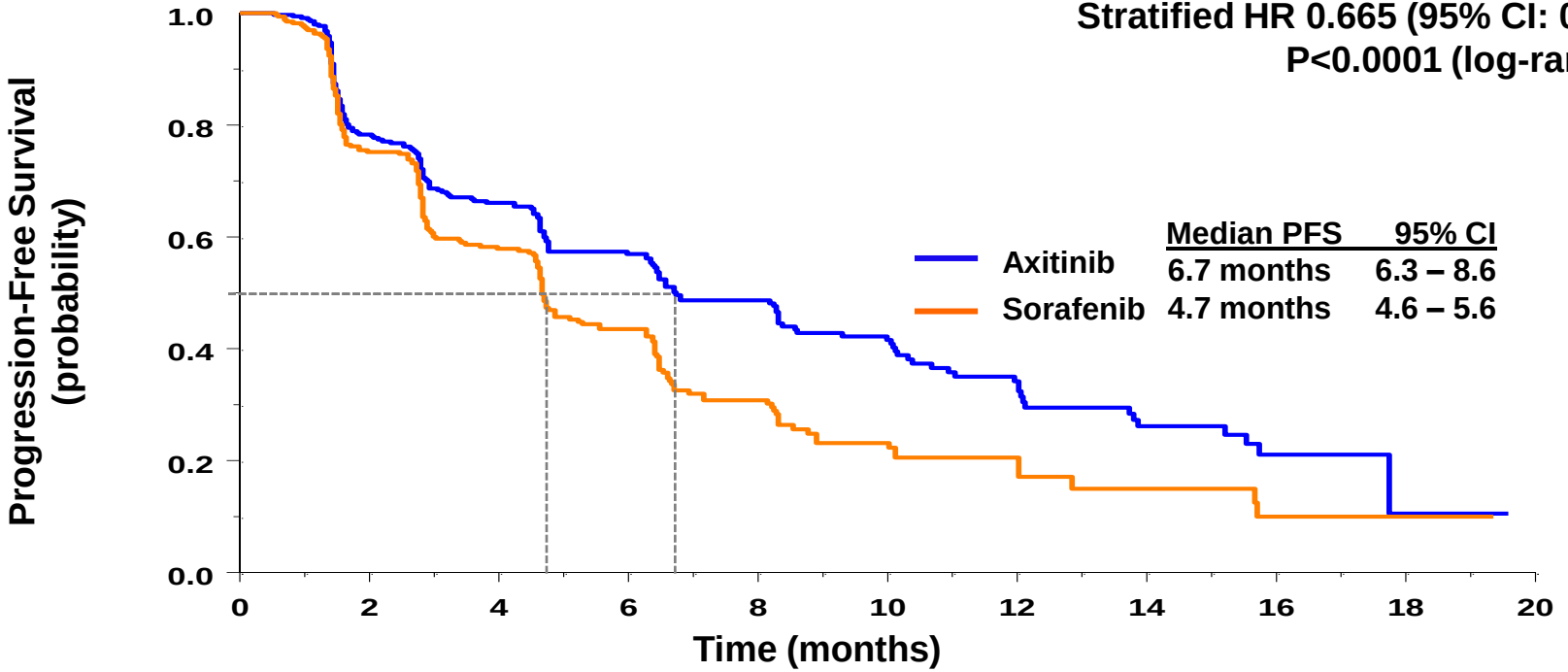
Concluding Remarks

Mace Rothenberg, MD

Senior Vice President Clinical Development and Medical Affairs,

Pfizer Oncology

Improvement Over Active Comparator

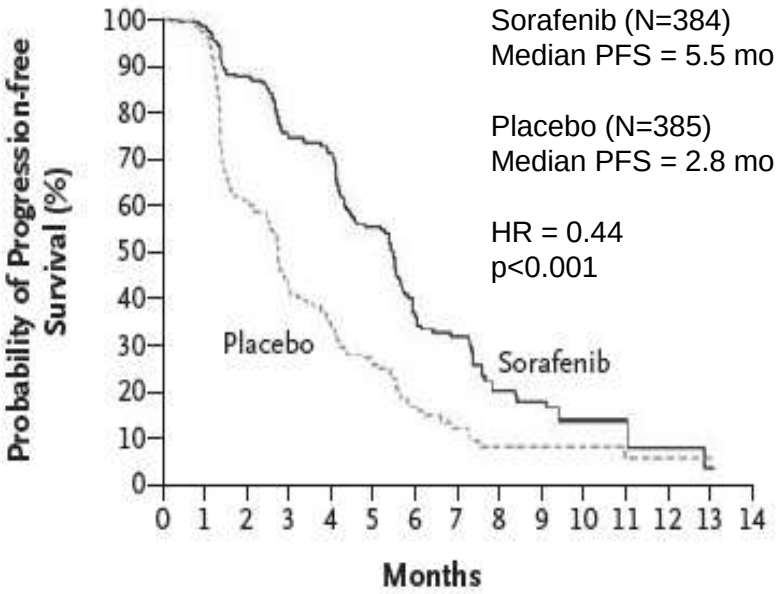


Overall Conclusions

- Robustly designed Phase 3 trial incorporating an active, targeted agent in the control arm
- Axitinib succeeded in this rigorous test, conferring clear benefit in the treatment of patients with advanced RCC
  - Statistically and clinically meaningful improvement in PFS over sorafenib
  - Overall mPFS: 6.7 vs 4.7 months ($p < 0.0001$) (HR = 0.665)
  - 2-fold improvement in ORR (19.4 vs 9.4%) with a median DR of 11 months
  - Beneficial effects observed across subgroups
  - Results in US patients consistent with the entire study population
- Superior efficacy achieved without increased risk of SAEs, Grade 3-4 AEs, or discontinuations due to AEs compared to sorafenib
  - AEs were typical for VEGFR TKIs, clinically manageable, and transient

Improvement Over Active Comparator

Sorafenib Phase 3
Registration Study (TARGET[1])

