Tivozanib for the Treatment of Advanced Renal Cell Carcinoma (RCC) in Adults

Meeting of the Oncologic Drugs Advisory Committee (ODAC)

May 2, 2013

Introduction

Bill Slichenmyer, MD, ScM
Chief Medical Officer
Aveo Oncology

Proposed Indication

Tivozanib for the treatment of advanced renal cell carcinoma (RCC)

Unmet Need

- Treatment for RCC has improved with introduction of targeted Tyrosine Kinase Inhibitors (TKIs)
- Toxicities may limit tolerability
- Additional options needed

Tivozanib is a TKI That Targets All 3 VEGF Receptors

- Angiogenesis inhibition via VEGFR 1-3
  - High potency and VEGFR selectivity
- Broad anti-tumor activity in pre-clinical models
- TKI class demonstrates consistent efficacy in RCC
  - Proof of concept demonstrated in Phase 2

Basis for NDA

- Positive phase 3 trial
- Tivozanib has greater efficacy compared with sorafenib, an approved multi-targeted TKI
- Safety profile as expected for a highly selective VEGFR inhibitor
- OS confounded by cross-over and more use of subsequent therapy in control arm
- Favorable benefit-risk profile was demonstrated

Tivozanib Agenda

Background on RCC and Unmet Need	**Daniel George, MD** Associate Professor of Medicine and Surgery Division of Medical Oncology; Division of Urology Duke University Medical Center
Efficacy & Safety	**Anna Berkenblit, MD** VP, Clinical Development AVEO Oncology
Clinical Interpretation & Benefit-risk	**Robert Motzer, MD** Attending Physician Memorial Sloan-Kettering Cancer Center, NY, NY

Additional Experts

Renal Cell Carcinoma	**Toni Choueiri, MD** Director of Kidney Cancer Center Dana Farber Cancer Institute, Boston, MA
Quality of Life	**David Cella, Ph.D.** Professor and Chair Northwestern University Feinberg School of Medicine, Chicago, IL
	Cristina Ivanescu, Ph.D. Principal Consultant Quintiles, Inc.
Independent Radiology Review	**Rick Patt, MD** Co-Founder/Principal, RadMD, New York, NY
Cardiology	**Guilherme Oliveira, MD** Staff, Cardio-Oncology Center Cleveland Clinic, OH

Background on RCC and Unmet Need

Daniel George, MD

Associate Professor of Medicine and Surgery

Division of Medical Oncology; Division of Urology

Director of Genitourinary Oncology

Duke Cancer Institute

Therapy Needs in Newly Diagnosed Metastatic Renal Cell Carcinoma

- Effective therapy
  - VEGFR inhibition is standard of care
- VEGFR products with different tolerability profile
  - Allow physicians to match to patient health and lifestyle

Therapeutic Strategies Based on the Biology of Clear Cell RCC

- 3 treatment modalities
  - VEGF pathway inhibition
  - mTOR signaling inhibition
  - Immune system modulation
- VEGFR inhibition with oral TKI is standard of care for RCC therapy
  - Sorafenib, sunitinib, pazopanib, axitinib

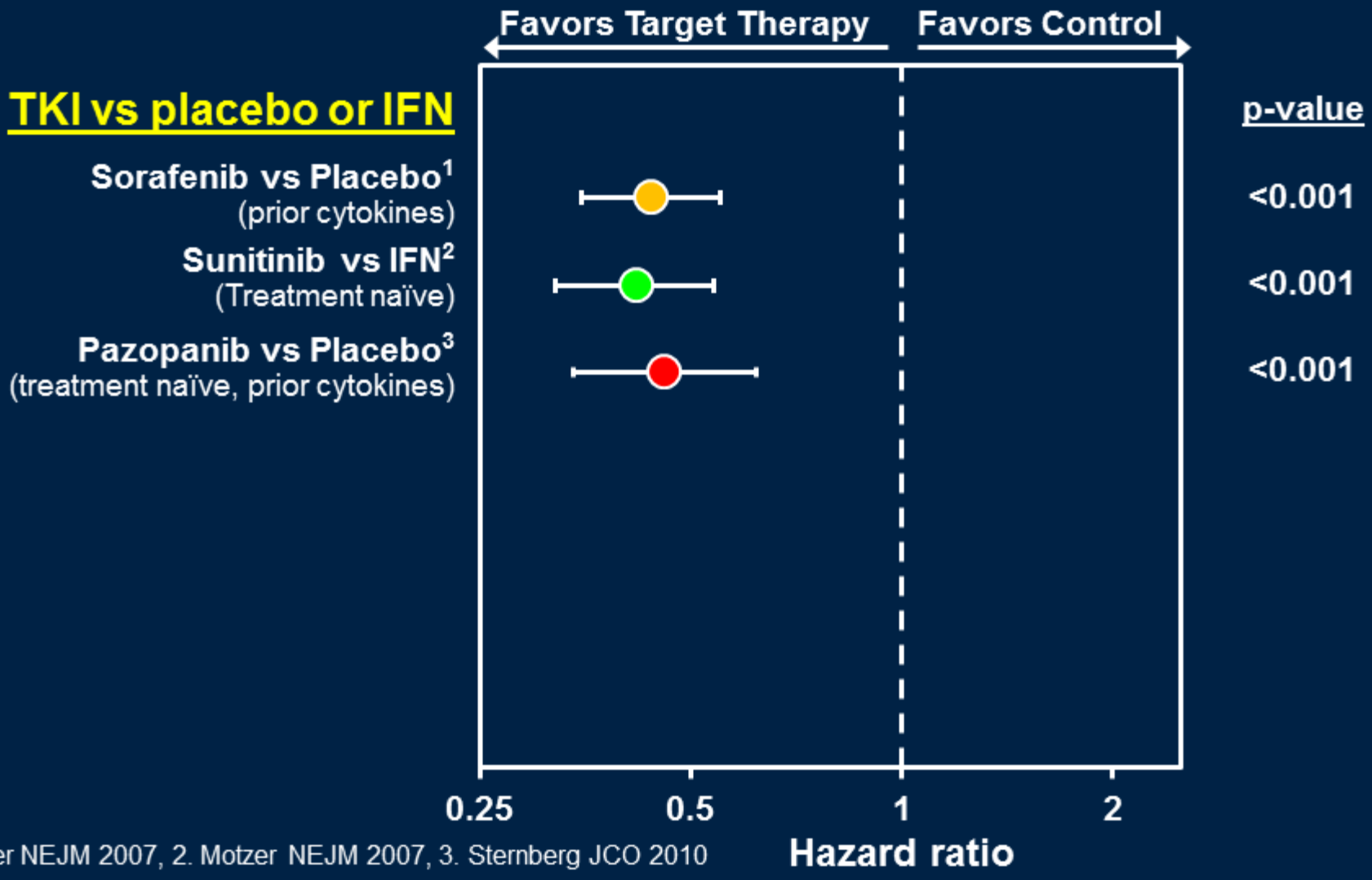
McDermott , *J Clin Oncol* (2005): Yang, *J Clin Oncol* (2003); Motzer, *J Clin Oncol* (2006); www.NCCN.org (2013)

NCCN Guidelines Recommend TKIs for Treatment of Clear Cell RCC

Setting	Prior Therapy	Level 1	≥ Level 2
1st Line	-	Sunitinib Pazopanib	Sorafenib
2nd Line	Prior cytokine	Sorafenib Sunitinib Pazopanib Axitinib	
	Prior VEGF TKI	Axitinib	Sorafenib Sunitinib Pazopanib

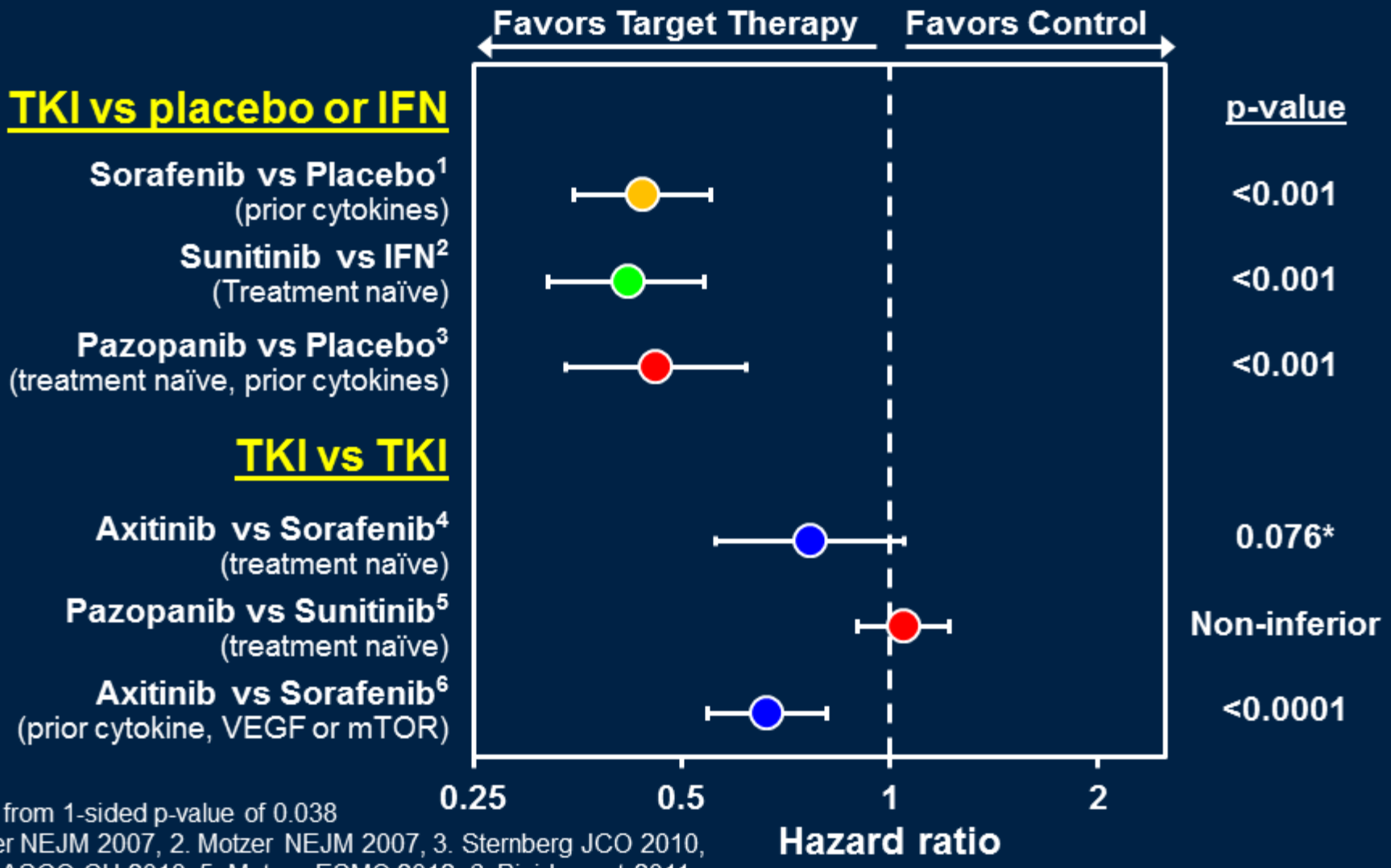
www.NCCN.org (2013)

Initial TKI Approvals Were Based on PFS Benefit Over Placebo or IFN



1. Escudier NEJM 2007, 2. Motzer NEJM 2007, 3. Sternberg JCO 2010

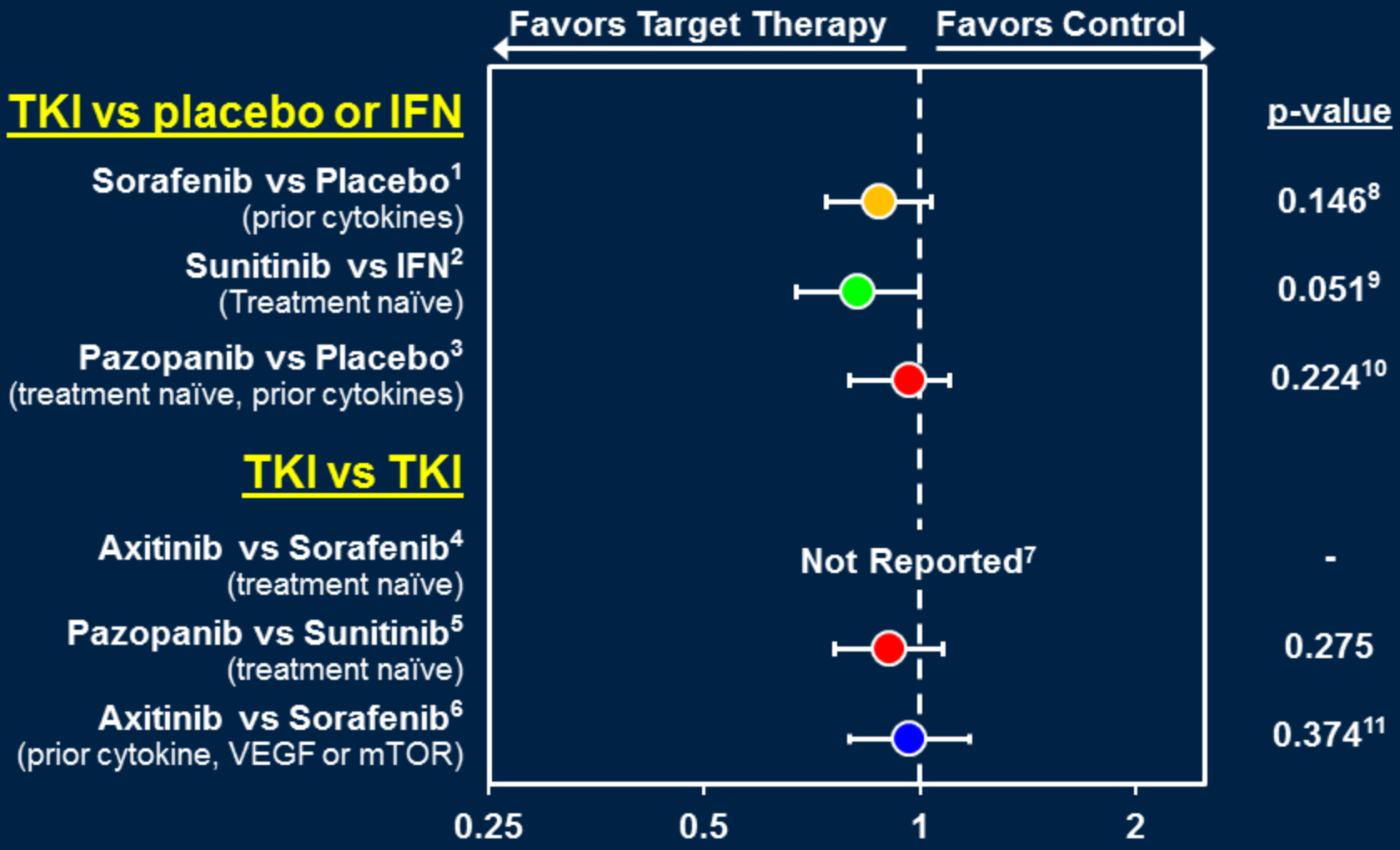
Newer Trials Compare PFS between TKIs



* Adapted from 1-sided p-value of 0.038

1. Escudier NEJM 2007, 2. Motzer NEJM 2007, 3. Sternberg JCO 2010,
4. Hutson ASCO-GU 2013, 5. Motzer ESMO 2012, 6. Rini Lancet 2011,

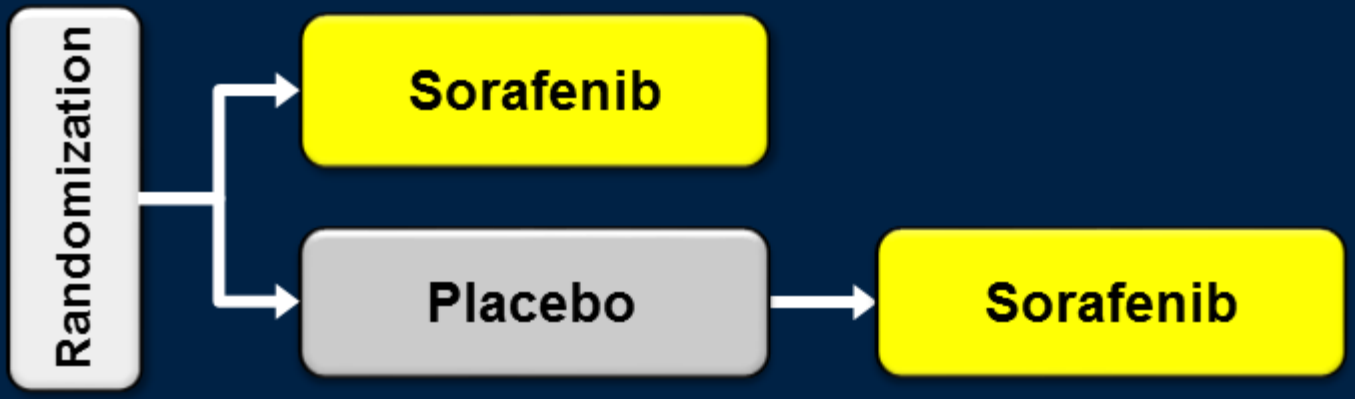
TKI Trials Showed No Overall Survival Difference



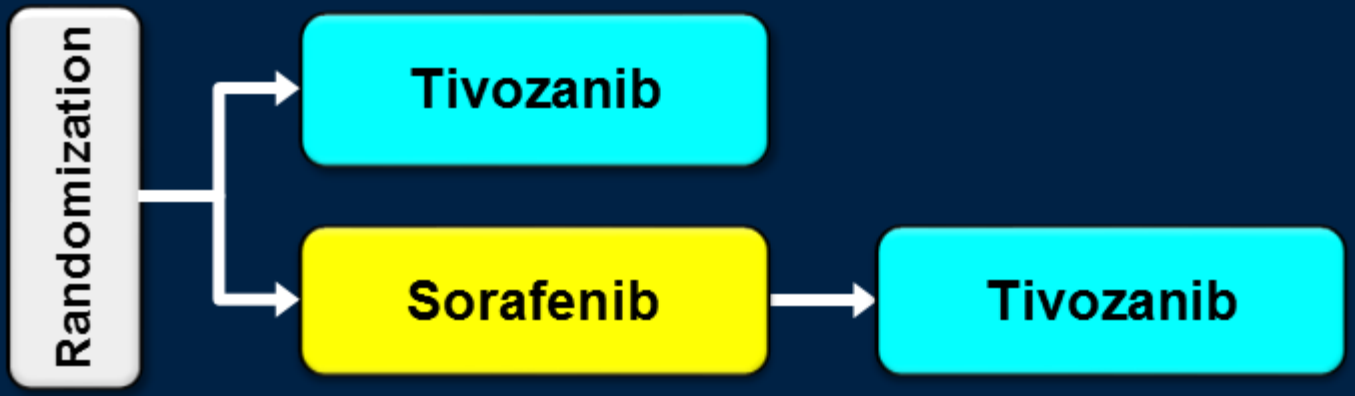
1. Escudier NEJM 2007, 2. Motzer NEJM 2007, 3. Sternberg JCO 2010, 4. Hutson ASCO-GU 2013, 5. Motzer ESMO 2012, 6. Rini Lancet 2011, 7. Hutson ASCO GU 2013, 8. Negrier Med Onc 2009, 9. Motzer, JCO 2009, 10. Sternberg Eur J Can 2013, 11. Motzer ESMO 2012

Subsequent TKI Use Confounds OS

1. 1 TKI vs 1 TKI (e.g., Sorafenib Trial[1])



2. 1 TKI vs 2 TKIs (Study 301)



1. Escudier, NEJM 2007

Adverse Events Commonly Reported for TKIs

- Hypertension
- HFS
- Diarrhea
- Fatigue
- LFT abnormalities
- Myelosuppression

Sutent PI. 2012, Sternberg JCO (2010) Nexavar PI, 2012, Inlyta PI, 2012

Adverse Events Commonly Associated with VEGFR Inhibition

	Adverse Events (All Grades)				Lab Abnormalities (All Grades)		
VEGFR TKI	HTN (%)	HFS (%)	Diarrhea (%)	Fatigue (%)	ALT Increased (%)	Thrombo-cytopenia (%)	Anemia (%)
Sunitinib[1]	34	29	66	62	51	68	79
Sorafenib[2]	17	30	43	37	NR	12	44
Pazopanib[3]	40	6	52	19	53	32	NR
Axitinib[4]	40	27	55	39	22	15	35

HTN = Hypertension; HFS = hand-foot syndrome; ALT = alanine aminotransferase; NR = not reported

1. Sutent PI (2012), 2 Nexavar PI (2012), 3. Votrient PI (2012), 4. Inlyta PI (2012)

New TKI Therapies Are Needed in RCC

- VEGFR TKIs are standard of care in RCC
  - Associated with chronic AEs and intolerability that impact daily activities
- Access to treatments with different AE profiles

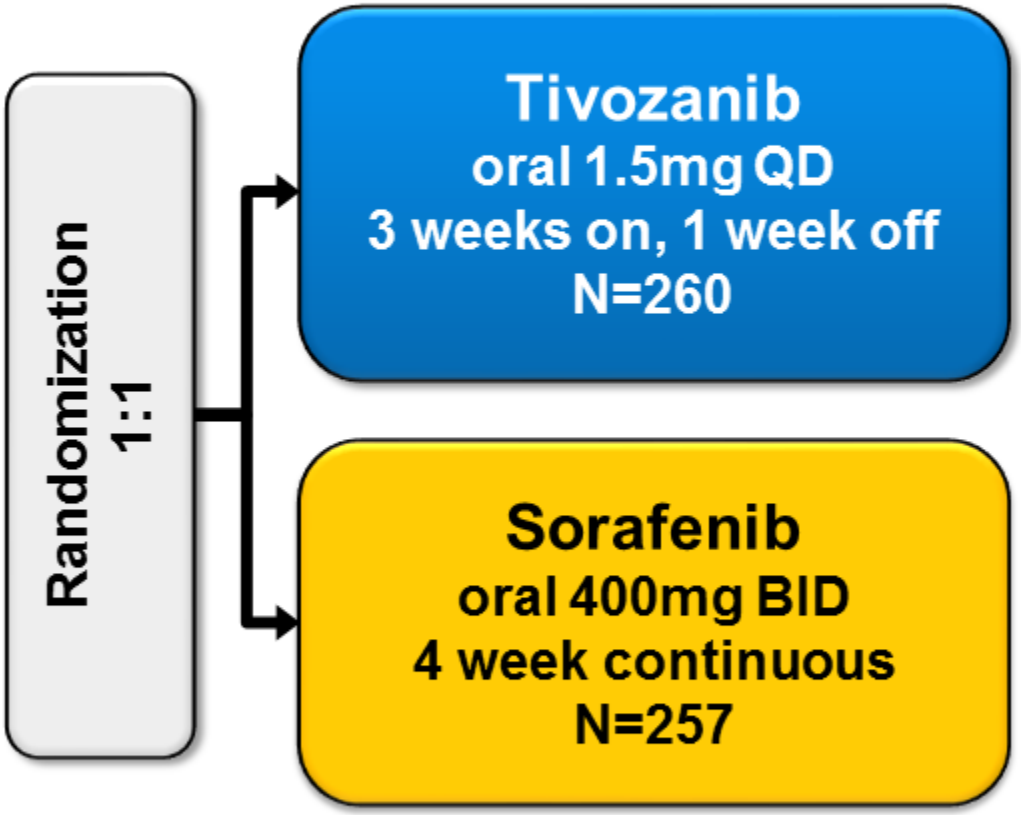
Tivozanib Efficacy & Safety

Anna Berkenblit, MD
VP, Clinical Development
AVEO Oncology

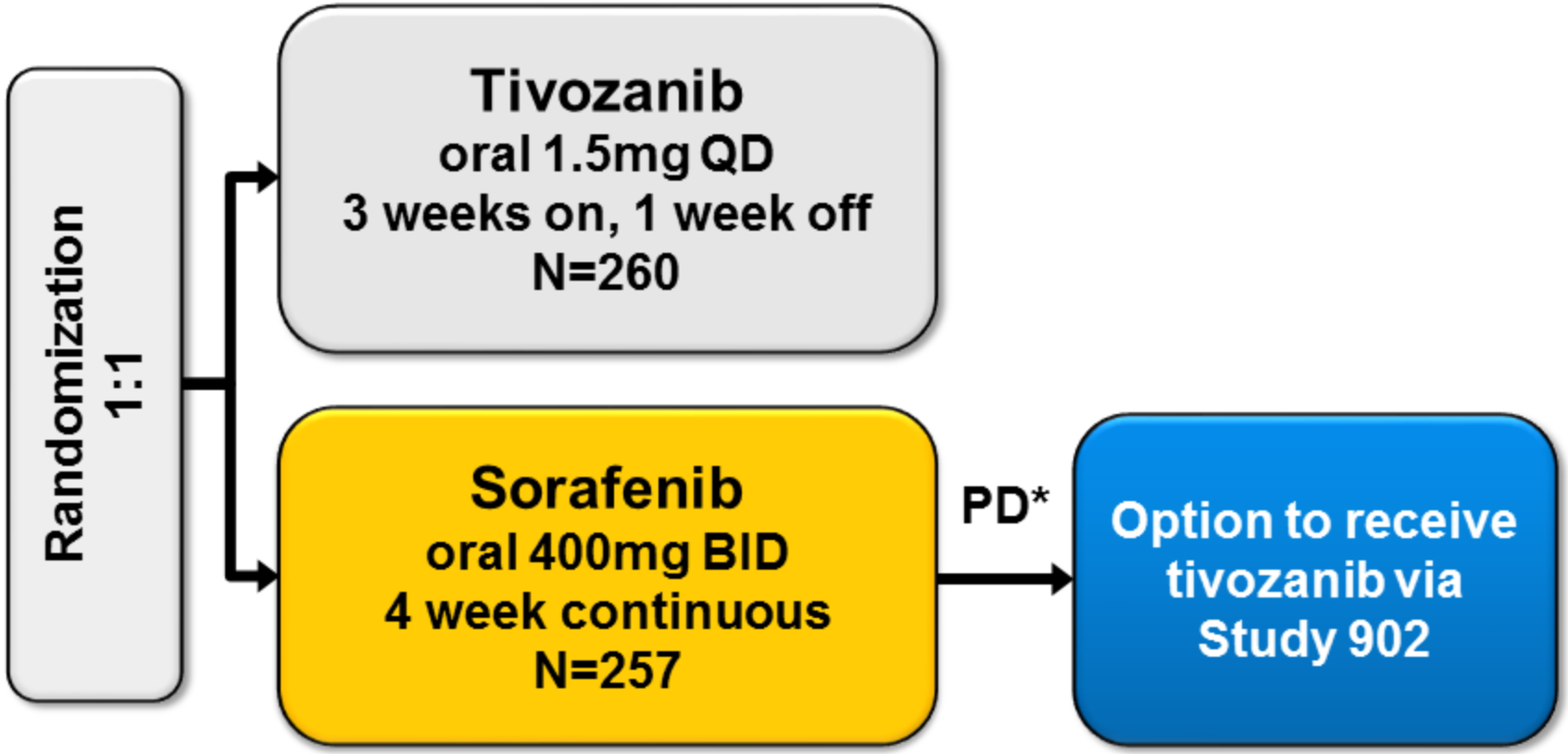
Tivozanib Efficacy & Safety in RCC Demonstrated by Pivotal Study 301

- Study 301 Design
- Study 301 Efficacy
- Study 301 Safety
- Study 301 Overall Survival

Study 301 Compared Tivozanib Versus Sorafenib in Patients with RCC



Sorafenib Patients With PD Could Receive Tivozanib (Study 902)



* Radiographic evidence of PD needed to enter Study 902

Study 301 RCC Eligibility Criteria

- RCC with clear cell component
- Nephrectomy (partial or complete)
- Measurable disease per RECIST version 1.0
- No or 1 prior systemic treatment for metastatic RCC
  - No prior VEGF or mTOR-targeted treatment
- ECOG performance status 0 or 1

Study 301 Stratified Based on 3 Criteria

- Prior treatment for RCC (0 or 1)
- # of metastatic sites (1 or ≥ 2)
- Geographic region
  - Central / Eastern Europe (CEE) = 88%
  - N. America* / Western Europe = 8%
  - Rest of World = 4%

* 16 (3%) from US

Study 301 Key Endpoints

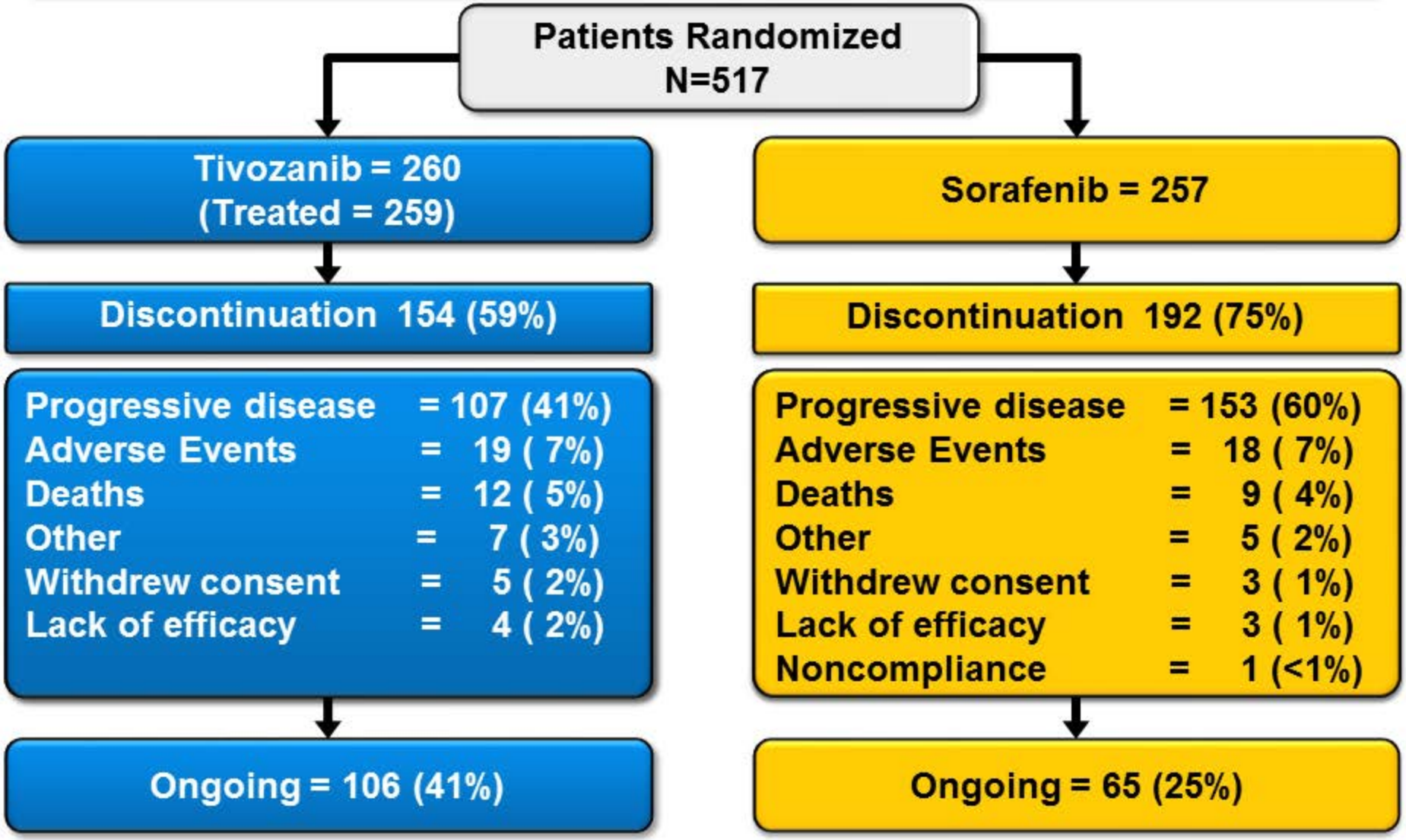
- Primary: PFS by Independent Radiology Review (IRR)
  - PFS analysis at 310 events by IRR
  - 2-sided $\alpha = 0.05$
- Key secondary endpoints
  - Overall Response Rate (ORR)
  - Overall Survival (OS)
  - Quality of Life (QoL)

Demographics & Disease Characteristics Generally Balanced

Study 301 Enrollment Characteristics	Tivozanib (N=260*)	Sorafenib (N=257)
Median age, years (range)	59 (23 – 83)	59 (23 – 85)
Male	71%	74%
ECOG PS 0	45%	54%
# Sites Involved (≥ 2)	94%	93%
# Organs Involved (≥ 2)	71%	66%
Prior Systemic Therapy (0)	70%	70%
MSKCC Prognostic Group		
Favorable	27%	34%
Intermediate	67%	62%
Poor	7%	4%

* 1 patient was randomized to tivozanib but not treated

Study 301: Subject Disposition



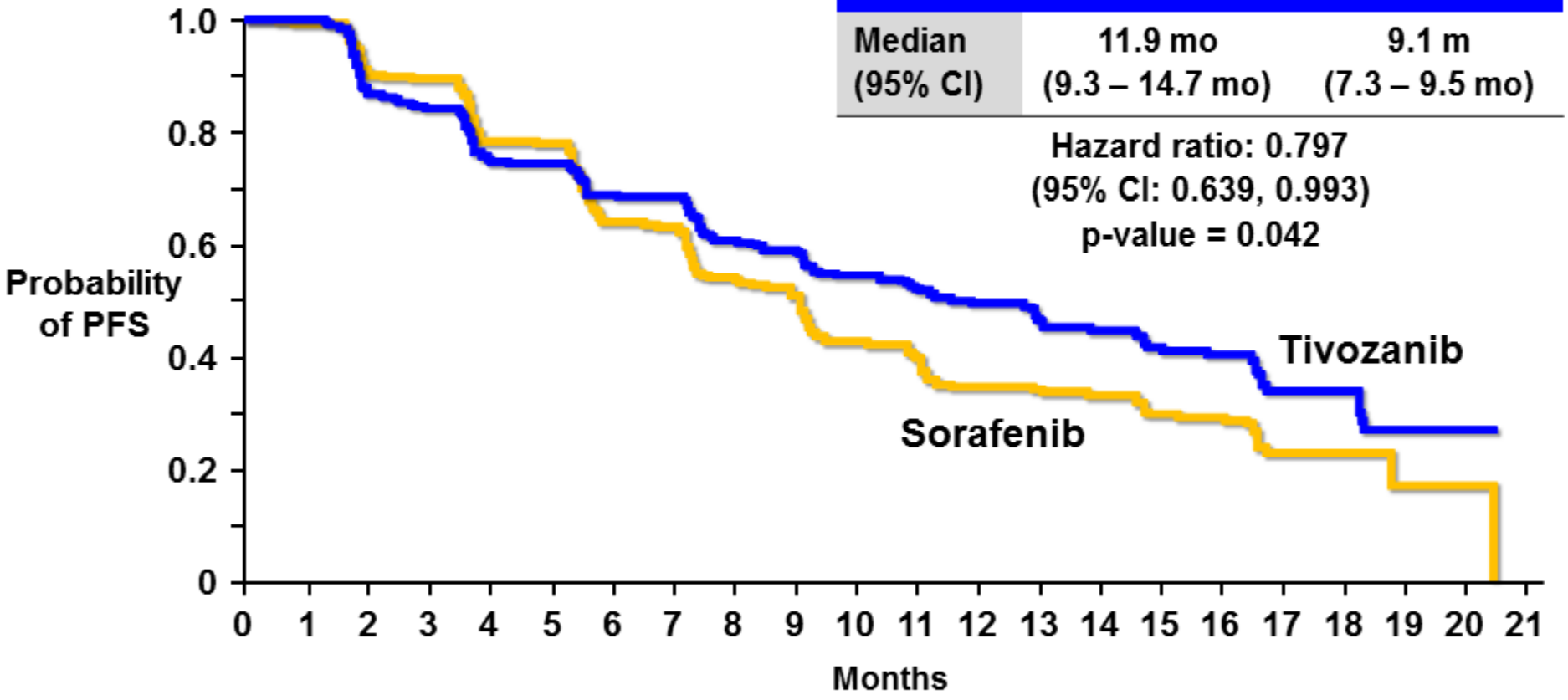
Tivozanib Efficacy & Safety in RCC Demonstrated by Pivotal Study 301

- Study 301 Design
- Study 301 Efficacy
- Study 301 Safety
- Study 301 Overall Survival

Study 301 Met Primary Endpoint PFS

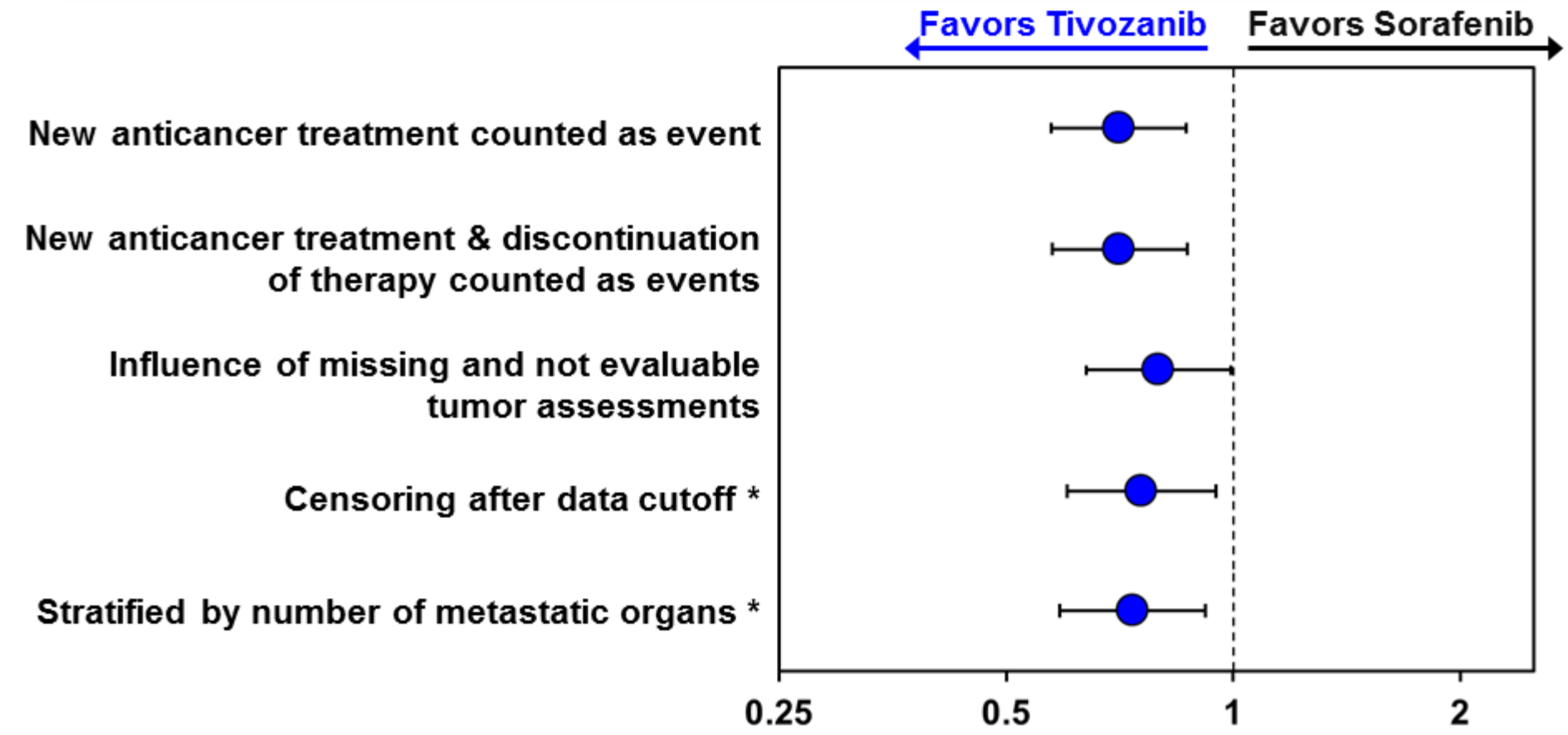
	Tivozanib N=260	Sorafenib N=257
Median (95% CI)	11.9 mo (9.3 – 14.7 mo)	9.1 m (7.3 – 9.5 mo)