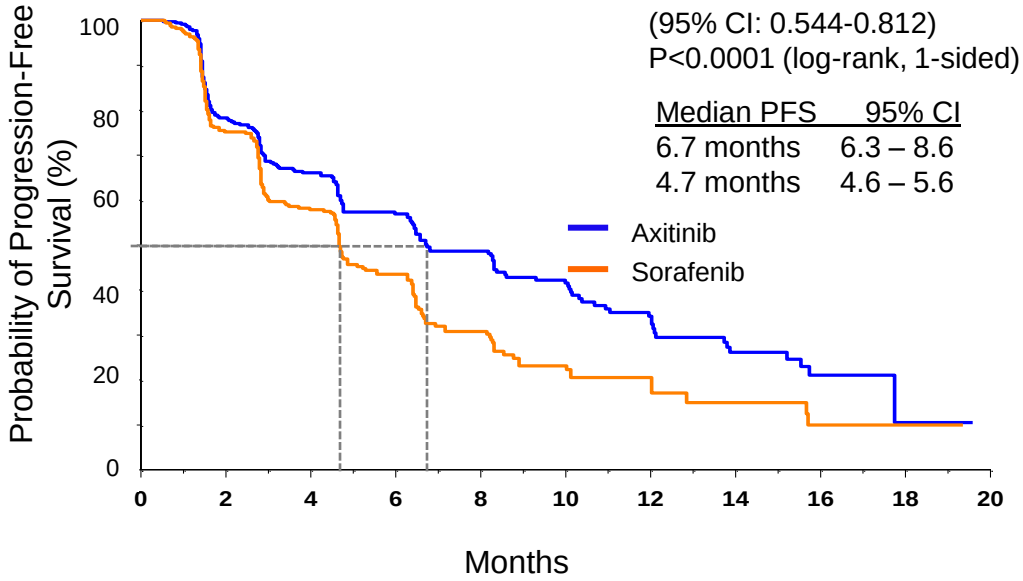


Sorafenib (N=384)
Median PFS = 5.5 mo

Placebo (N=385)
Median PFS = 2.8 mo

HR = 0.44
p<0.001

Axitinib Phase 3
Registration Study (AXIS[2])



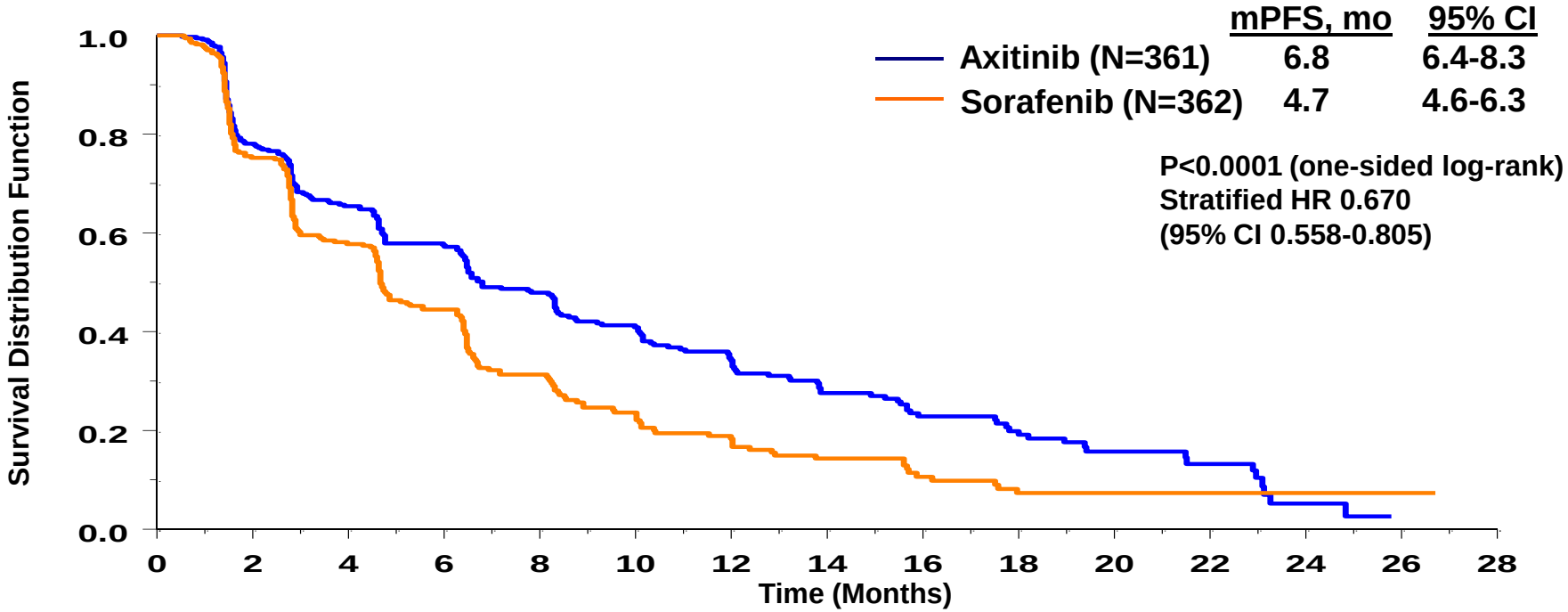
Stratified HR 0.665
(95% CI: 0.544-0.812)
P<0.0001 (log-rank, 1-sided)