Hazard ratio: 0.797
(95% CI: 0.639, 0.993)
p-value = 0.042



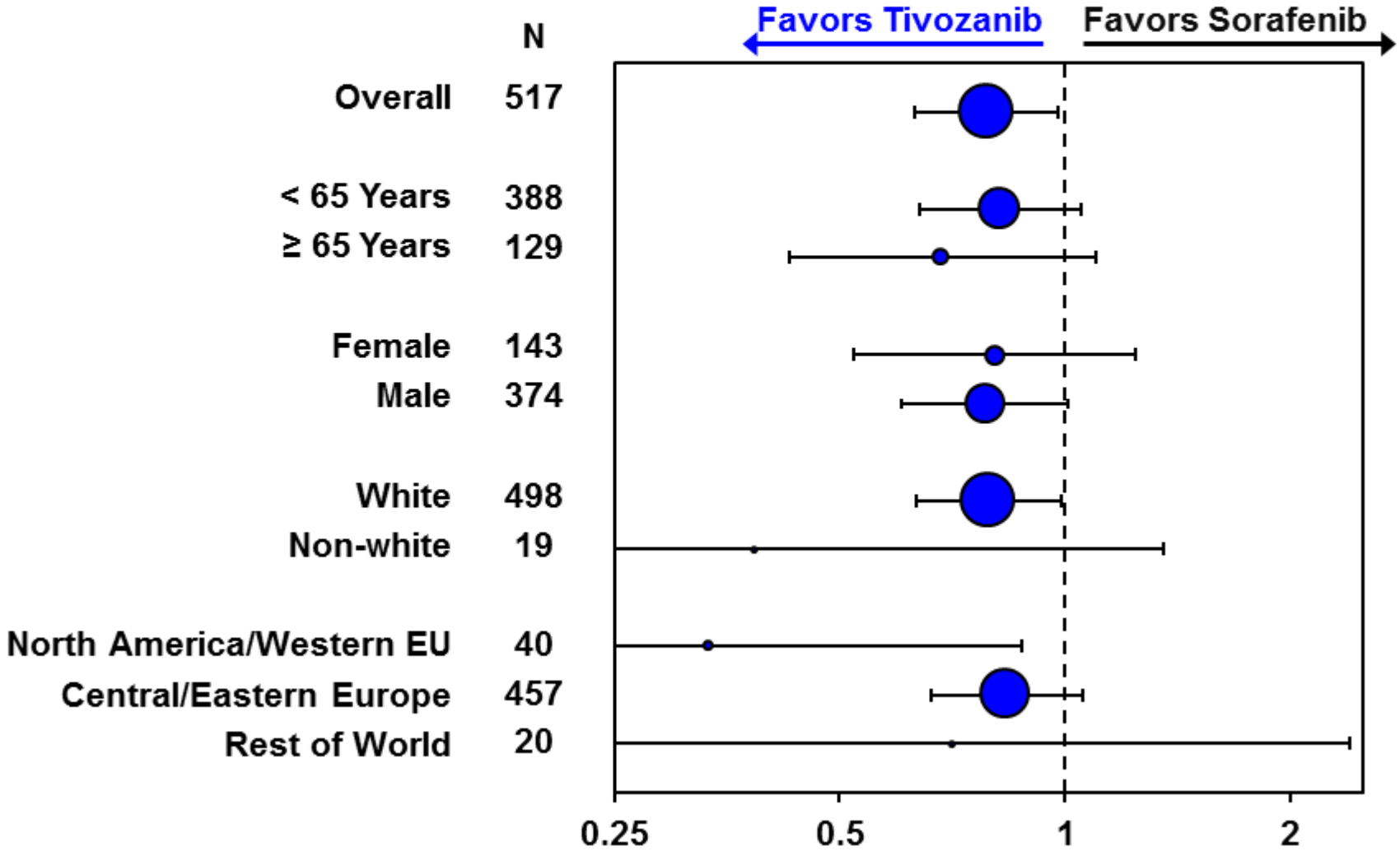
# At Risk																						
Tivozanib	260	257	217	210	181	179	164	163	144	140	126	117	109	100	94	68	65	29	29	2	2	0
Sorafenib	257	253	218	212	184	183	146	144	120	113	91	84	73	68	64	46	44	19	18	2	2	0

Study 301 PFS Sensitivity Analyses Demonstrate Consistency of Results

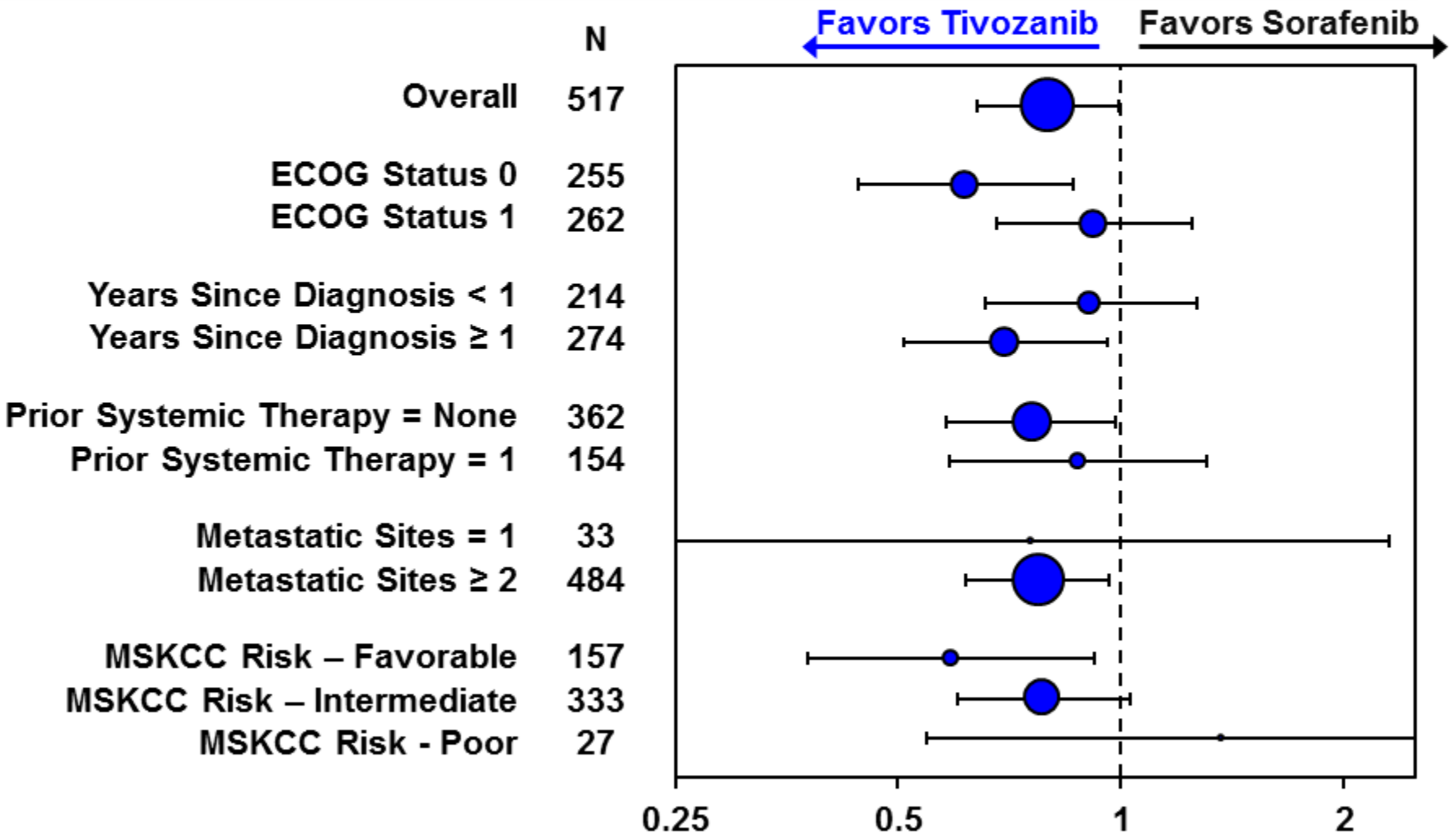


* Not pre-specified in SAP

Tivozanib PFS Benefit Across Demographic Subgroups



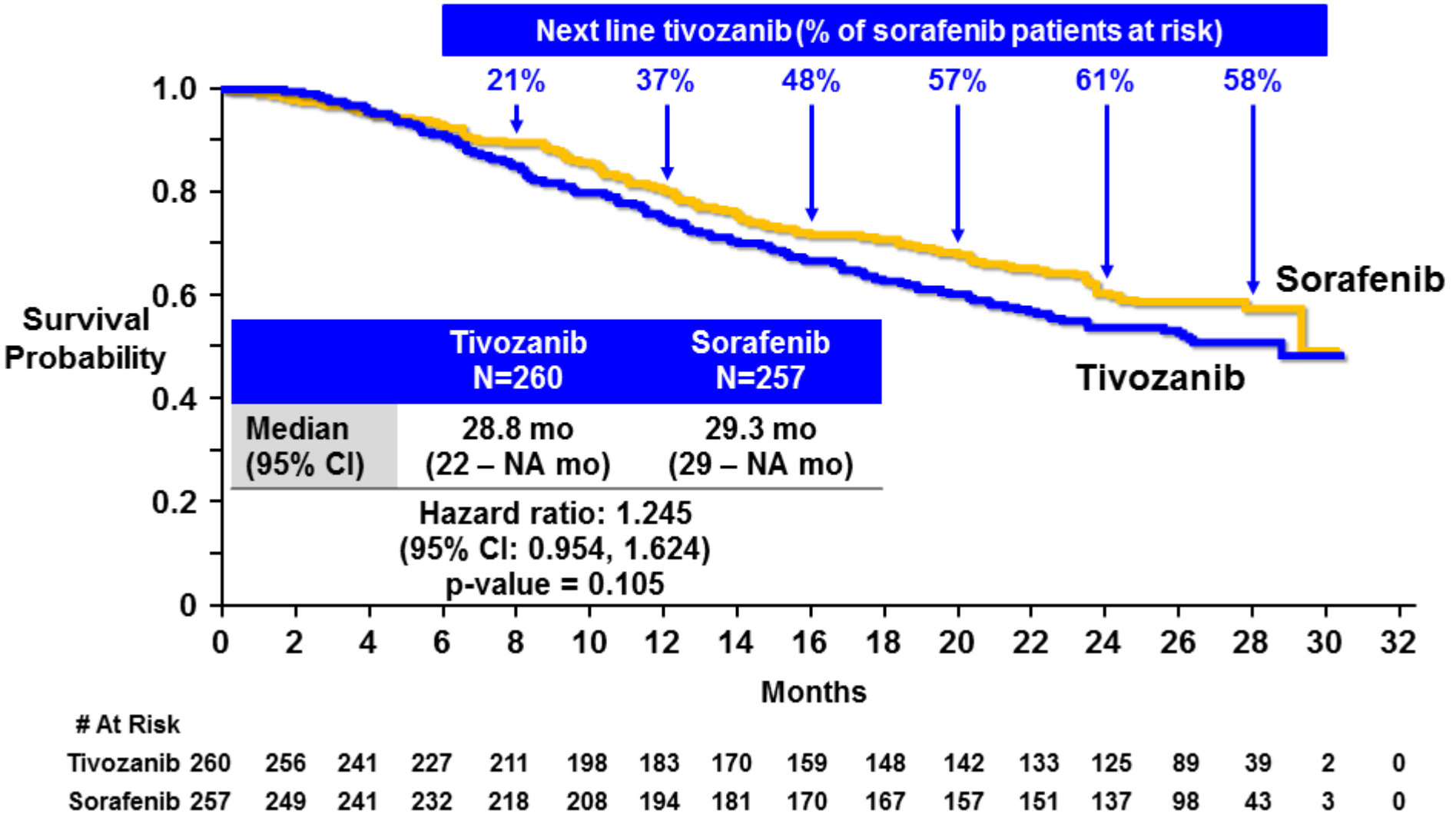
Tivozanib PFS Benefit Across Disease Characteristic Subgroups



Tivozanib Demonstrated Improved ORR Compared to Sorafenib

	Tivozanib	Sorafenib	P-value	Odds Ratio (95% CI)
Confirmed ORR by IRR	**33%**	**23%**	**0.014**	**1.625 (1.103, 2.395)**
Complete Response	1%	<1%		
Partial Response	32%	22%		

Overall Survival in Study 301



Tivozanib Efficacy Summary

- Statistically significant and clinically meaningful improvement in PFS compared to an approved TKI comparator (sorafenib)
- ORR consistent with PFS
- Benefit consistent across multiple subgroups and sensitivity analyses

Tivozanib Efficacy & Safety in RCC Demonstrated by Pivotal Study 301

- Study 301 Design
- Study 301 Efficacy
- Study 301 Safety
- Study 301 Overall Survival

Safety Exposures

	Tivozanib n
Healthy volunteers & patients with various tumors	1,090
Patients with RCC (4 monotherapy studies)	785
Pivotal Phase 3 RCC study	259

Tivozanib RCC Exposures by Month

Exposed to Tivozanib as 1st line or 2nd line therapy	Tivozanib (N=785)	
	n	%
≤ 12 months	519	66
> 12 - ≤ 24 months	172	22
> 24 months	94	12

- Study 301 median duration of exposure
  - Tivozanib = 12.0 months
  - Sorafenib = 9.5 months

Study 301 Safety Overview

	Tivozanib Study 301 (N=259) %	Sorafenib Study 301 (N=257) %
Any AE	90.7	96.9
Any AE Grade ≥ 3	61.4	69.6
Any AE leading to discontinuation	13.1	12.5
Any AE leading to dose modification	24.7	52.1
Any SAE	25.9	21.4
Deaths within 30 days	8.1	5.4

AEs Grade ≥ 3 Reported in Either Treatment Group (≥ 3%)

	Tivozanib Study 301 (N=259)	Sorafenib Study 301 (N=257)
	%	%
Any AE	90.7	96.9
Any AE Grade ≥ 3	61.4	69.6
Hypertension	25.5	17.5
Fatigue	5.4	3.5
Asthenia	3.9	2.7
Disease progression	3.1	0.8
Lipase increased	3.1	9.3
Diarrhea	2.3	6.6
Back pain	3.1	1.9
Anemia	2.7	3.5
Hand foot syndrome	1.9	16.7

AEs Leading to Reduction and/or Interruption in Either Group (≥ 2%)

	Tivozanib Study 301 (N=259)	Sorafenib Study 301 (N=257)
	%	%
Any AE leading to dose reduction and/or interruption	24.7	52.1
Hypertension	7.7	6.2
Diarrhea	3.9	7.8
Hand foot syndrome	3.1	23.3
Vomiting	1.9	2.3
Fatigue	0.8	2.3
Lipase increased	0.8	3.5

SAEs Occurring in Either Treatment Group (≥ 1%)

	Tivozanib Study 301 (N=259)	Sorafenib Study 301 (N=257)
	%	%
Any SAE	25.9	21.4
Disease progression	3.1	0.8
Anemia	1.5	1.6
Cerebrovascular accident	1.2	1.2
Fatigue	1.2	0.4
Hypertension	1.2	0.8
Ischemic stroke	1.2	-
Pulmonary embolism	1.2	0.8
Myocardial infarction	0.8	1.6
Dyspnea	0.8	1.2
Pneumonia	0.4	1.2
Cholecystitis (acute)	-	1.2

Selected VEGF TKI AEs and Lab Abnormalities of Interest

- Hypertension
- Arterial thromboembolic events
- Hemorrhage
- Lab Abnormalities
  - Liver function tests
  - Amylase & lipase
  - Proteinuria
  - Thyroid function tests

Hypertension (HTN)

	Tivozanib Study 301 (N=259)		Sorafenib Study 301 (N=257)	
	n	%	n	%
Any HTN AE*	120	46.3	93	36.2
Any HTN AE* Grade ≥ 3	71	27.4	47	18.3
HTN leading to dose modification	20	7.7	16	6.2
HTN SAE	3	1.2	2	0.8
HTN leading to discontinuation	2	0.8	1	0.4
Death due to hypertension	1	0.4	0	0

*Includes preferred terms hypertension, essential hypertension, BP increased, labile hypertension, hypertensive retinopathy and hypertensive crisis

Arterial Thrombotic and Embolic AEs Grade ≥ 3

	Tivozanib Study 301 (N=259)		Sorafenib Study 301 (N=257)	
	n	%	n	%
Any AE Grade ≥ 3	9	3.5	7	2.7
Ischemic stroke	3	1.2	0	-
Acute myocardial infarction	2	0.8	2	0.8
Myocardial infarction	2	0.8	4	1.6
Transient ischemic attack	1	0.4	0	-
Retinal artery thrombosis	1	0.4	0	-
Pulmonary artery thrombosis	0	-	1	0.4

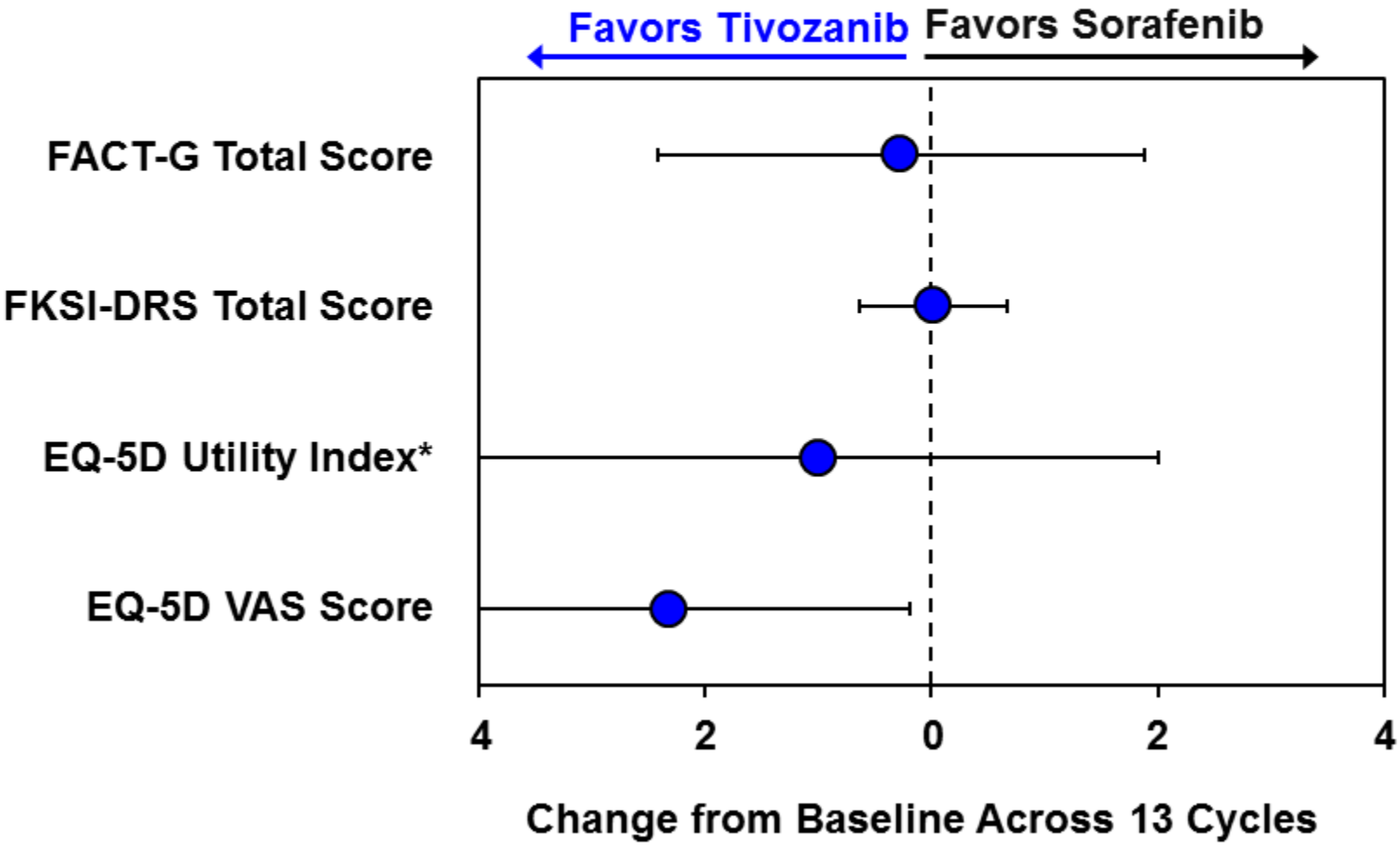
Hemorrhage AEs Grade ≥ 3

	Tivozanib Study 301 (N=259)		Sorafenib Study 301 (N=257)	
	n	%	n	%
Any AE Grade ≥ 3	7	2.7	3	1.2
Epistaxis	0	-	2	0.8
Aortic aneurysm rupture	1	0.4	0	-
Hematemesis	1	0.4	0	-
Hemorrhagic stroke	1	0.4	0	-
Hemorrhoidal hemorrhage	1	0.4	0	-
Postmenopausal hemorrhage	1	0.4	0	-
Purpura	1	0.4	0	-
Small intestinal hemorrhage	1	0.4	0	-
Postprocedural hemorrhage	0	-	1	0.4

Selected Lab Abnormalities

	Tivozanib Study 301 (N=259)	Sorafenib Study 301 (N=257)
	%	%
Chemistries Grade ≥ 3		
ALT increase	0.8	3.5
AST increase	1.9	3.9
Bilirubin increase	0.8	1.2
Amylase increase	4.6	6.6
Lipase increase	11.2	24.5
Low phosphate	4.2	26.1
Protein in urine	3.1	2.7
TSH > 10 mIU/L and T3 < LLN	8.9	1.9

No Clinically Relevant Difference in QoL



*EQ-5D Utility Index was multiplied by 100 to make scales comparable

Tivozanib Safety Summary

- Tivozanib safety profile as expected
  - Hypertension
- Less AEs requiring dose modification
  - Hand foot syndrome and diarrhea
- Similar rate of arterial thromboembolic events
- Higher rate of hemorrhage
- No Hy's law hepatotoxicity
- No clinically meaningful impact on QoL

Tivozanib Efficacy & Safety in RCC Demonstrated by Pivotal Study 301

- Study 301 Design
- Study 301 Efficacy
- Study 301 Safety
- Study 301 Overall Survival

Factors Evaluated for Impact on OS

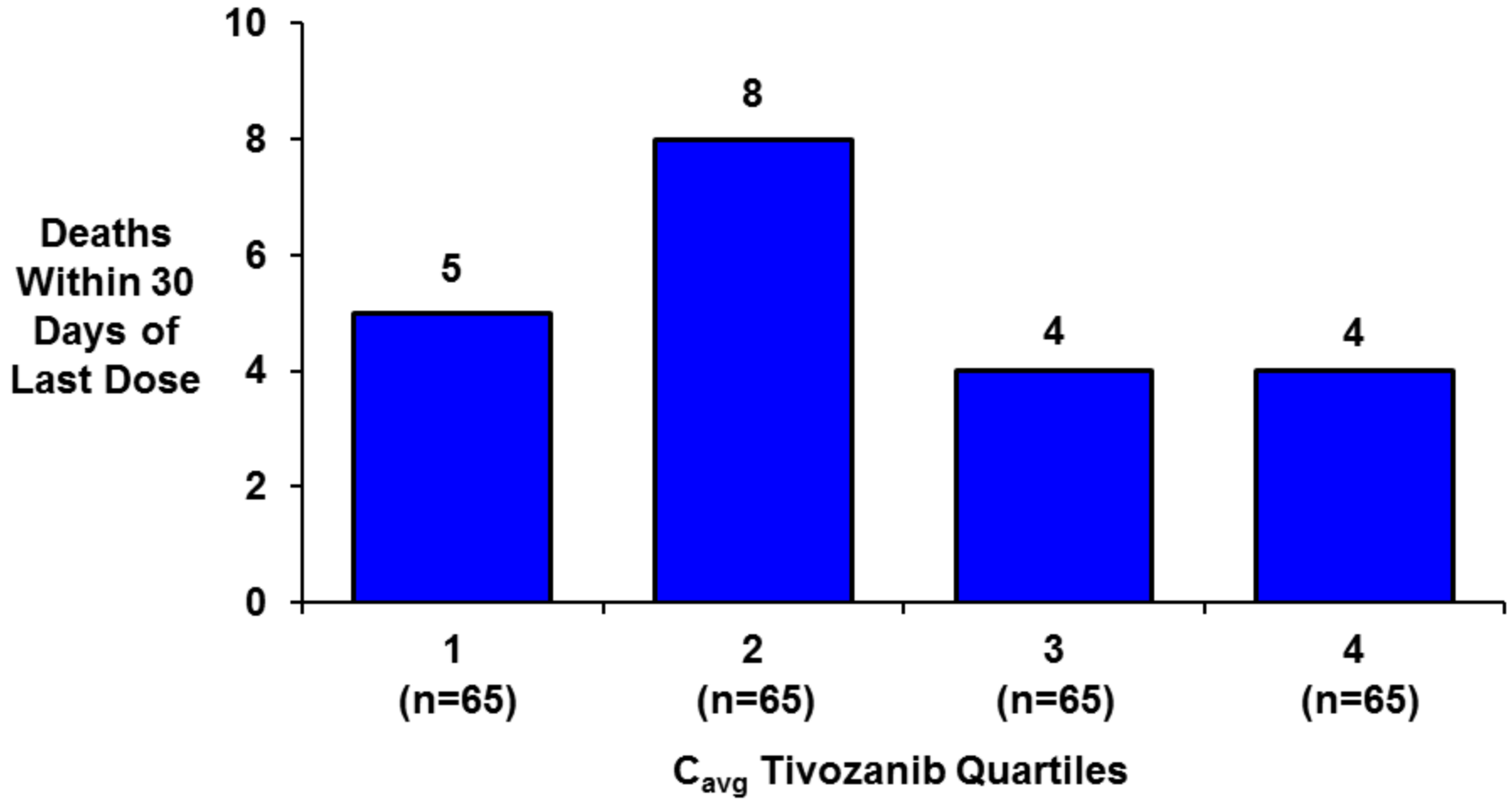
- Examination of fatal adverse events
- Correlation of tivozanib serum concentration with fatal AEs and OS
- Utilization of next line cancer therapy, including crossover from sorafenib to tivozanib

Deaths Within 30 Days of Last Dose

Study 301	Tivozanib (N=259) n	Sorafenib (N=257) n
All	21 (8.1%)	14 (5.4%)
Deaths due to progressive disease (incl. CNS mets, spinal cord compression)	8	2
Deaths due to AEs	13	12
Cardiac failure (acute)	2	2[a]
Myocardial infarction	2	0
Pulmonary embolism	1	2[a]
Cerebrovascular accident	1	3
Coronary artery disease	1	2
Hypertension	1	0
Aortic aneurysm rupture	1	0
Post-procedural hemorrhage	0	1
Other	4	3

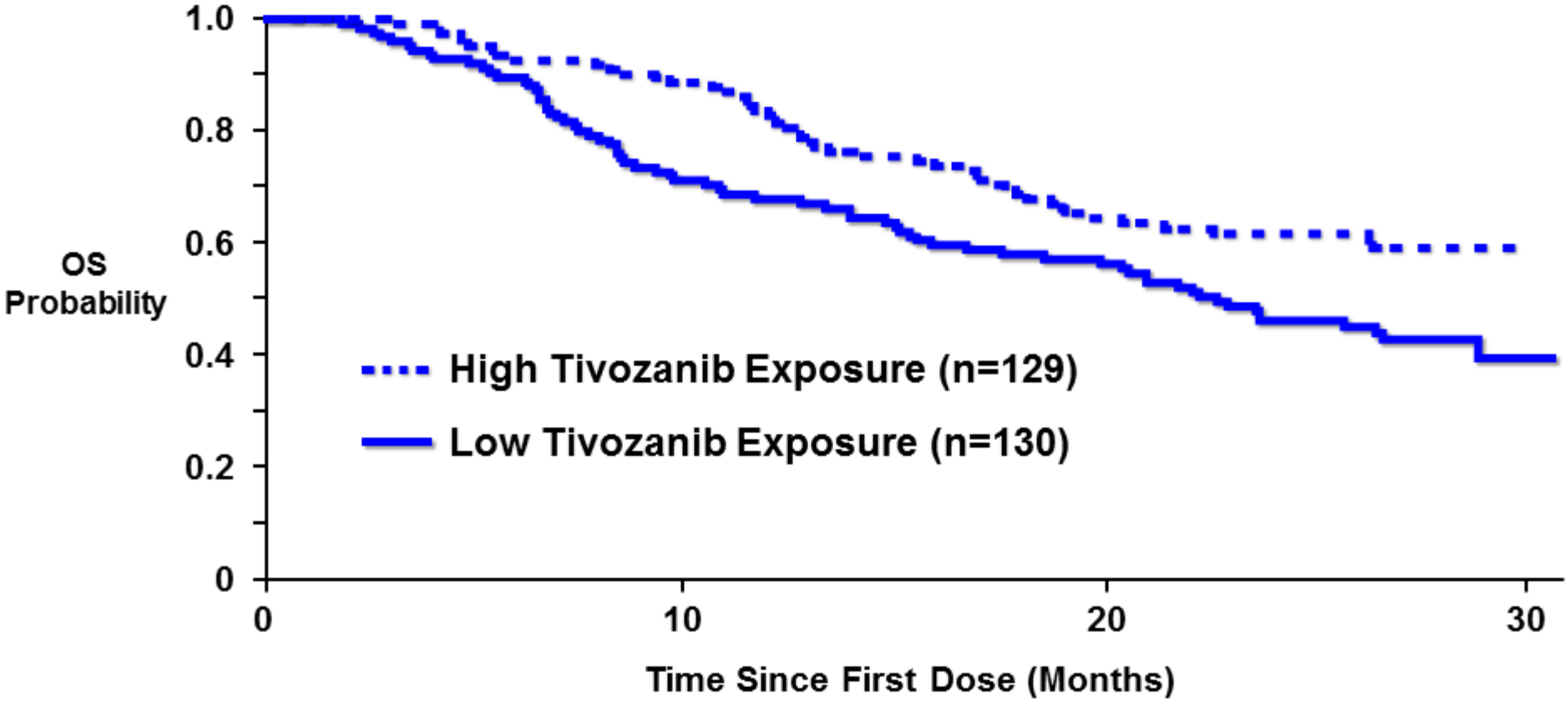
a. 1 death reported as cardiac failure also reported as pulmonary embolism

No Association Between Tivozanib Serum Concentration and Fatal Events

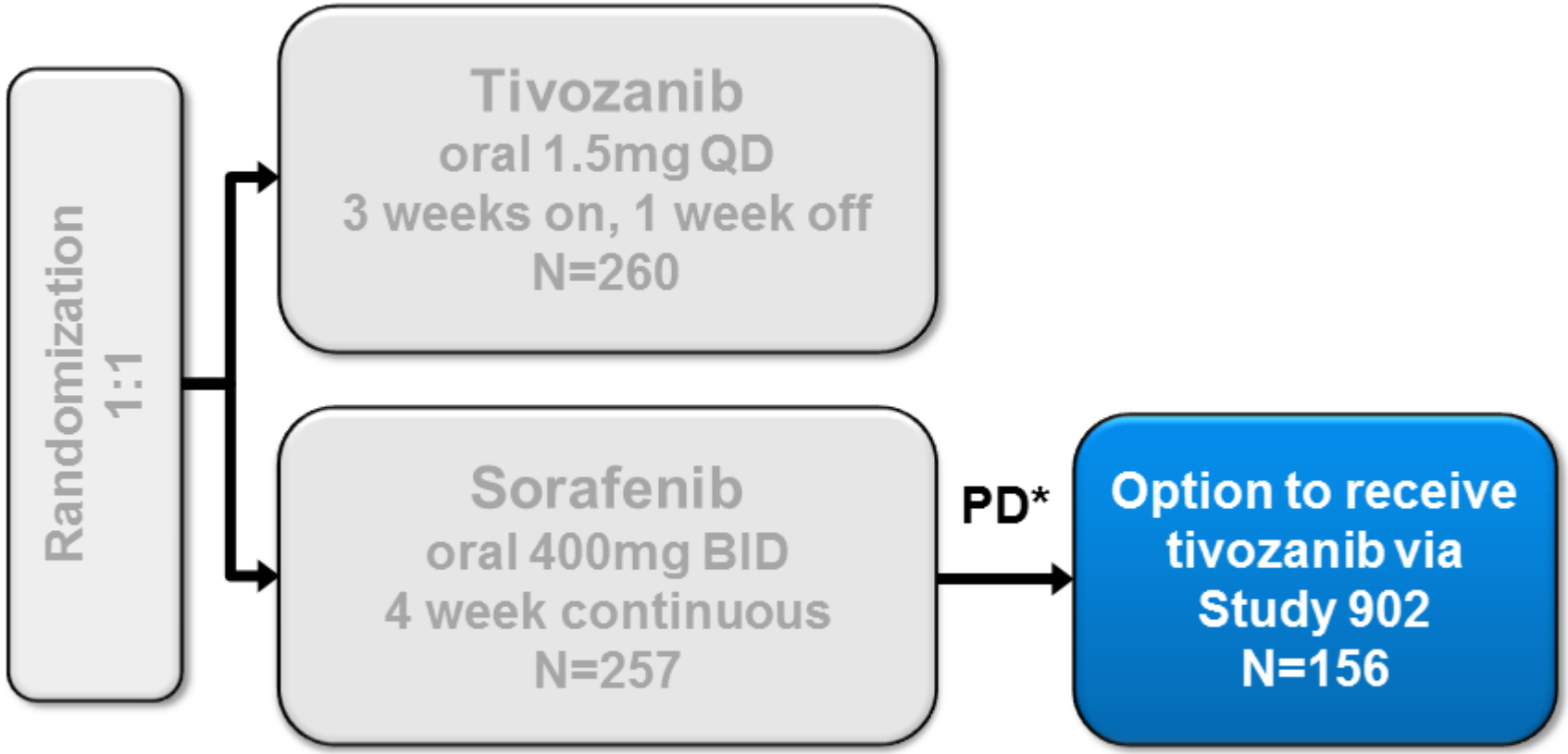


Study 301: C_{avg} – average serum concentration

No Association Between High Serum Concentration and Long-term Mortality



Sorafenib Patients With PD Could Receive Tivozanib (Study 902)



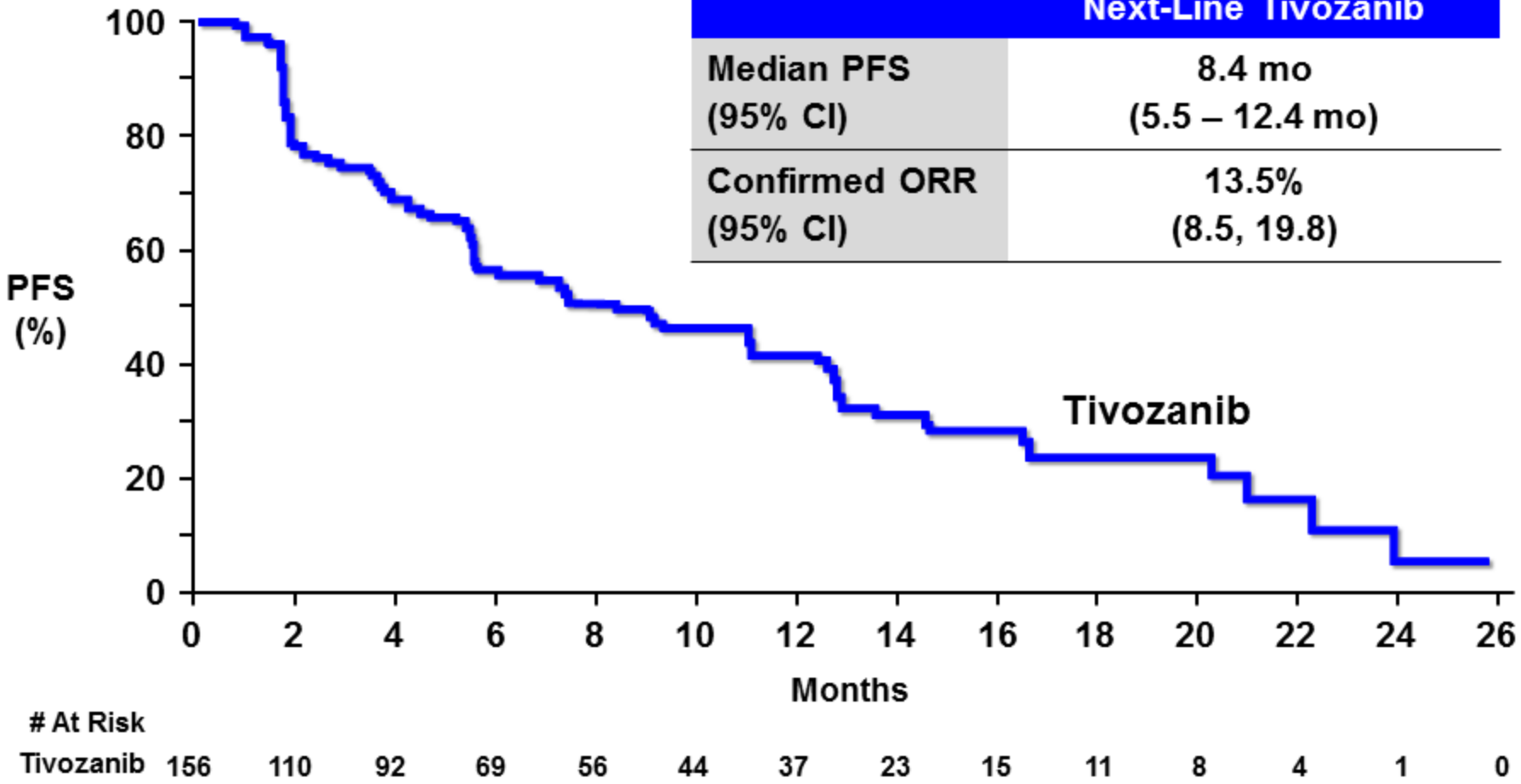
* Radiographic evidence of PD needed to enter Study 902

Next-Line Targeted Therapy

ITT Population	Tivozanib Study 301 (N=260)	Sorafenib Study 301 (N=257)
Next-line targeted therapy (%)	34 (13%)	162 (63%)
Tivozanib (Study 902)	0	156
Off-protocol	34	6

Study 902 Antitumor Activity of Tivozanib After PD on Sorafenib

	Next-Line Tivozanib
Median PFS (95% CI)	8.4 mo (5.5 – 12.4 mo)
Confirmed ORR (95% CI)	13.5% (8.5, 19.8)



Overall Survival Summary

- OS is confounded by differential use of next-line targeted therapy
- Fatal adverse events and serum exposure do not explain OS
- OS on both arms are among the longest seen in pivotal RCC trials

Clinical Interpretation and Benefit-risk of Tivozanib in RCC

Robert Motzer, MD
Attending Physician
Memorial Sloan-Kettering Cancer Center, NY
Professor of Medicine
Weil College of Medicine, Cornell Univ, NY

RCC Therapy Goal is to Improve Survival and Maintain Daily Lifestyle

- TKIs with activity against VEGFRs are standard of care for advanced RCC
- Further improvement needed
  - Improve efficacy & disease control
  - Acceptable safety & tolerability
  - Access to therapies with different toxicities to allow individualization

Characteristics of Tivozanib

- Highly potent and selective for VEGFR
- Favorable pharmacokinetic profile with once-daily dosing
- No interaction with CYP3A4 inhibitors

Recommendation for TKIs for Treatment of Clear-cell RCC

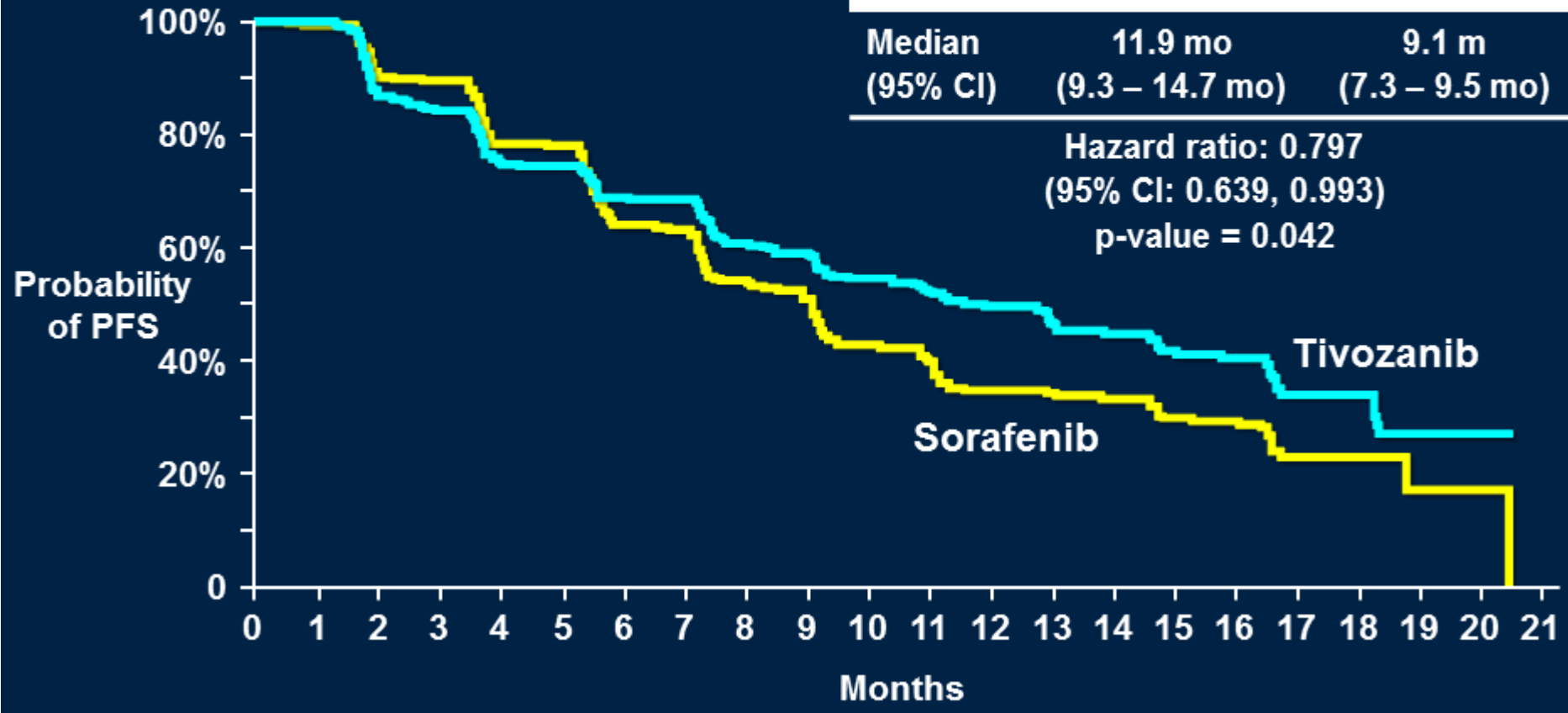
Setting	Prior Treatment	Level 1	≥ Level 2
1st Line		Tivozanib Sunitinib Pazopanib	Sorafenib
2nd Line	Prior cytokine	Tivozanib Sorafenib Sunitinib Pazopanib Axitinib	
	Prior VEGF TKI	Axitinib	Tivozanib* Sorafenib Sunitinib Pazopanib