Median PFS	95% CI
6.7 months	6.3 – 8.6
4.7 months	4.6 – 5.6

[1]Escudier B, et al. N Eng J Med. 2007; 356: 125-34; [2]Phase 3 study A4061032

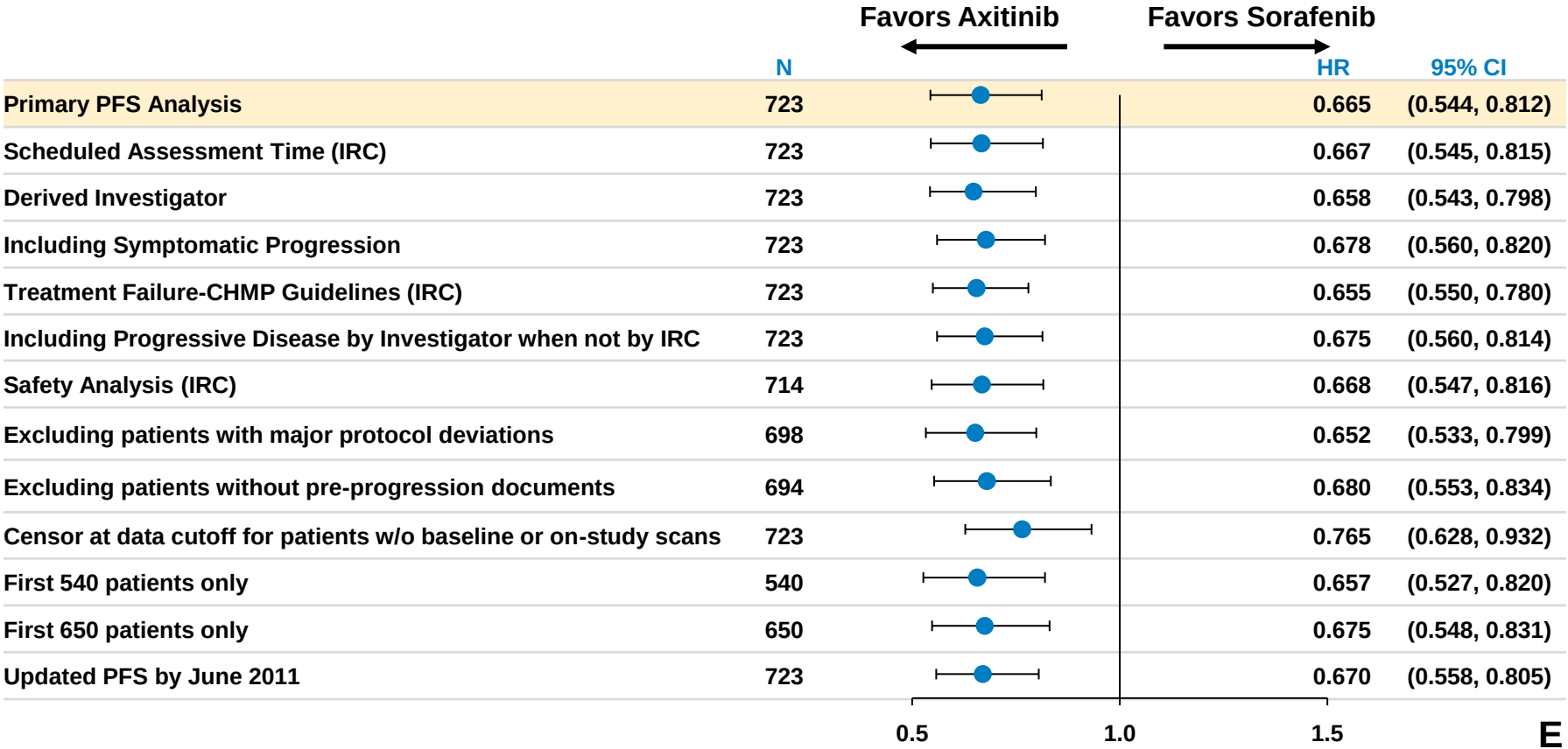
E 2

K-M curve for updated PFS (IRC) with data cutoff June 2011



At Risk															
Axitinib	361	258	204	169	126	102	77	50	35	26	15	10	3	0	0
Sorafenib	362	226	160	117	69	46	33	22	13	9	5	2	2	1	0

Robustness of PFS Effect of Axitinib Examined Using Multiple Sensitivity Analyses



Reasons for Censoring (IRC) Due to Missing Baseline or On-Study Scan

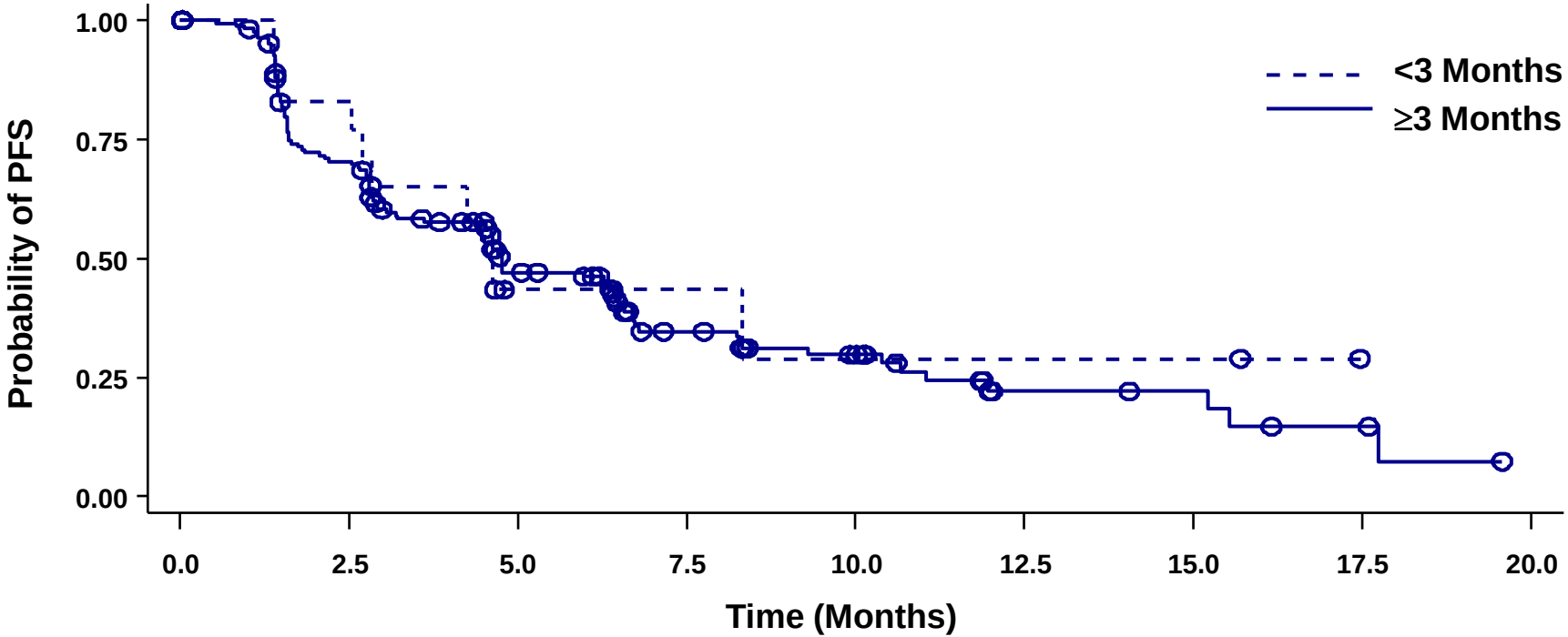
Reason for Missing Baseline or On-Study Scan	Axitinib N=14 n(%)	Sorafenib N=28 n(%)
Discontinuation Prior to First Scan		
Adverse Event	2 (14.3)	7 (25.0)
Subject Refused Continued Treatment	2 (14.3)	6 (21.4)
Protocol Violation	3 (21.4)	5 (17.9)
Global Deterioration of Health Status	1 (7.1)	1 (3.6)
Lost to Follow-up	1 (7.1)	
Other		1 (3.6)
IRC assessment unavailable	5 (35.7)	7 (32.1)
On study <6 wks		1 (3.6)

PFS (IRC) – Sensitivity Analysis 7 (Missing Baseline or On-Study Scan)

	PFS Analysis based on IRCAssessment		Sensitivity Analysis Analysis 7	
	Axitinib N=361	Sorafenib N=362	Axitinib N=361	Sorafenib N=362
Number with Event	192	210	192	210
Number Censored	169	152	169	152
Median PFS (months) (95% CI)	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	8.2 (6.4, 9.3)	4.9 (4.7, 6.4)
Hazard Ratio (95% CI)	0.665 (0.544, 0.812)		0.765 (0.628, 0.932)	
p-value (log-rank test)	<0.0001		0.0036	

Patients with missing baseline or on-study scan were censored on 31AUG2010

Progression Free Survival by Duration of Prior Sunitinib (< 3 mo. vs ≥ 3 mo.) – Axitinib Arm



Continuation on Assigned Treatment Past Progression (Investigator)

Prior therapy	Randomized group	N	PD per Investigator n (%)	Continuing on Treatment >28 days n (% of PD patients)	Continuing on Treatment >56 days n (% of PD patients)
All	Axitinib	361	187 (51.8)	50 (26.7)	35 (18.7)
	Sorafenib	362	214 (59.1)	74 (34.6)	44 (21.5)
Sunitinib	Axitinib	194	109 (56.2)	23 (21.1)	14 (12.8)
	Sorafenib	195	121 (62.1)	37 (30.6)	18 (14.9)
Cytokines	Axitinib	126	55 (43.7)	20 (36.4)	16 (29.1)
	Sorafenib	125	69 (55.2)	29 (42.0)	22 (31.9)

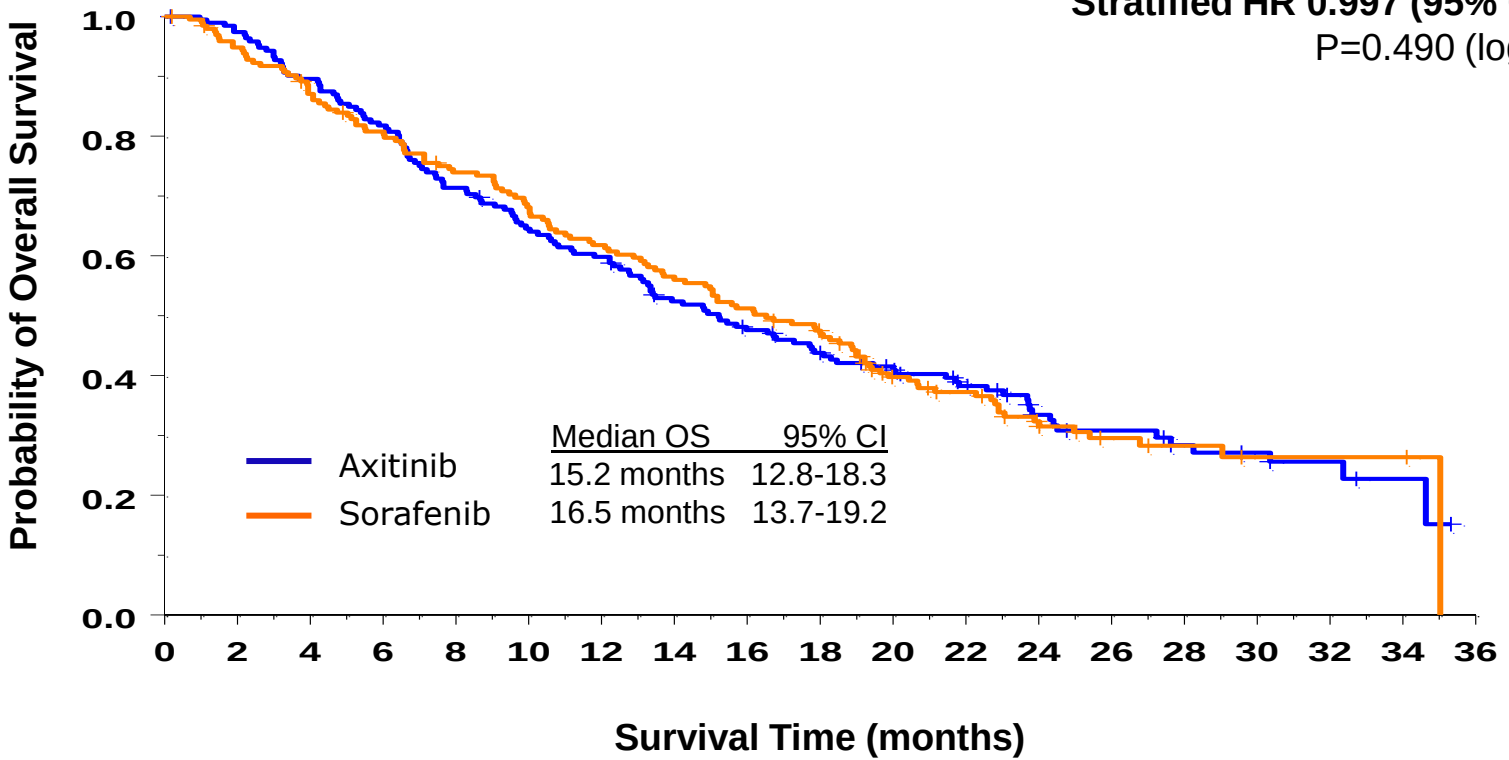
Follow-up Systemic Therapy Use (Discontinued Patients) Overall (Nov. 1, 2011 data cutoff)