Based on www.NCCN.org (2013), * Median PFS following PD = 8.4 months

Study 301: Significant PFS Benefit as Initial Targeted Therapy

	Tivozanib N=260	Sorafenib N=257
Median (95% CI)	11.9 mo (9.3 – 14.7 mo)	9.1 m (7.3 – 9.5 mo)

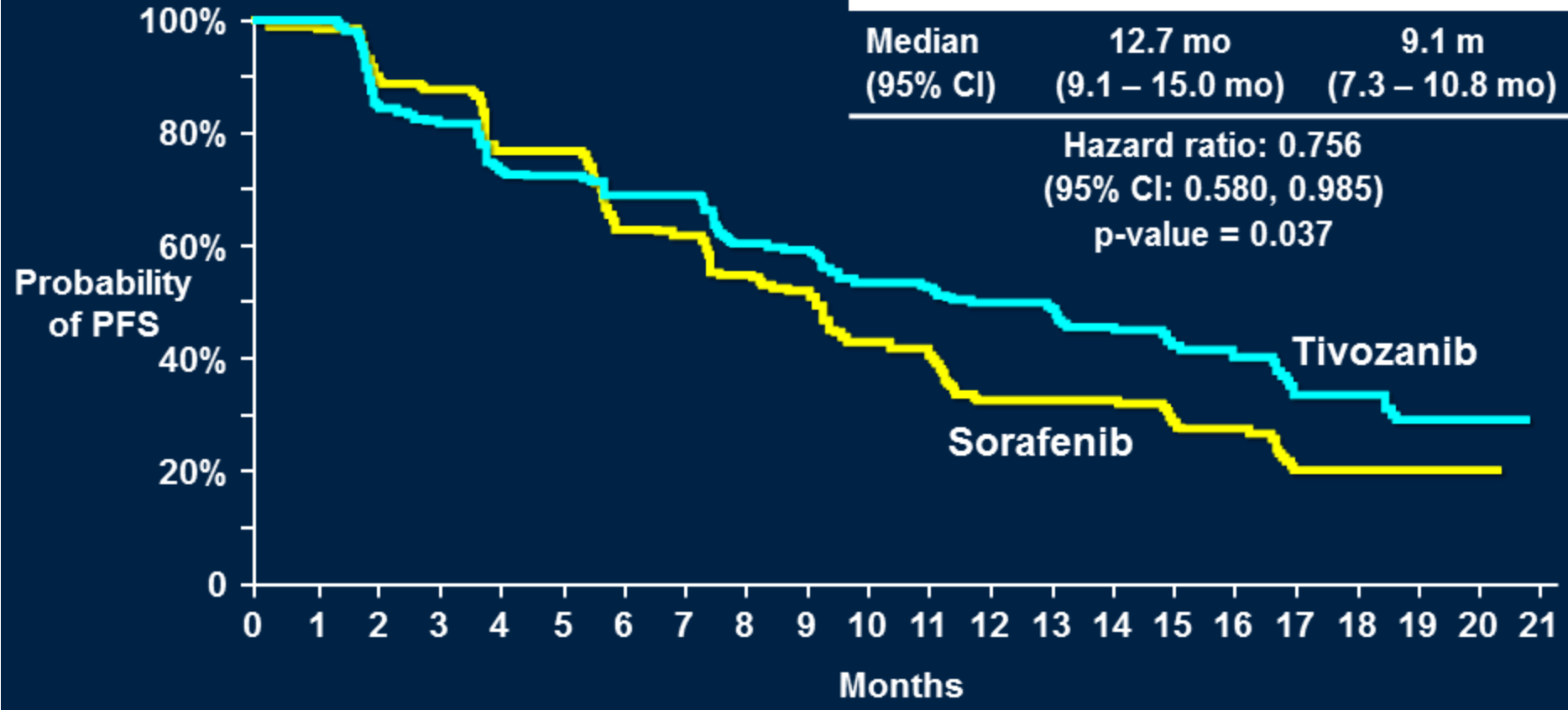
Hazard ratio: 0.797
(95% CI: 0.639, 0.993)
p-value = 0.042



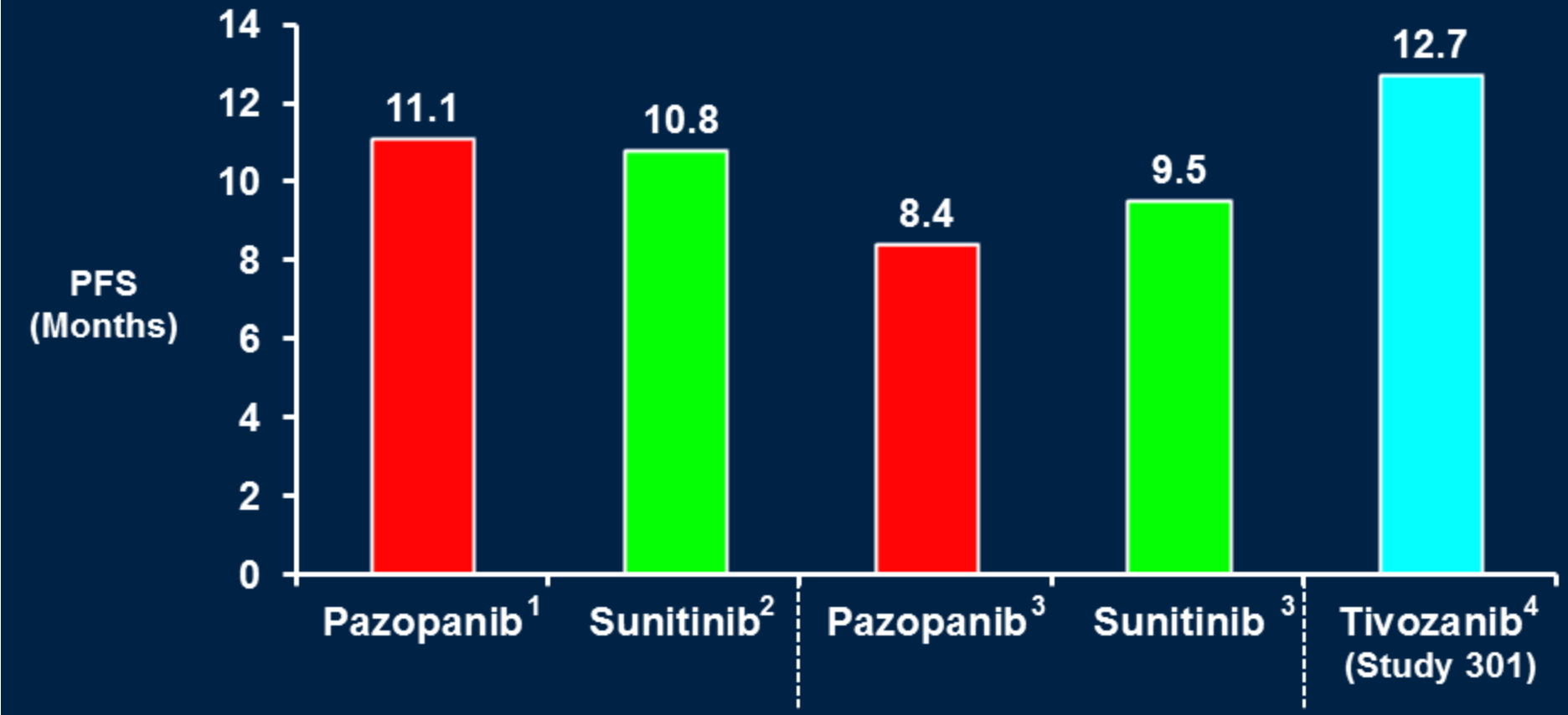
Study 301: PFS Benefit in Treatment Naïve RCC Subgroup

	Tivozanib N=181	Sorafenib N=181
Median (95% CI)	12.7 mo (9.1 – 15.0 mo)	9.1 m (7.3 – 10.8 mo)

Hazard ratio: 0.756
(95% CI: 0.580, 0.985)
p-value = 0.037

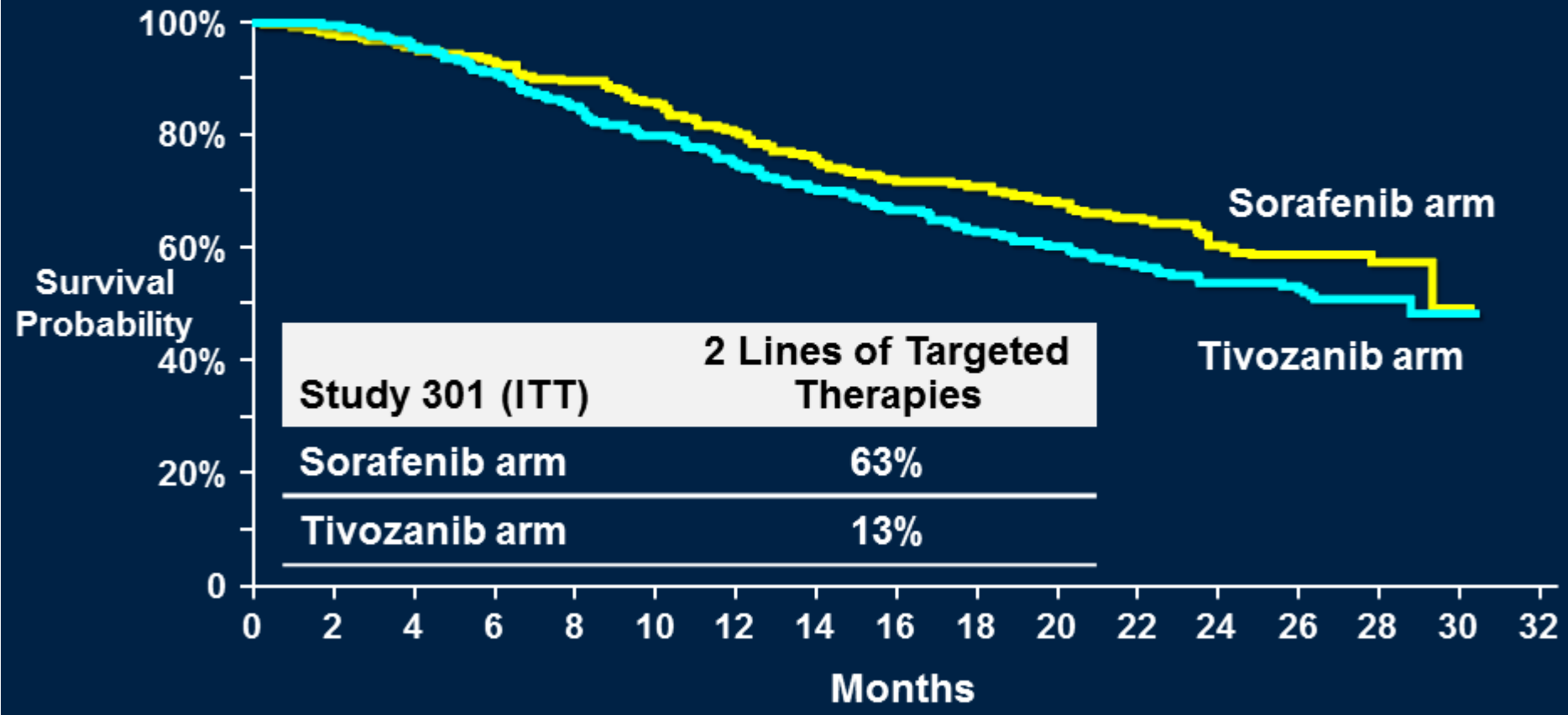


Tivozanib PFS is Similar to Other TKIs in Treatment Naïve RCC Patients

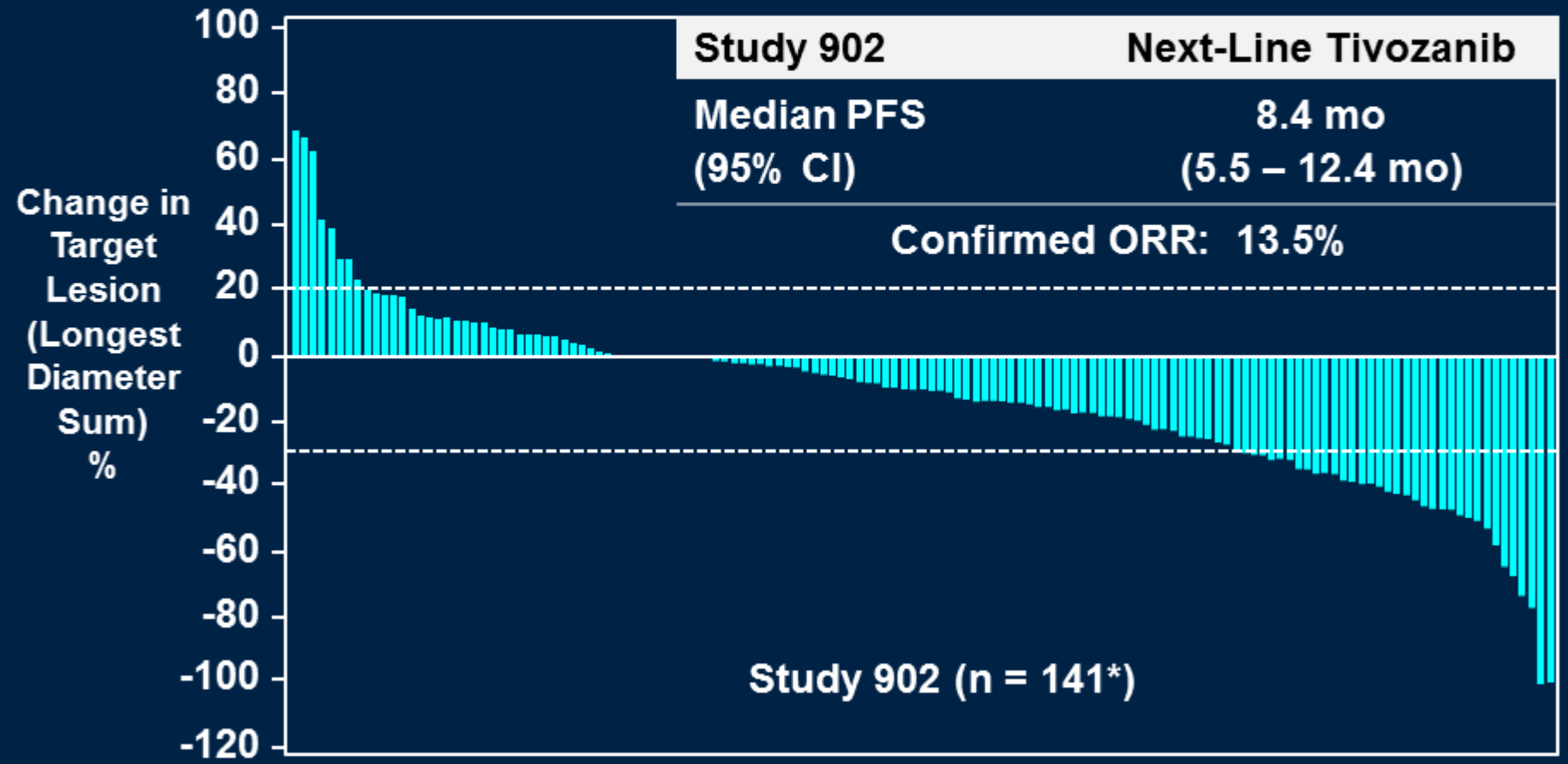


1. Votrient PI 2012, 2. FDA Briefing Book, 3. Motzer R, ESMO 2012, 4. Motzer ASCO (2012) (abstr 4501)

Study 301: Overall Survival Results

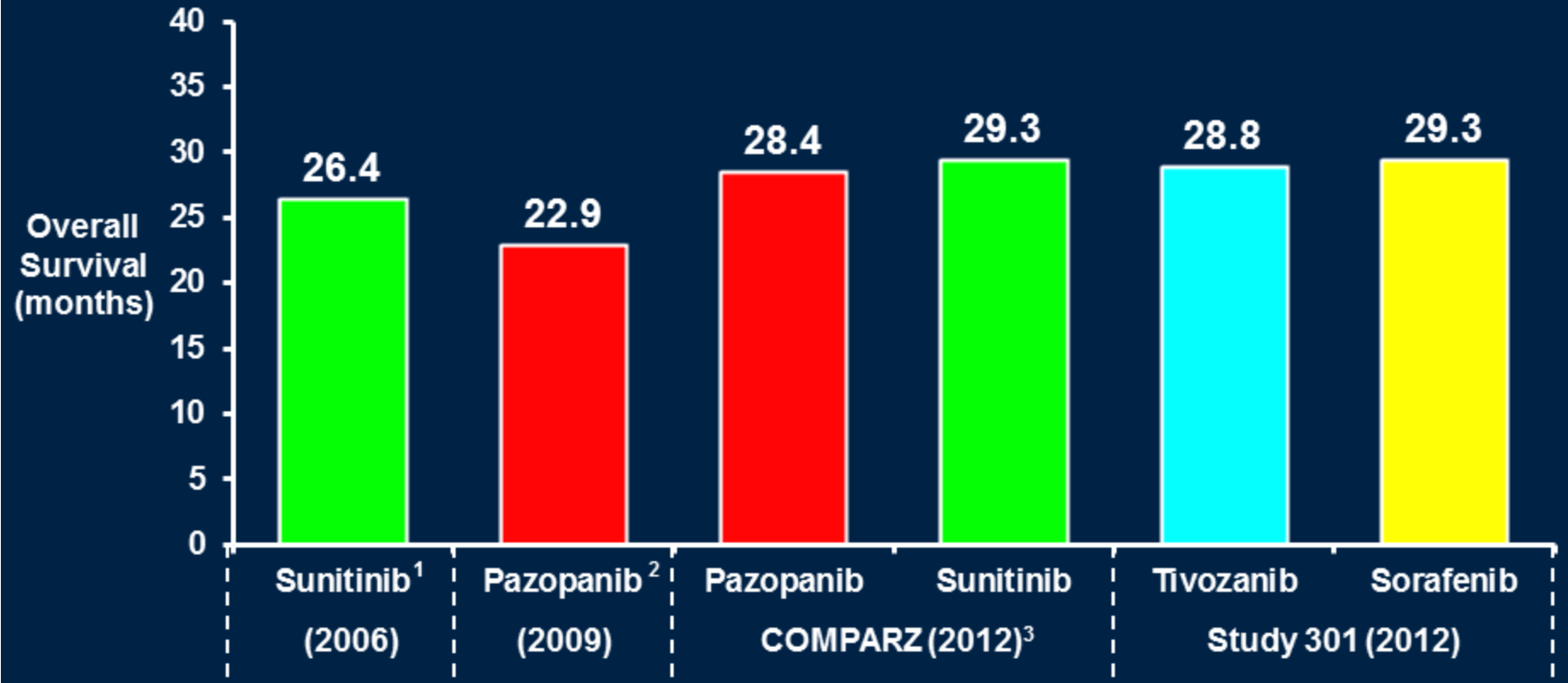


Target Lesion Change from Baseline in Patients on Tivozanib After Sorafenib



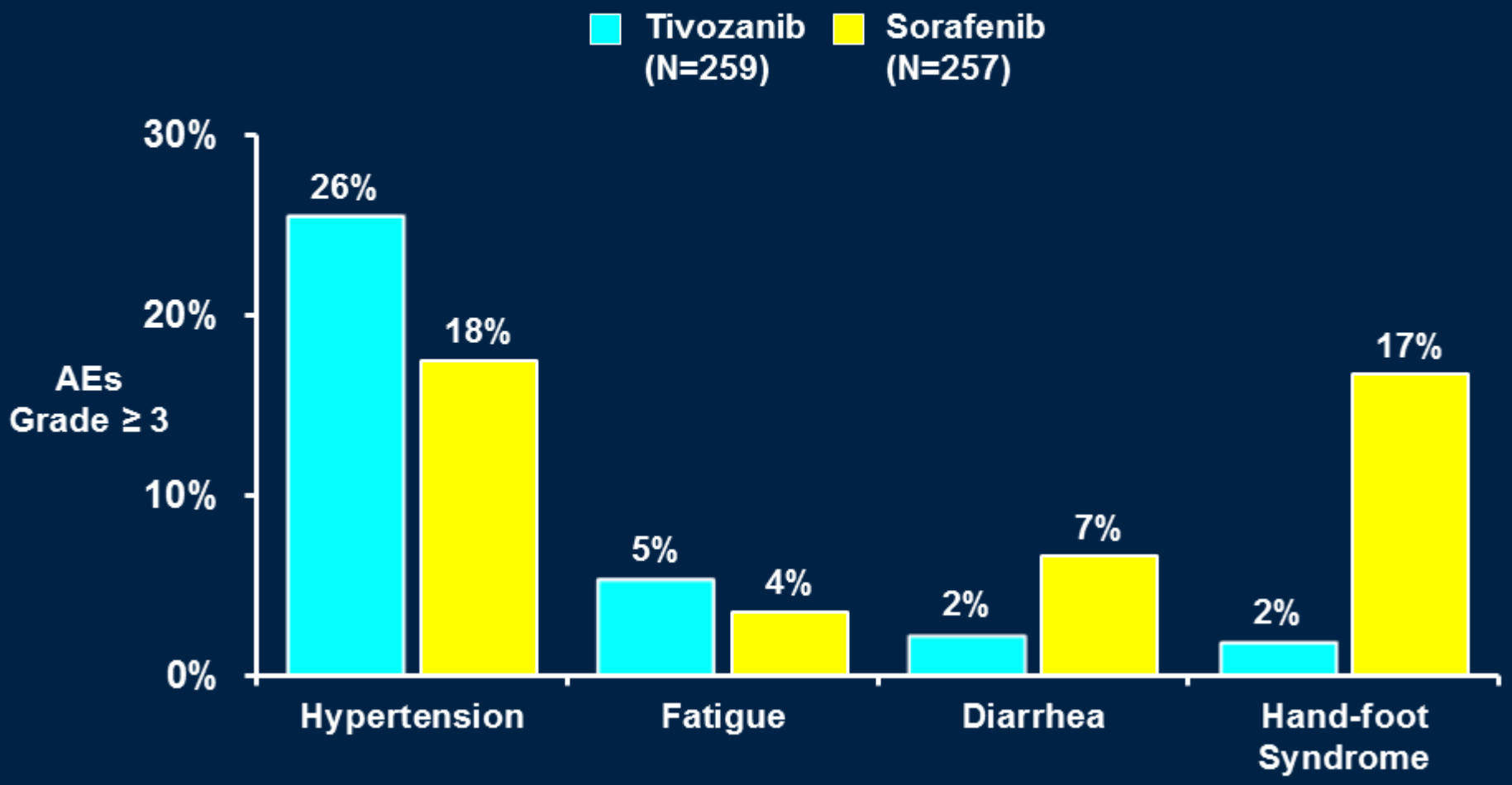
* n=141 Patients had measurable disease at baseline and at least one subsequent scan