	Axitinib N=320	Sorafenib N=332
Any Systemic Therapy	54%	57%
>1 Systemic Therapy	26%	27%
Everolimus	35%	34%
Sorafenib	16%	8%
Sunitinib	12%	16%
Temsirolimus[a]	6%	10%
Bevacizumab	5%	8%
Pazopanib	6%	8%

[a]Includes sirolimus

Final Overall Survival (data cutoff 1Nov2011)
Sunitinib Refractory Subgroup

Stratified HR 0.997 (95% CI 0.782-1.270)
P=0.490 (log-rank, 1-sided)



E 305

Items Included in the FKSI Scales

FKSI-15

- Lack of energy
- Bone pain
- Short of breath
- Coughing
- Hematuria
- Pain
- Bothered by fevers
- Fatigue
- Losing weight

Appetite

Side effects

Enjoying life

Worsened condition

Ability to work

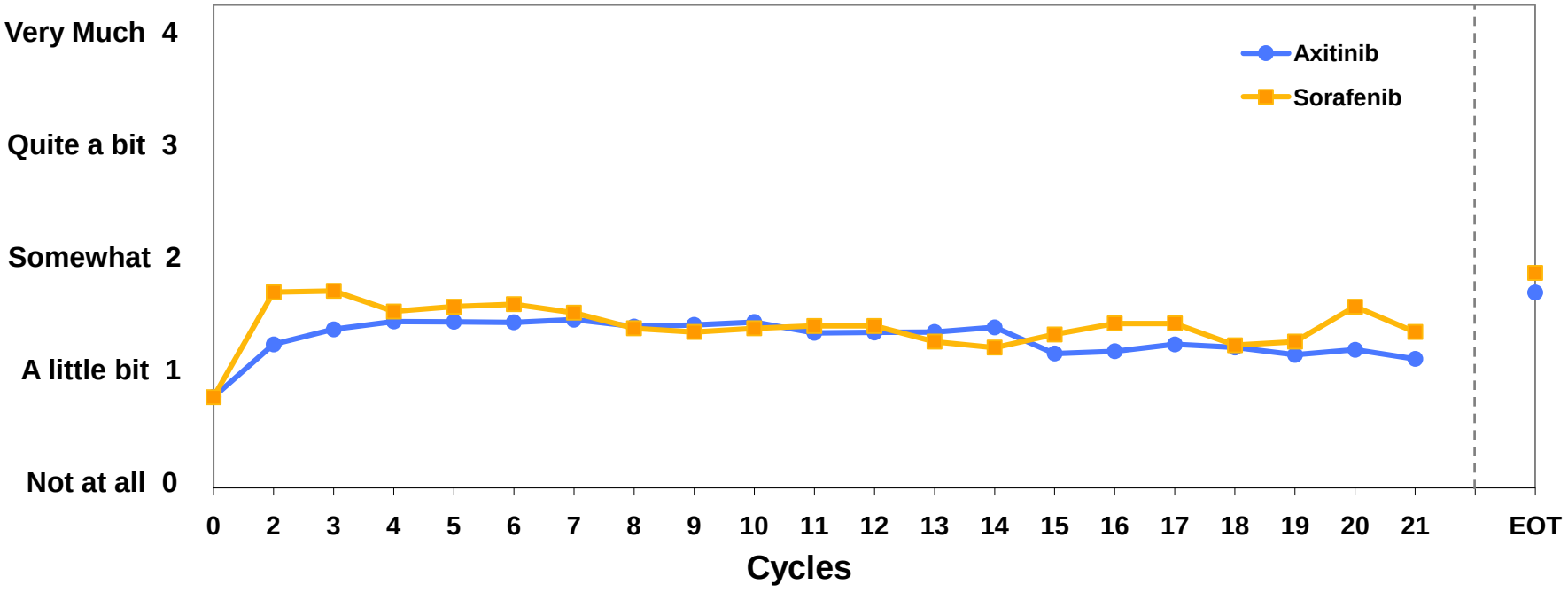
Sleep

FKSI-DRS*

- Lack of energy
- Bone pain
- Short of breath
- Coughing
- Hematuria
- Pain
- Bothered by fevers
- Fatigue
- Losing weight

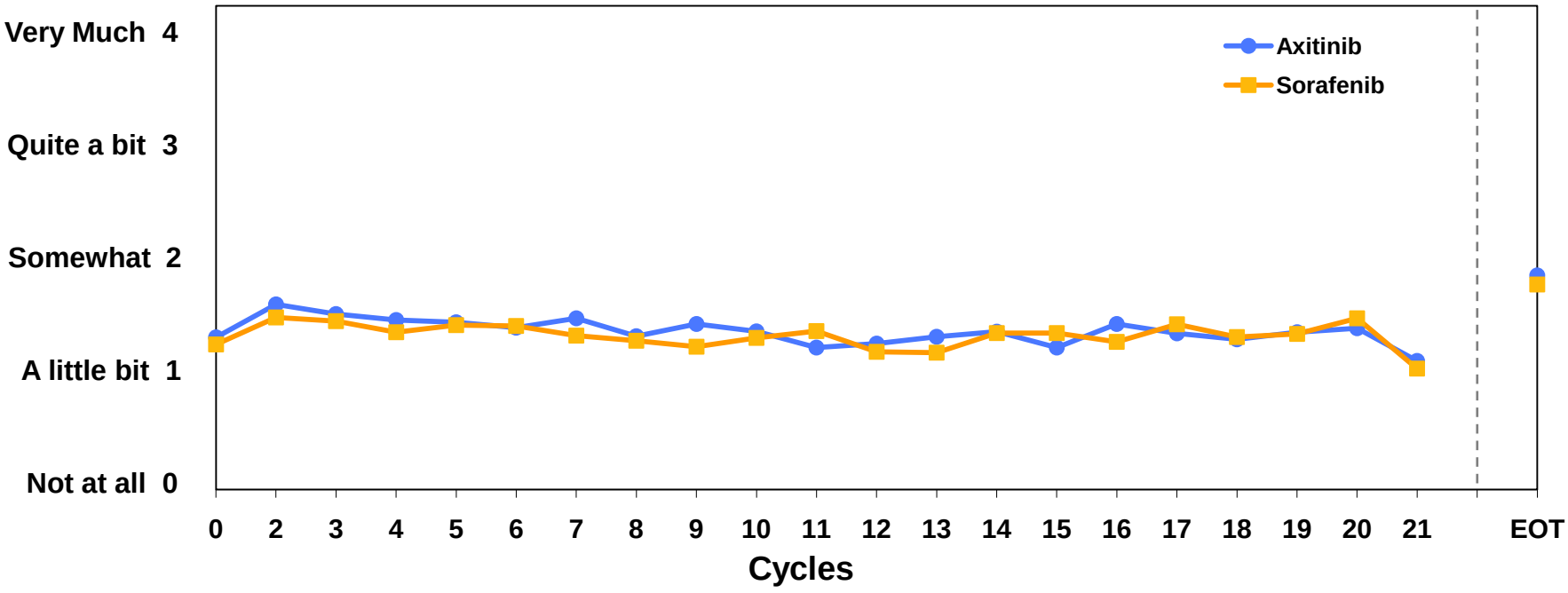
Functional Assessment of Cancer Therapy–Kidney Symptom Index–15 item (FKSI-15)
*Disease related symptoms (DRS)

FKSI-15 # 2: I Am Bothered by Side Effects of Treatment



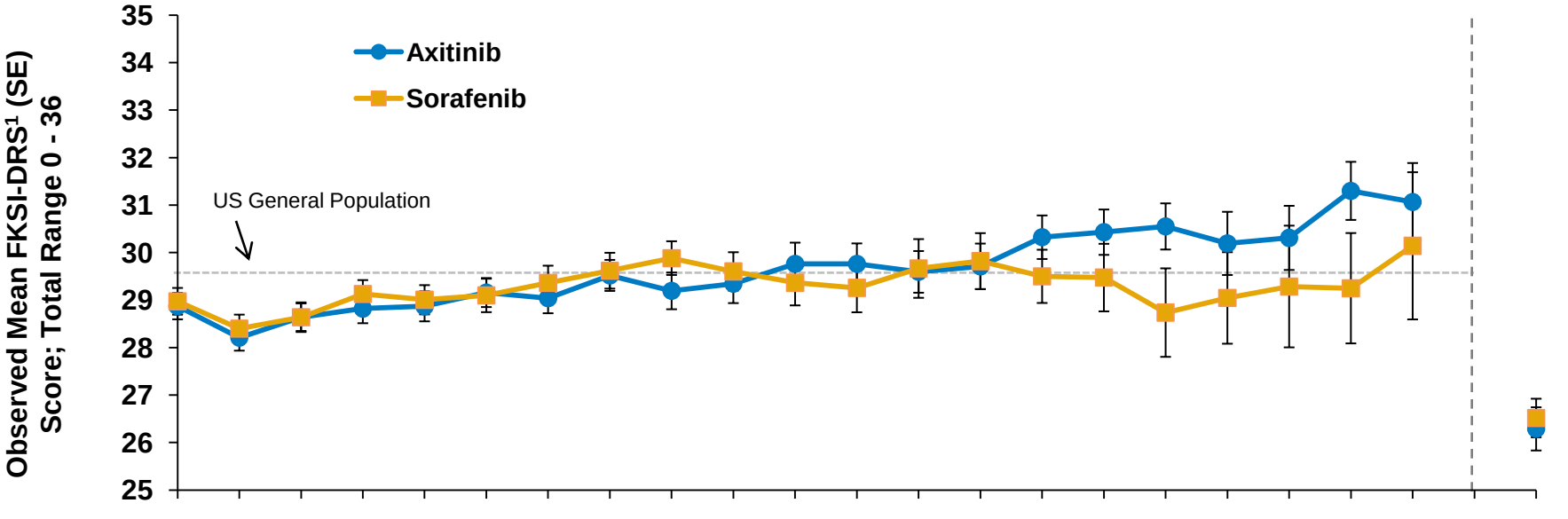
Axitinib	327	327	285	260	246	219	212	179	166	148	127	112	93	82	63	54	48	37	30	21	15	164
Sorafenib	317	302	249	226	206	181	162	139	121	98	89	73	61	57	41	36	28	22	14	12	7	193

FKSI-15 # 6: I Feel Fatigued



Axitinib	345	329	286	262	245	219	211	182	168	150	127	111	95	82	63	54	48	37	30	21	16	167
Sorafenib	342	301	250	225	206	182	161	139	121	98	87	72	61	58	41	36	30	23	14	12	7	194