Study 301 Median OS Results Similar to Other 1st Line Therapies for RCC

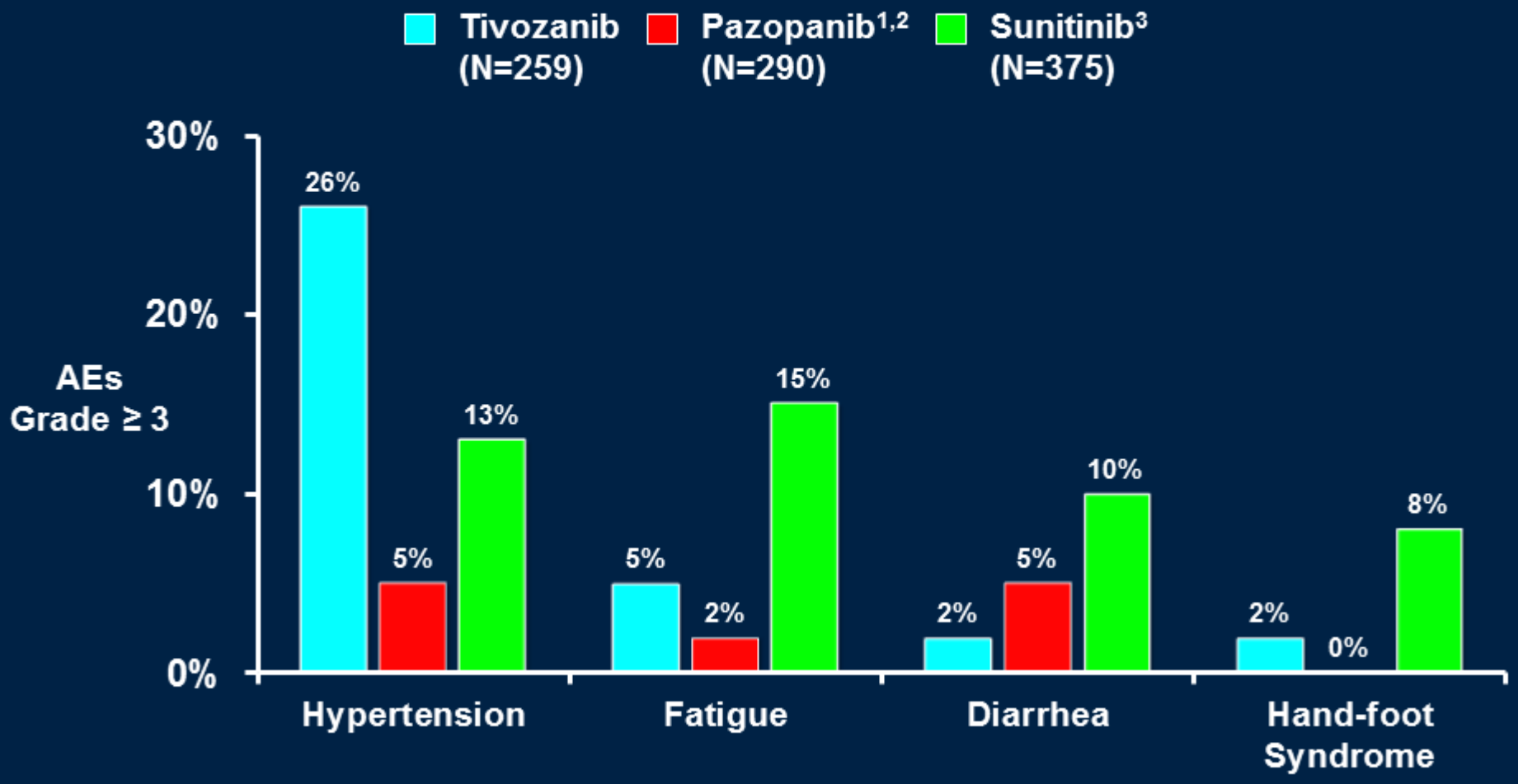


1. Motzer JCO 2009, 2. Votrient PI 2012, 3. Motzer ESMO 2012

Study 301: Tivozanib has Different Safety Profile Compared to Sorafenib

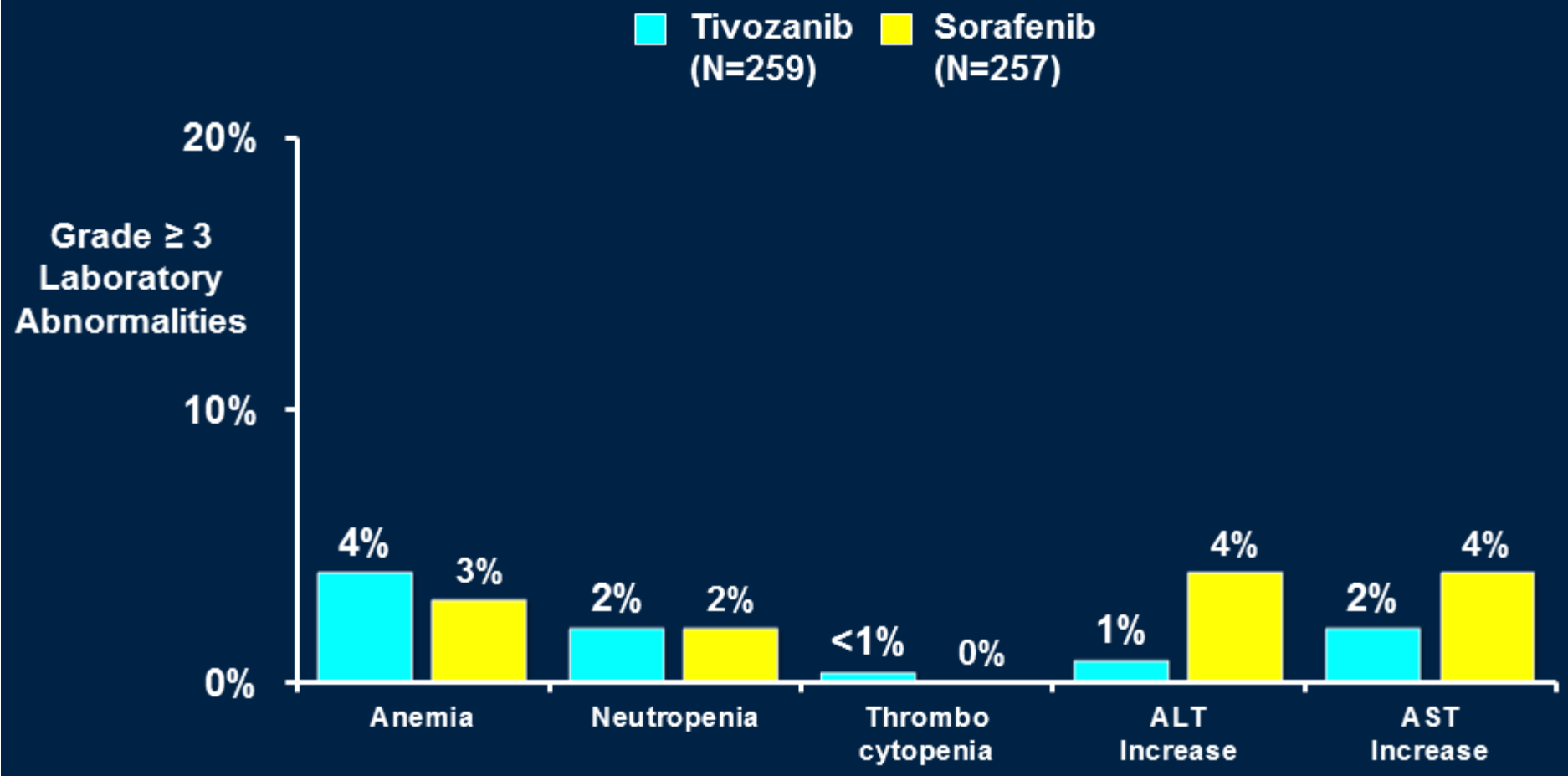


Tivozanib has Different Safety Profile Than Other 1st Line Oral TKIs

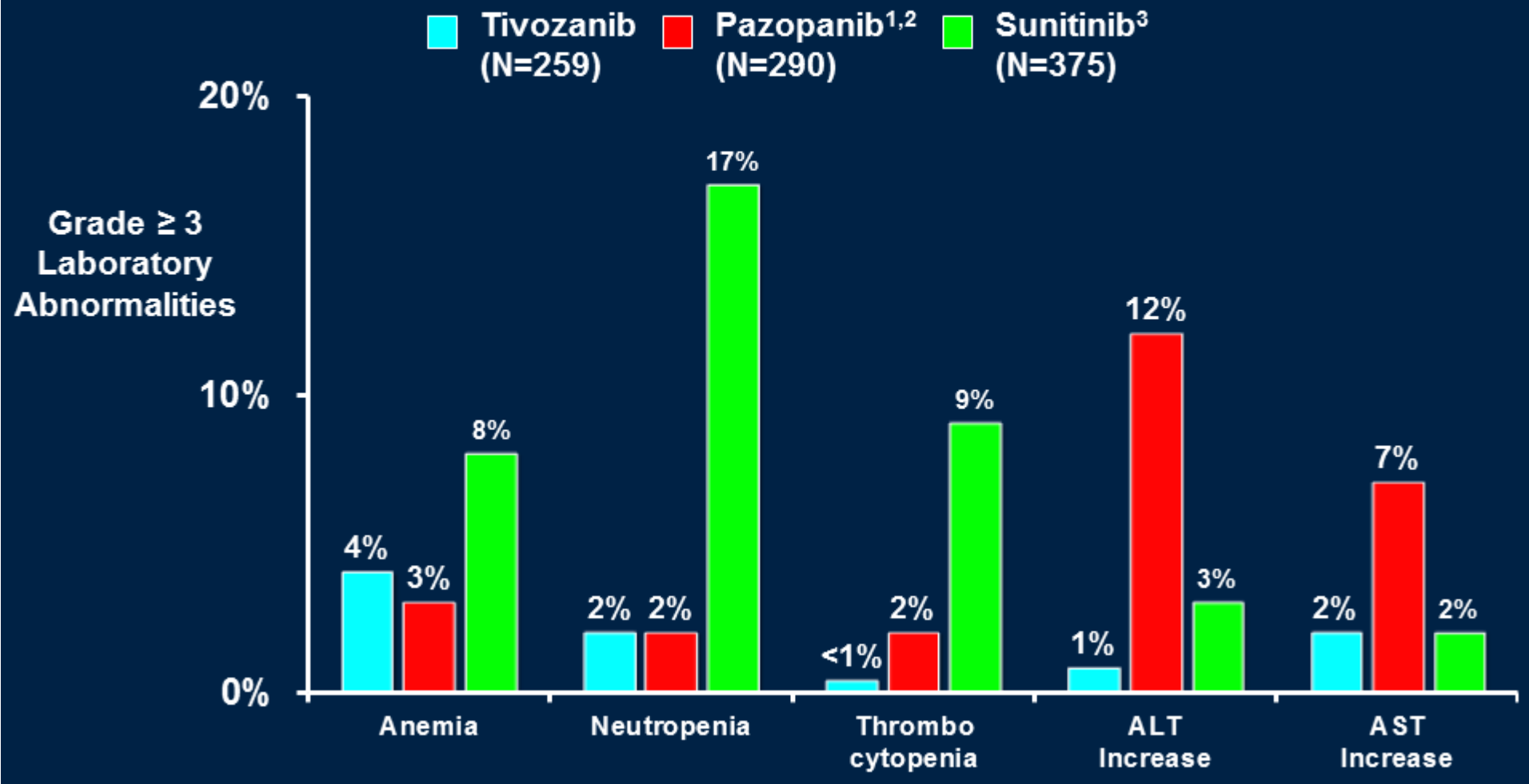


1. Votrient NDA CDER Medical Review Table 44, 2. Sutent PI 2012

Study 301: Tivozanib has Different Lab Abnormalities Compared to Sorafenib



Tivozanib has Different Lab Abnormalities Than Other 1st Line TKIs



1. Votrient PI 2012, 2. Votrient NDA CDER Medical Review Table 46, 3. Sutent PI 2012

Tivozanib Demonstrates Favorable Benefit-risk

- Meets precedent for RCC approval
  - PFS benefit over sorafenib
  - Consistent efficacy results
  - OS confounded by subsequent therapy
- Different AE profile than sorafenib and other TKIs
  - Monitor and treat hypertension

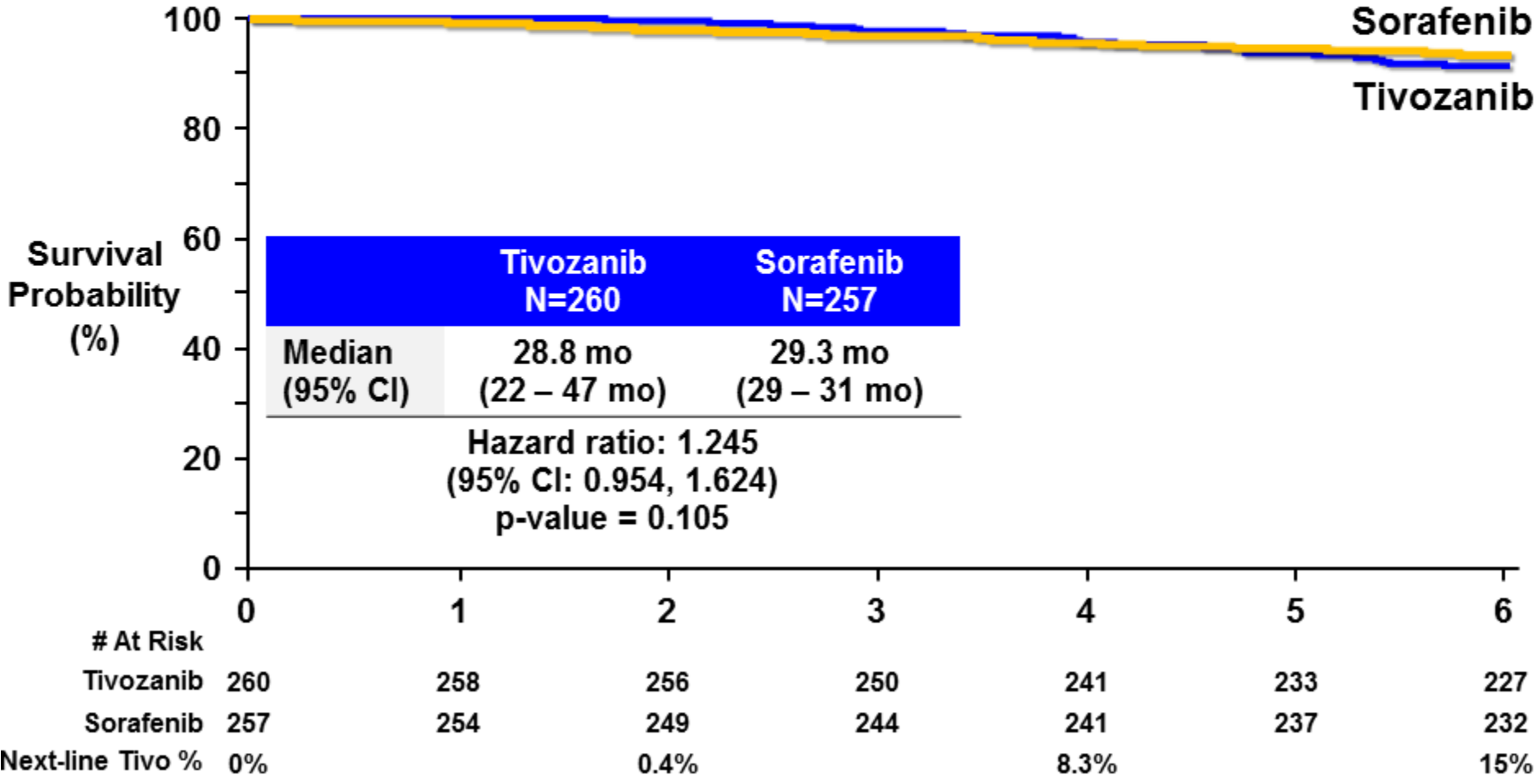
Tivozanib for the Treatment of Advanced Renal Cell Carcinoma (RCC) in Adults

Meeting of the Oncologic Drugs Advisory Committee (ODAC)

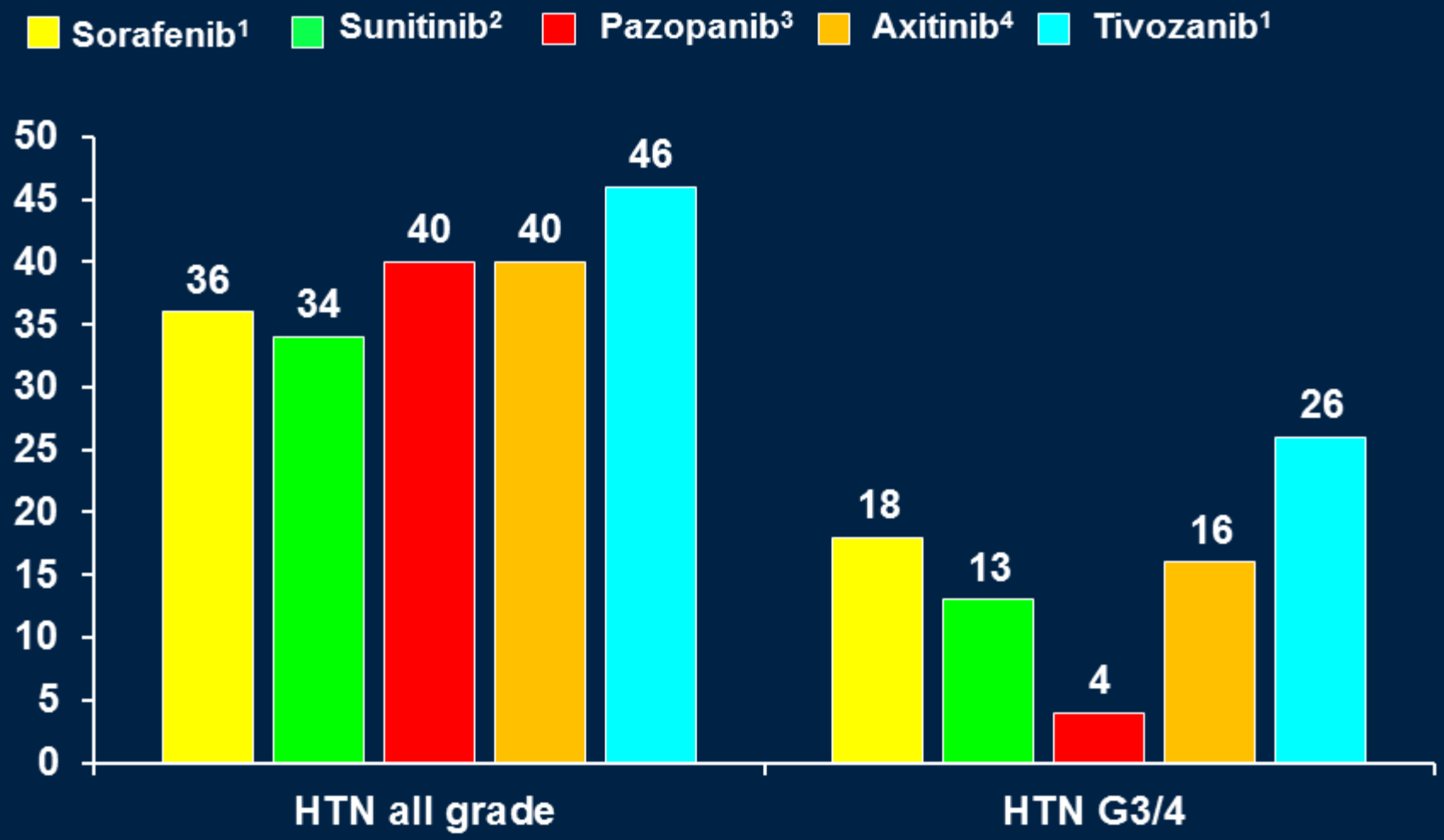
May 2, 2013

BACKUP SLIDES

OS Curves Study 301: Truncated at 6 months



Hypertension is a Common Adverse Event with TKIs



[2]TIVO-1 [2]Sunitinib PI (2012), [3]Pazopanib PI (2012) [4]Axitinib PI (2013)