Patient-reported Disease-Related Symptoms on Treatment and at End of Treatment

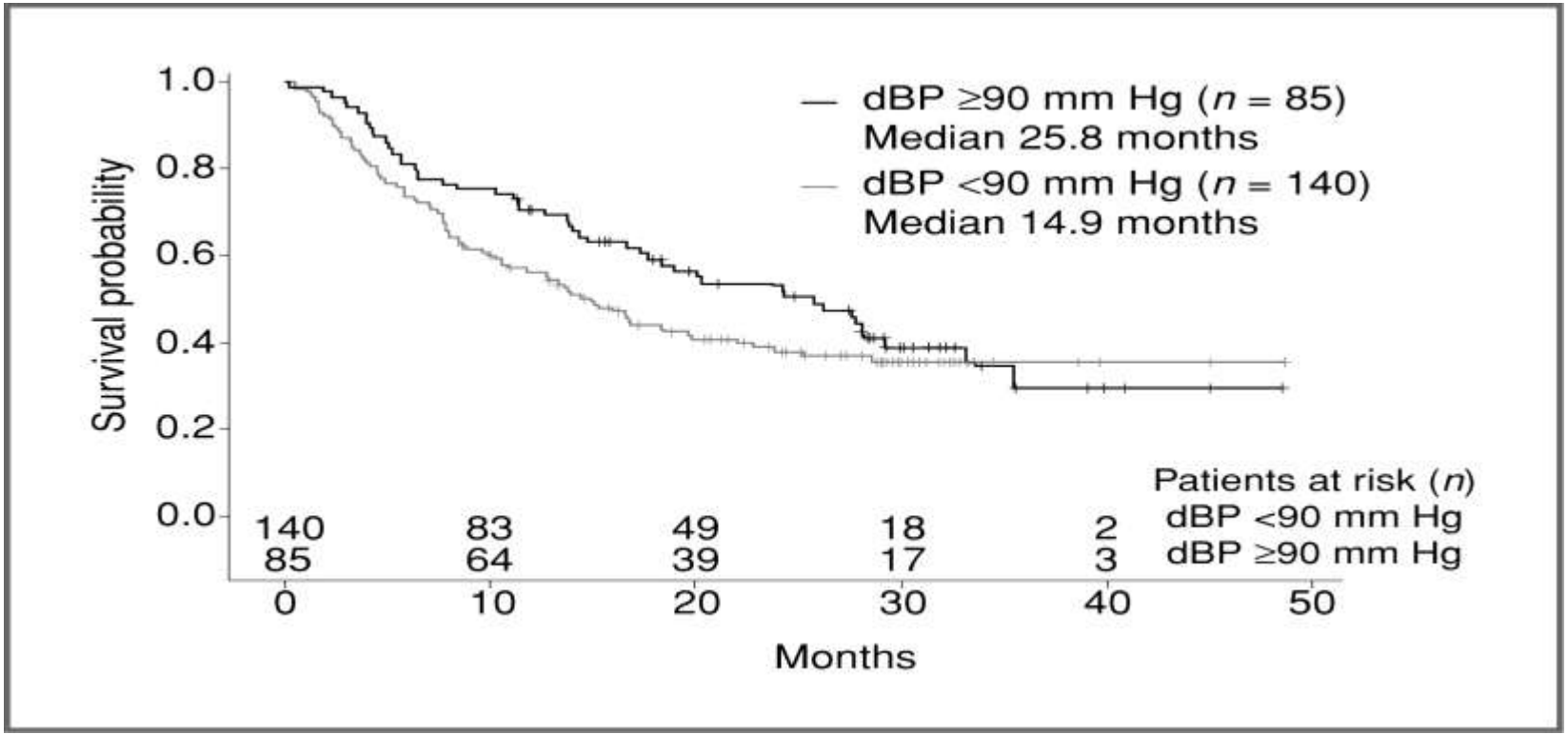


Axitinib	346	319	279	257	238	213	206	177	163	146	122	110	92	81	61	52	47	36	29	20	15	163
Sorafenib	341	296	244	220	202	178	157	135	117	96	85	70	58	54	38	34	28	22	14	12	7	191

[1]FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms

Minimally Important Difference= 3 Points

Phase 2 Studies: KM Estimates of Median Overall Survival in Patients With and Without dBP≥90 mm Hg



Rini B I et al. Clin Cancer Res 2011;17:3841-3849

Table 23. Pivotal Phase 3 RCC Study A4061032: Summary of Treatment-Emergent, All-Causality Adverse Events for ≥5% of Patients[a]