Overview of Sorafenib Tolerability

Study	Reductions %	Interruptions %	Discontinuations %
TARGET [1,]	10	14	10
AXIS[2]	52	80	13
TIVO-1	44	70	5
Additional Studies			
AGILE[3]	43	78	8

1 Nexavar FDA Briefing book ; 2 AXIS FDA Briefing Book; 3 Hutson ASCO GU 2013;

Overview of Sorafenib Safety (All Grades)

Study	HTN %	HFS %	Fatigue %	Diarrhea %
TARGET [1,2]	17	30	37	43
AXIS[3,4]	29	51	32	53
TIVO-1	34	54	16	32
Additional Studies				
AGILE[5]	29	39	26	40
Sorafenib P2[6]	46	54	22	56
Range	17-46	30-54	16-37	32-53

1 Nexavar PI; 2 NEJM, Escudier; 3 Inlyta PI; 4 Rini Lancet 2011; 5 Hutson ASCO GU 2013; 6 Rini ASCO GU 2011

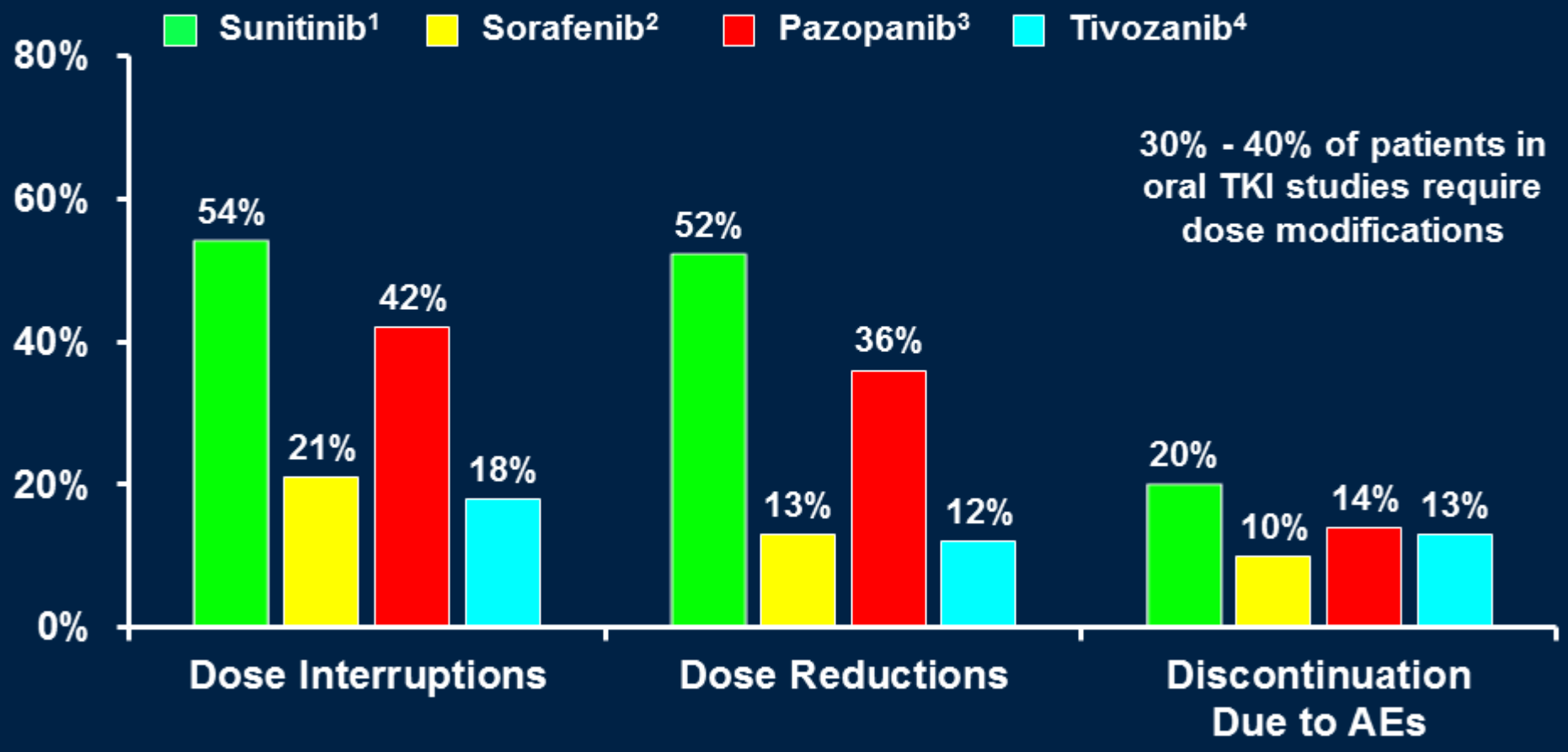
Relationship of Dose Reduction on PFS: Between Arms (Study 301)

Patients With Dose Reduction	Tivozanib (n=36)	Sorafenib (n=114)
Median PFS in months (95% CI)	11.3 (9.1, NA)	9.2 (8.1, 12.8)
Hazard Ratio (95% CI)	0.802 (0.493, 1.306)	
Patients Without Dose Reduction	**Tivozanib (n=224)**	**Sorafenib (n=143)**
Median PFS in months (95% CI)	11.9 (9.1, 14.7)	7.5 (5.7, 9.6)
Hazard Ratio (95% CI)	0.717 (0.551, 0.934)	

Sorafenib: Range of Reported PFS Results

Trial	Phase	Population	PFS (months)
SOR (TARGET, Escudier - NEJM 2007)	3	Previously Treated	5.5
SOR vs. IFN (Escudier - JCO 2009)	2	Treatment Naïve	5.7
SOR vs. SOR +IFN (Jonasch - Cancer 2010)	2	Treatment Naïve	7.39
SOR (Bellmunt – Clin.& Transl Onc.2010)	2	Treatment Naïve	7.5
SOR + placebo (Rini AMG- Cancer 2012)	2	Treatment Naïve	9.0
SOR (TIVO-1)	3	Previously treated + Treatment naïve	9.1

Dose Reductions and Interruptions Are an Indicator of Patient Tolerability



*Does not include patients who in addition to AEs, had concurrent other reasons at the time they discontinued

1. Sutent [prescribing information]. 2011: 2. Escudier B, et al. 2007; 3. pazopanib [prescribing information, 2009; 4. Data on file

Dose Reductions by Region Study 301

	Central/Eastern Europe		North America/Western Europe		Rest of World	
	Tivozanib (N=228)	Sorafenib (N=228)	Tivozanib (N=22)	Sorafenib (N=18)	Tivozanib (N=9)	Sorafenib (N=11)
	(%)	(%)	(%)	(%)	(%)	(%)
Any dose reduction	16	44	23	44	11	45

AEs (≥ Grade 3) by Race Occurring in ≥ 3% of Patients in Any Subgroup - Core RCC Monotherapy Studies

	Non-white (N=45)		White (N=740)	
	N	%	N	%
Any Grade ≥ 3 AE	27	60	406	55
Hypertension	9	20	153	21
Lipase increased	3	6.7	23	3.1
Hand foot syndrome	3	6.7	8	1.1
Anemia	3	6.7	12	1.6
Asthenia	3	6.7	36	4.9
Jaundice	2	4.4	0	-
Abdominal pain	2	4.4	4	0.5
Hypokalemia	2	4.4	0	-
Amylase increased	2	4.4	13	1.8
Dyspnea	2	4.4	24	3.2
Fatigue	0	-	40	5.4

Characteristics of Black Patients in Tivozanib Clinical Trials (Slide 1 of 2)

Patient #	Cancer	MHx of HTN	/# anti-HTN meds at baseline	Max Grade HTN on study	HTN meds added? adjusted	Max BP after start of anti-HTN
301-186-011	clear cell RCC	Gr 3	2	Gr 3	Yes	146/90
202-003-001	clear cell RCC	Gr 3	2	Gr 3	Yes	179/100
202-008-001	non-clear cell RCC	Gr 3	3	None	NA	NA
202-008-002	clear cell RCC	Gr 3	2	None	NA	NA
202-008-003	clear cell RCC	No	N/A	None	NA	NA
202- 010-001	clear cell RCC	Gr 3	4	Gr 3	Yes	148/92, 142/99
202-022-002	clear cell RCC	Gr 3	2	None	NA	NA
102-004-028	clear cell RCC	Gr 3	2	None	NA	NA
103-001-003	stomach adenocarcinoma	No	N/A	None	NA	NA

Characteristics of Black Patients in Tivozanib Clinical Trials (Slide 2 of 2)

Patient #	Cancer	MHx of HTN	# anti-HTN meds at baseline	Max Grade HTN on study	HTN meds added? adjusted	Max BP after start of anti-HTN
105-001-002	moderately differentiated non small cell carcinoma	Gr 2	1	2	NA	NA
105-001-009	moderate to poorly differentiated adenocarcinoma	Gr 2	1	None	NA	NA
112-002-011	poorly differentiated adenocarcinoma of the colon	Gr 2	1	3	yes	UNK - last BP was 9 days before start of CM
112-003-009	pancreatic islet cell	Gr 2	1	None	NA	NA
112-008-003	breast	No	N/A	Gr 3	yes	124/70
114-003-002	breast	No	N/A	3	yes	146/105, 155/97
114-003-005	pancreatic	Gr 2	1	NA	NA	NA

Tivozanib Baseline Demographics (Core RCC Studies)

	TOTAL Tivozanib (N=786)	Study 201 Tivozanib (N=272)	Study 202 Tivozanib (N=105)	Study 902 Next-line Tivozanib (N=149)	Study 301 Tivozanib (N=260)
Sex					
Male	72%	70%	77%	71%	71%
Female	28%	30%	23%	29%	29%
Median Age (Years)	58	56	61	60	59
Age Group					
<65 years	75%	81%	62%	72%	75%
≥65 years	25%	19%	38%	28%	25%
Race					
White	94%	93%	89%	97%	96%
Black/African American	1%	-	6%	-	<1%
Asian	4%	7%	3%	3%	4%
Other	<1%	-	3%	-	-

Protocol Violations (Study 301)

Violation Category	Tivozanib	Sorafenib
Eligibility Criteria	13	14
Inclusion Criteria	7	7
Exclusion Criteria	6	7
Prohibited Medications	24	30
Prohibited Therapies (Radiation Therapy)	4	1

Median Time From First Dose Until Death (within 30 Days) in Study 301

	Tivozanib-Arm (N=21)	Sorafenib-Arm (N=14)
Time from first dose to death (months)		
Mean (Std)	9.3 months (5.8)	6.0 months (6.4)
Median [Q1, Q3]	8 months (5.0, 13)	3.5 months (1.4, 8.5)
Min, Max	1.5, 21 months	0, 22 months

Deaths due to Disease Progression Tivozanib – Study 301

Patient	Preferred Term	# days 1st dose to death	# days last dose to death	RECIST response at last assessment per IRR	# days last assess ment to death
435-009	Spinal Cord Compression	233	30	PD	29
436-002	Disease Progression	560	7[a]	PD[b]	61
454-005	Disease Progression	66	22	n/a	76
454-011	Disease Progression	187	27	PD	75
494-001	Disease Progression	380	16	PD	50
495-010	Renal Cancer	249	7[a]	SD	26
497-001	Metastases to CNS	280	27	PD	19
497-004	Disease Progression	511	5	PD	6

a These two patients died while on study drug
b Last assessment based on investigator rather than IRR

‘Real world’ Retrospective Registry

- Duke- ACORN Practice of mRCC patients
- 384 patients analyzed from Jan 2007 to May 2011
- Median survival for patients treated with 1 vs 2 TKI: 18.2 vs 35.2 months

Harrison, ASCO 2012

Reasons for Censoring PFS

	Tivozanib (N=260)		Sorafenib (N=257)	
	n	%	n	%
Total number of subjects censored	107	41.2	89	34.6
Ongoing treatment	73	28.1	40	15.6
Discontinued treatment due to investigator assessed PD (without PD by IRR assessment)	19	7.3	37	14.4
Discontinued treatment due to AE without PD by IRR assessment	8	3.1	5	1.9
Discontinued treatment due to withdrawal of consent without PD by IRR assessment[1]	4	1.5	2	0.8
Discontinued treatment due to lack of efficacy without PD by IRR assessment	1	0.4	1	0.4
Other[1]	2	0.8	4	1.6

1. A total 5 subjects (3 subjects in the tivozanib arm and 2 subjects in the Sorafenib arm) did not have IRR assessments post-baseline. Four of these 5 subjects had a primary reason for discontinuation of withdrawal of consent. 1 subject (assigned to Sorafenib) had a primary reason for discontinuation of other

History for Analysis Plan Stratification Factors (PFS, OS)

- For the primary inferential comparison of the treatment effect
- (SAP v1.0) Fully stratified analysis (original protocol) using all 3 stratification factors used for randomization
- (SAP v1.1) Unstratified analysis
- (SAP v2.0) Stratified analysis using: number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥2)

PFS Sensitivity Analysis

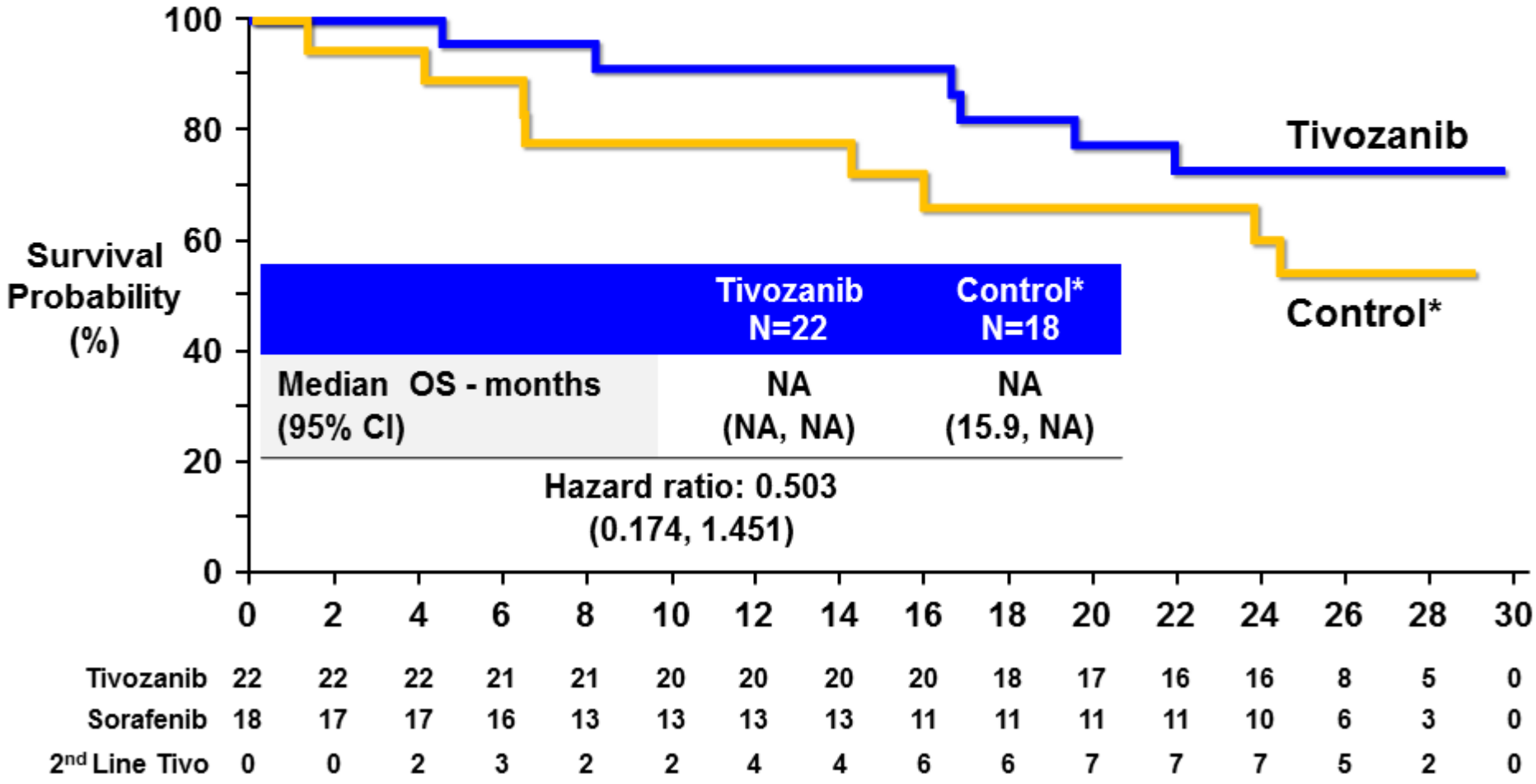
For subjects with event by INV but not by IRR, assume event at a future scheduled assessment by IRR

For subjects with event by INV but not by IRR Assume event	Hazard Ratio (95% CI)
At the next scheduled assessment for tivozanib arm only. (sorafenib arm unchanged)	0.884 (0.714, 1.094)
At the next scheduled assessment for both tivozanib and sorafenib arms	0.747 (0.611, 0.915)
After 2 more assessments for sorafenib arm Next visit for tivozanib arm	0.824 (0.673, 1.008)
After 3 more assessments for sorafenib arm Next visit for tivozanib arm	0.871 (0.710, 1.068)
After 4 more assessments for sorafenib arm Next visit for tivozanib arm	0.898 (0.732, 1.102)

Overall Survival by Geographic Region

	Tivozanib Mediaon OS	Sorafenib Median OS	HR (95% CI)
North America/ Western Europe (n=40)	**NA (NA, NA)**	**NA (15.9, NA)**	**0.503 (0.174, 1.451)**
Central/Eastern Europe (n=457)	**26.3 (20.8, NA)**	**29.3 (27.8, NA)**	**1.300 (0.986, 1.716)**
Rest of World (n=20)	**26.2 (5.1, NA)**	**NA (NA, NA)**	**3.646 (0.329, 40.40)**

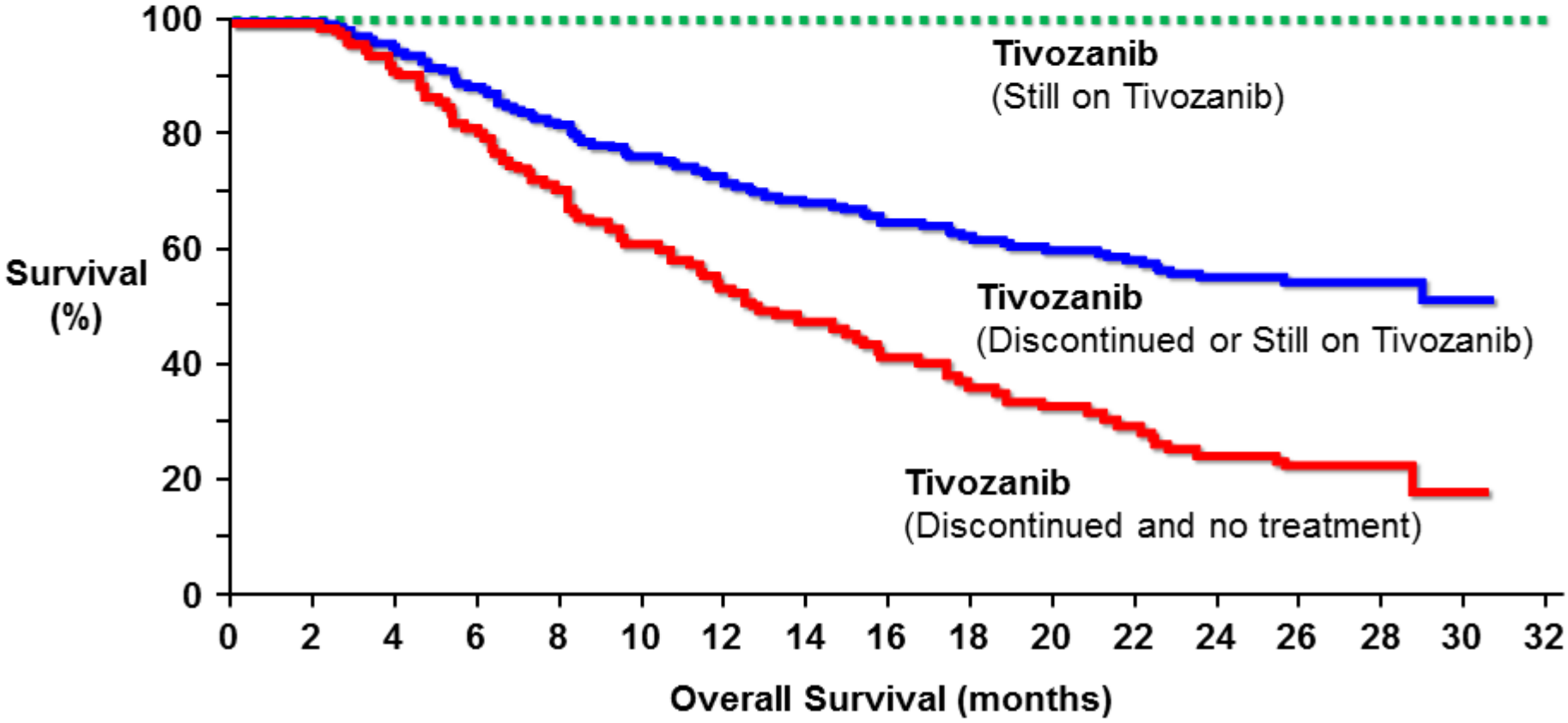
OS Trend in Favor of Tivozanib in NA/WE Patients



* Control = sorafenib randomization, plus crossover patients

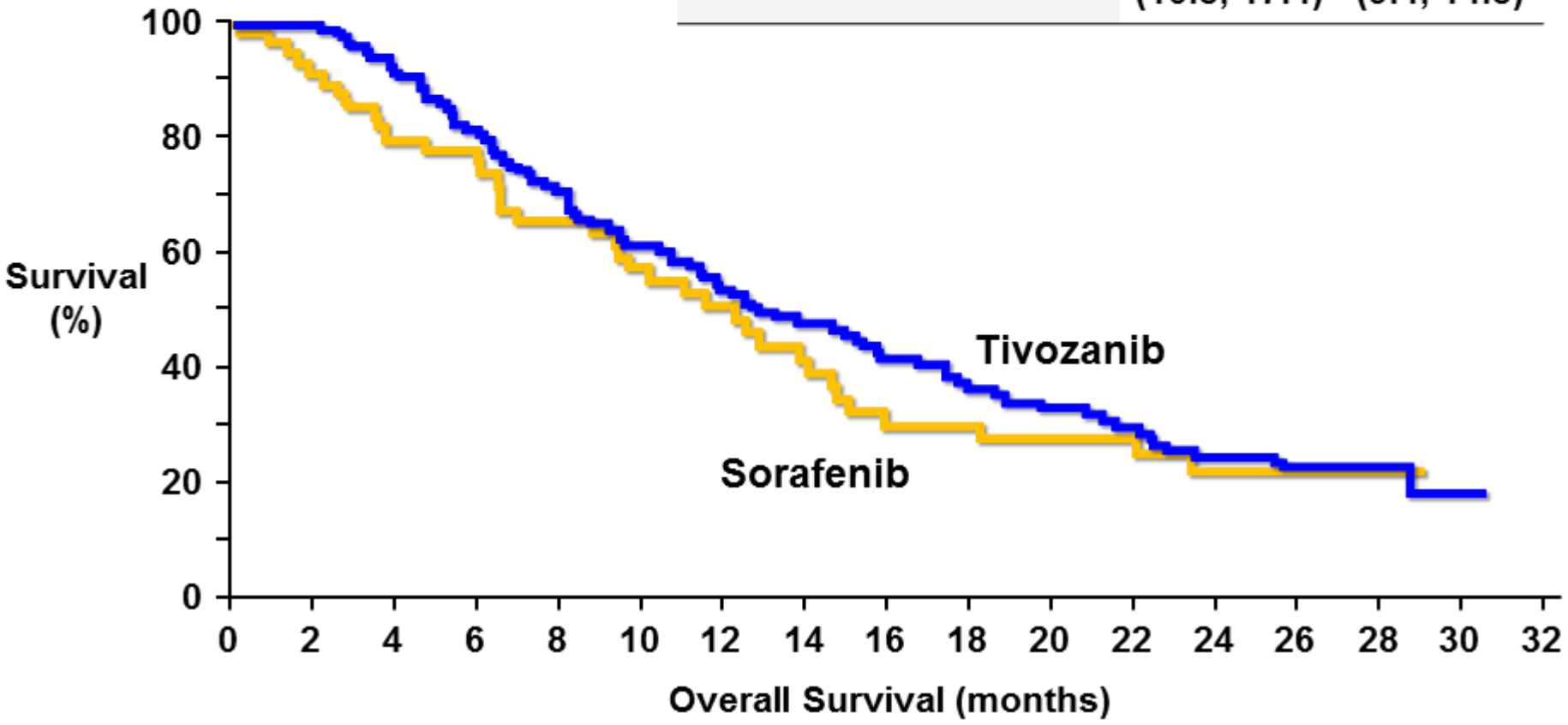
Tivozanib OS: 1 Line of Therapy Consists of 2 Groups

	Still on Tivozanib N=71	Discontinued or Still on Tivozanib N=192	Discontinued Tivozanib and received no other treatment n=121
Median (95% CI)	NA	NA (22.5, NA)	12.9 (10.8, 17.4)



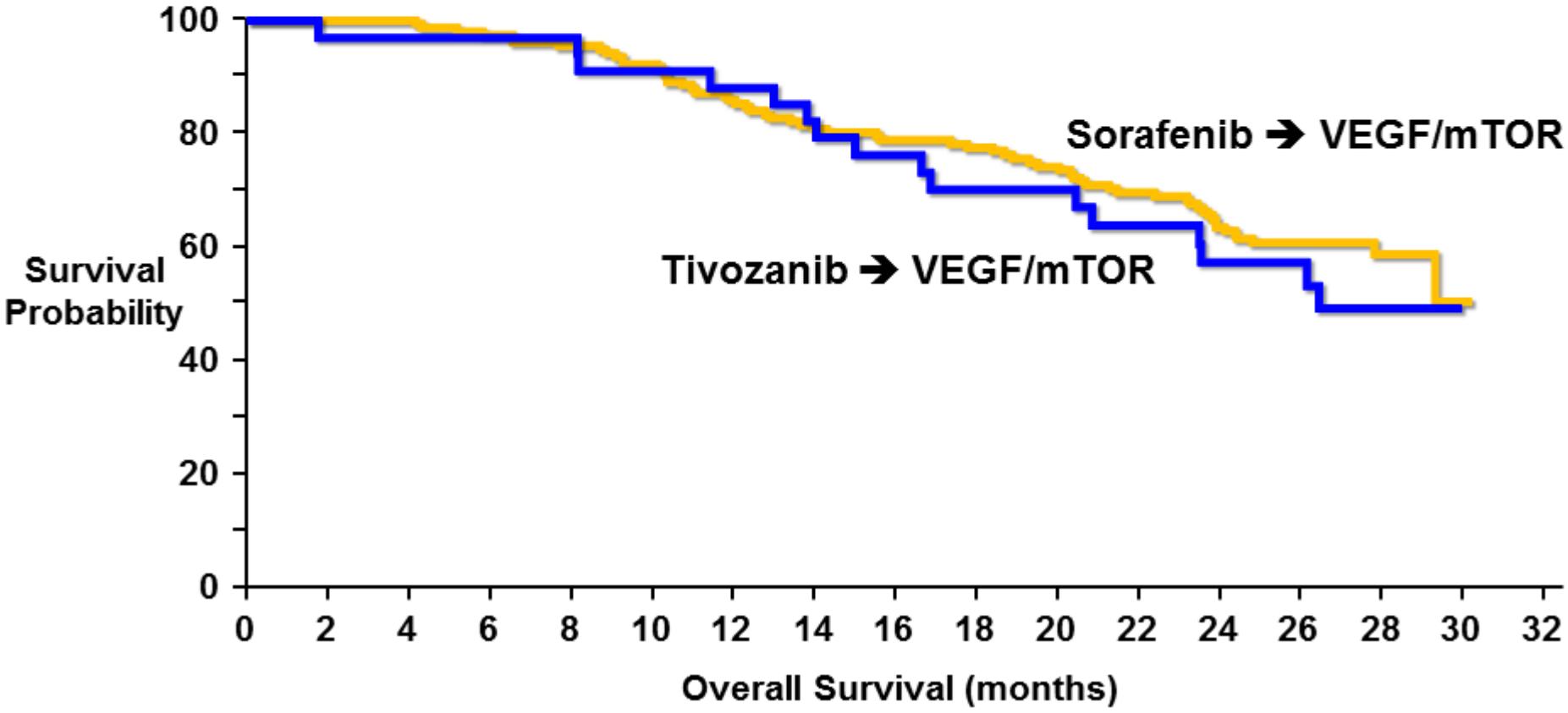
Overall Survival: "1 vs. 1" No Subsequent Treatment after Discontinuing Randomized Therapy

	Tivozanib N=121	Sorafenib N=58
Median (95% CI)	12.9 (10.8, 17.4)	12.3 (9.4, 14.8)

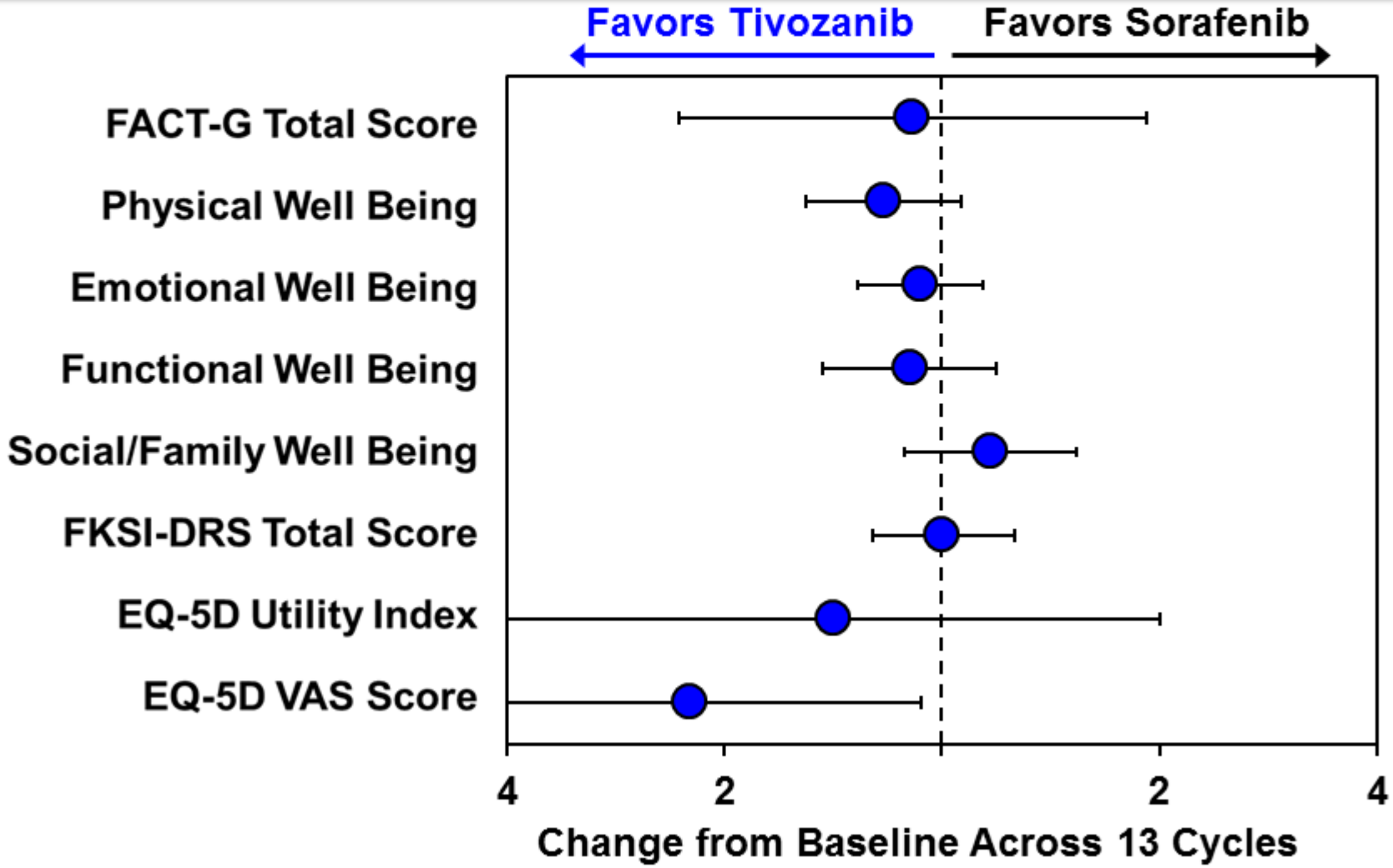


Overall Survival: "2 vs. 2": Next-line Targeted Therapy

	Tivozanib N=34	Sorafenib N=162
Median (95% CI)	26.45 (20.83, NA)	NA (29.31, NA)

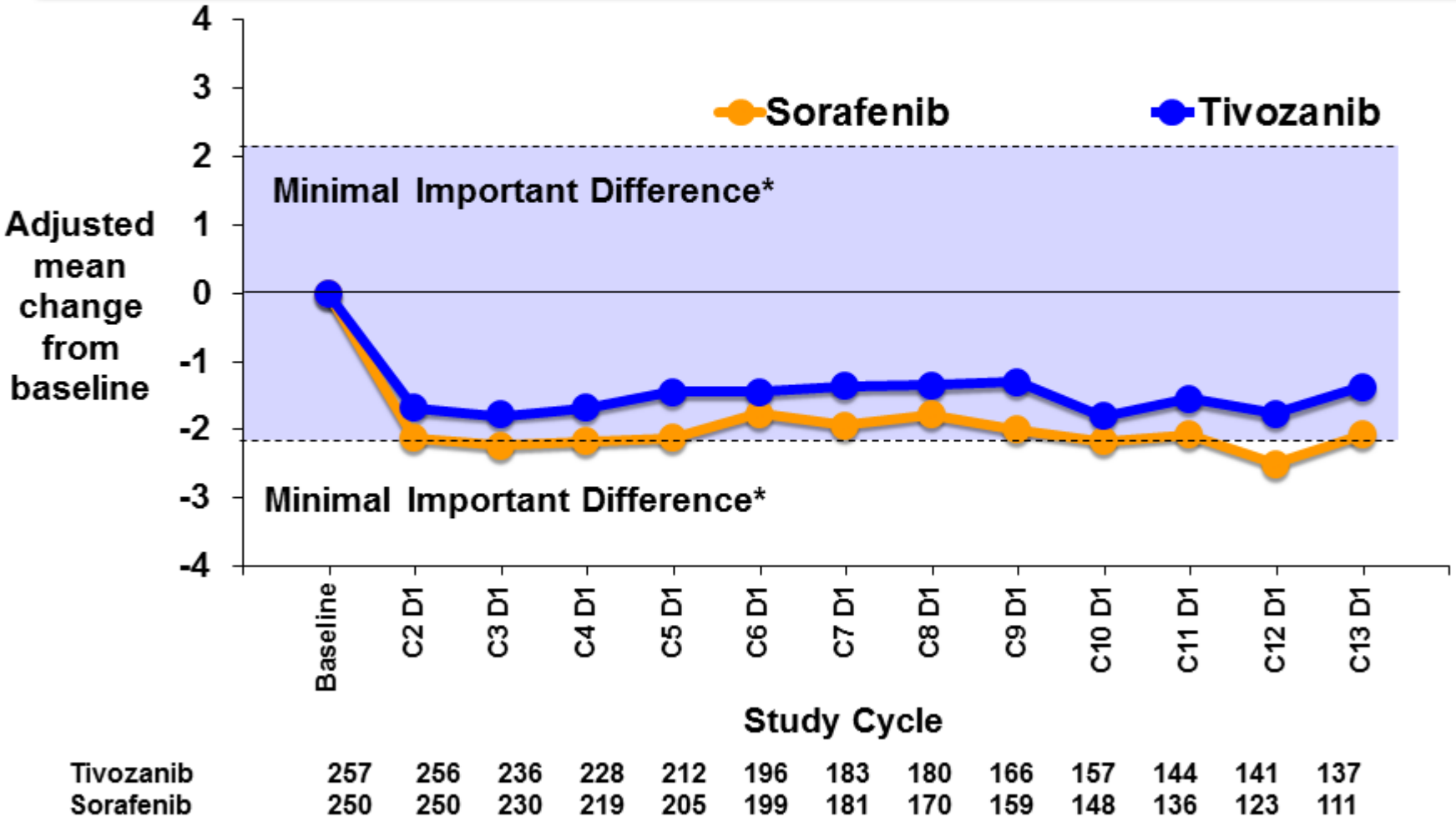


Change from Baseline of PRO tools



*EQ-5D Utility Index was multiplied by 100 to make scales comparable

Change from Baseline Physical Well Being (I am bothered by…)



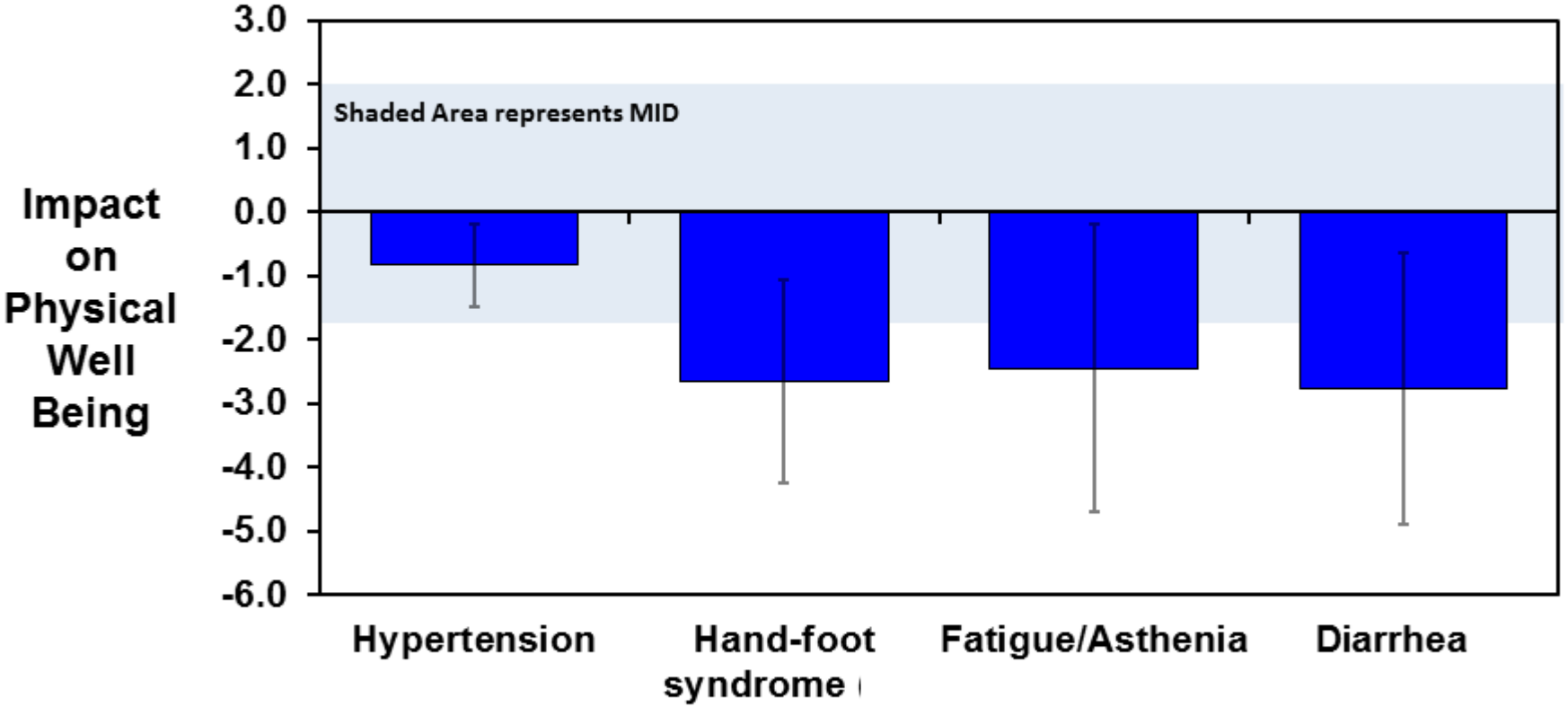
Tivozanib	257	256	236	228	212	196	183	180	166	157	144	141	137
Sorafenib	250	250	230	219	205	199	181	170	159	148	136	123	111

* Lower boundary for clinically meaningful change in QoL

Yost et al. Health Prof (2005)

PWB; 7 items; score range 0-28

Impact of Grade ≥3 Adverse Events on Physical Well Being



	Hypertension	Hand-foot syndrome	Fatigue/Asthenia	Diarrhea
Percentage of Incidences in Study 301	22%	9.5%	8%	4.5%