	Axitinib		Sorafenib	
Preferred Term[b]	Prior Sunitinib N=190	Prior Cytokines N=126	Prior Sunitinib N=190	Prior Cytokines N=123
	n (%)	n (%)	n (%)	n (%)
Any AEs	184 (96.8)	116 (92.1)	185 (97.4)	120 (97.6)
Diarrhea	117 (61.6)	62 (49.2)	109 (57.4)	56 (45.5)
Decreased appetite	80 (42.1)	29 (23.0)	65 (34.2)	23 (18.7)
Fatigue	76 (40.0)	45 (35.7)	71 (37.4)	30 (24.4)
Nausea	75 (39.5)	26 (20.6)	53 (27.9)	14 (11.4)
Hypertension	64 (33.7)	60 (47.6)	34 (17.9)	52 (42.3)
Dysphonia	63 (33.2)	37 (29.4)	24 (12.6)	15 (12.2)
Vomiting	60 (31.6)	16 (12.7)	44 (23.2)	10 (8.1)
Palmar-plantar erythrodysaesthesia syndrome	54 (28.4)	36 (28.6)	85 (44.7)	71 (57.7)
Asthenia	54 (28.4)	11 (8.7)	33 (17.4)	8 (6.5)
Weight decreased	53 (27.9)	25 (19.8)	42 (22.1)	23 (18.7)
Constipation	45 (23.7)	17 (13.5)	45 (23.7)	18 (14.6)
Hypothyroidism	40 (21.1)	24 (19.0)	20 (10.5)	7 (5.7)
Dyspnea	34 (17.9)	14 (11.1)	25 (13.2)	11 (8.9)
Abdominal pain	33 (17.4)	11 (8.7)	24 (12.6)	9 (7.3)
Mucosal inflammation	33 (17.4)	9 (7.1)	31 (16.3)	6 (4.9)
Arthralgia	32 (16.8)	17 (13.5)	28 (14.7)	10 (8.1)
Pain in extremity	30 (15.8)	12 (9.5)	23 (12.1)	20 (16.3)
Back pain	29 (15.3)	13 (10.3)	24 (12.6)	15 (12.2)
Headache	29 (15.3)	13 (10.3)	23 (12.1)	11 (8.9)
Cough	28 (14.7)	19 (15.1)	33 (17.4)	19 (15.4)
Stomatitis	26 (13.7)	21 (16.7)	18 (9.5)	15 (12.2)
Rash	26 (13.7)	16 (12.7)	62 (32.6)	36 (29.3)
Abdominal pain upper	23 (12.1)	4 (3.2)	11 (5.8)	2 (1.6)
Dysgeusia	23 (12.1)	12 (9.5)	14 (7.4)	11 (8.9)
Proteinuria	22 (11.6)	10 (7.9)	9 (4.7)	13 (10.6)
Dizziness	20 (10.5)	8 (6.3)	3 (1.6)	8 (6.5)
Dry skin	20 (10.5)	9 (7.1)	19 (10.0)	10 (8.1)
Pyrexia	18 (9.5)	5 (4.0)	25 (13.2)	10 (8.1)
Disease progression	17 (8.9)	2 (1.6)	12 (6.3)	1 (0.8)
Dyspepsia	16 (8.4)	17 (13.5)	5 (2.6)	3 (2.4)
Insomnia	15 (7.9)	11 (8.7)	10 (5.3)	4 (3.3)
Dehydration	14 (7.4)	7 (5.6)	6 (3.2)	1 (0.8)
Epistaxis	14 (7.4)	6 (4.8)	9 (4.7)	4 (3.3)
Pruritus	14 (7.4)	6 (4.8)	22 (11.6)	18 (14.6)
Hypotension	14 (7.4)	4 (3.2)	7 (3.7)	1 (0.8)
Myalgia	13 (6.8)	9 (7.1)	6 (3.2)	3 (2.4)
Chest pain	13 (6.8)	3 (2.4)	9 (4.7)	3 (2.4)
Musculoskeletal pain	12 (6.3)	3 (2.4)	17 (8.9)	3 (2.4)
Oropharyngeal pain	12 (6.3)	7 (5.6)	13 (6.8)	4 (3.3)
Anxiety	11 (5.8)	0	5 (2.6)	1 (0.8)
Edema peripheral	10 (5.3)	3 (2.4)	13 (6.8)	5 (4.1)
Urinary tract infection	10 (5.3)	2 (1.6)	10 (5.3)	1 (0.8)
Paresthesia	10 (5.3)	0	8 (4.2)	4 (3.3)
Musculoskeletal chest pain	10 (5.3)	5 (4.0)	8 (4.2)	2 (1.6)
Flatulence	9 (4.7)	7 (5.6)	5 (2.6)	2 (1.6)
Anemia	9 (4.7)	2 (1.6)	29 (15.3)	7 (5.7)

Part 1 of 2

Table 23. Pivotal Phase 3 RCC Study A4061032: Summary of Treatment-Emergent, All-Causality Adverse Events for ≥5% of Patients[a]

	Axitinib		Sorafenib	
Muscle spasms	8 (4.2)	2 (1.6)	11 (5.8)	2 (1.6)
Pain	7 (3.7)	8 (6.3)	10 (5.3)	3 (2.4)
Alopecia	7 (3.7)	6 (4.8)	59 (31.1)	44 (35.8)
Erythema	5 (2.6)	2 (1.6)	23 (12.1)	11 (8.9)
Dry mouth	5 (2.6)	7 (5.6)	5 (2.6)	0
Lipase increased	4 (2.1)	5 (4.0)	2 (1.1)	16 (13.0)
Malaise	3 (1.6)	3 (2.4)	1 (0.5)	7 (5.7)
ALT increased	3 (1.6)	4 (3.2)	6 (3.2)	7 (5.7)
Rectal hemorrhage	1 (0.5)	7 (5.6)	4 (2.1)	1 (0.8)
Blood amylase increased	1 (0.5)	5 (4.0)	2 (1.1)	11 (8.9)
Pain of skin	1 (0.5)	0	12 (6.3)	2 (1.6)
Hypophosphatemia	0	0	6 (3.2)	7 (5.7)

AE = adverse event; ALT = alanine aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; n = number of patients fitting specified criteria

[a] Either treatment arm, by decreasing frequency based on axitinib-treated patients who received prior sunitinib.

[b] MedDRA (version 13.1) coding dictionary applied.

Part 2 of 2

MSKCC 1999 vs 2004

Criteria	1999 First Line mRCC	2004 Second Line mRCC
Hemoglobin	Yes	Yes
Corrected Calcium	Yes	Yes
ECOG PS	No	0 vs. 1
LDH	Yes	N/A
Nephrectomy	Yes	N/A

Motzer RJ, et al. *J Clin Oncol* 1999;17:2530-40

Motzer RJ, Bacik, J, et al. *J Clin Oncol* 2004;22:454-463

Prior Systemic Therapy based on IVRS data in Bevacizumab Subgroup

	Axitinib N=29	Sorafenib N=30
Bevacizumab + IFN alfa*	**17**	**18**
Bevacizumab + Temsirolimus	**7**	**8**
Bevacizumab + Other	**5**	**4**

*eCRF data-Bevacizumab containing regimen:axitinib N=31 (8.6%) and sorafenib N=29 (8.0%)

1 subject stratified to previous cytokine-containing regimen and 1 subject stratified to previous sunitinib-containing regimen; however eCRF data indicates previous bevacizumab-containing regimen

1 subject stratified to previous bevacizumab-containing regimen; however eCRF data indicates previous temsirolimus-containing regimen