TIVO-3: A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib to Sorafenib in Subjects with Refractory Advanced Renal Cell Carcinoma (RCC)

Brian I. Rini, Sumanta K. Pal, Bernard Escudier, Michael B. Atkins, Thomas E. Hutson, Camillo Porta, Elena Verzoni, Michael N. Needle, David F. McDermott

Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; City of Hope, Duarte, CA; U1015 INSERM, Gustave Roussy Cancer Campus, Paris Saclay University, Villejuif, France; Georgetown Lombardi Comprehensive Cancer Center, Medstar Georgetown University Hospital, Washington, DC; Baylor Sammons Cancer Center-Texas Oncology, Dallas, TX; IRCCS San Matteo University Hospital Foundation, Pavia, Italy; Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy; Aveo Oncology, Cambridge, MA; Beth Israel Deaconess Medical Center, Boston, MA

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*Last 36 months

Tivozanib: Properties & Clinical Experience in RCC

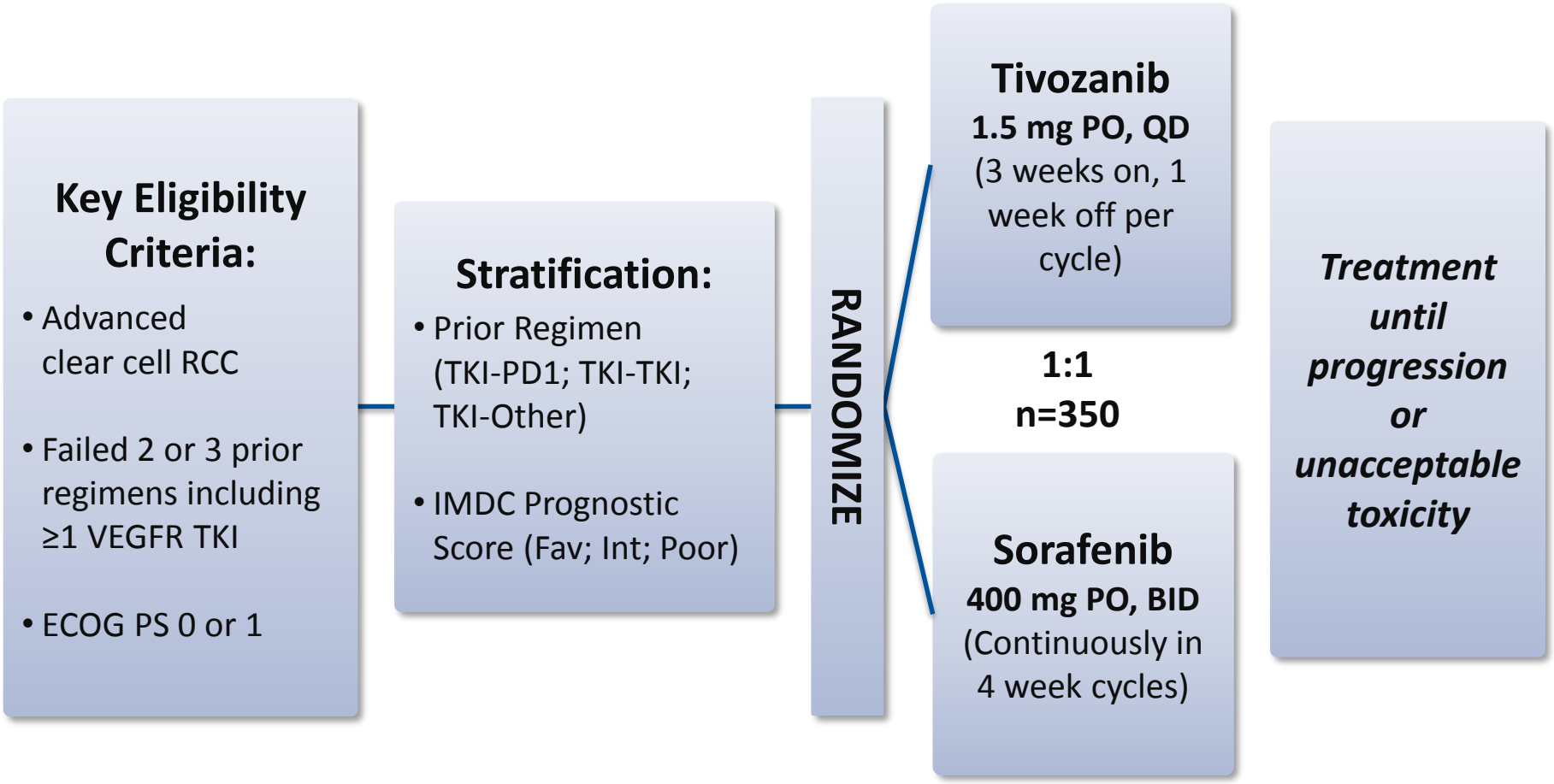
- Tivozanib is a potent, selective inhibitor of VEGFR 1, 2 & 3 with a long half-life designed to optimize VEGFR blockade and minimize off-target toxicities[1,2]

- TIVO-1: 1st line Phase III RCC study of tivozanib vs. sorafenib[3]
  - Superior PFS by IRC (11.9 mo vs. 9.1 mo; HR 0.80; p=0.04)
  - ORR 33% vs. 23%
  - OS 28.8 mo vs. 29.3 mo (HR 1.25; p=0.105)
  - Received 1st line EMA approval (Aug 2017)

- Study 902: 2nd line single arm RCC study in VEGFR TKI failures[4]
  - PFS (investigator-assessed) 11.0 mo / OS 21.4 mo / ORR 18%

1. Nakamura K et al. Cancer Res 2006;66:9134–9142.
2. Eskens FA et al. Clin Cancer Res 2011;17:7156–7163
3. Motzer R et al. Journal of Clinical Oncology 2013; Volume 31, Number 30
4. Hutson et al, Tivozanib vs sorafenib targeted therapy for RCC: final results of a Phase 3 trial (901) and efficacy results of a second line tivozanib extension study (902) ASCO 2015

TIVO-3: Study Design



IMDC, International Metastatic RCC Database Consortium; **QD,** once per day**; BID,** twice per day; **PO**, oral administration

Study Objectives

- **Primary Endpoint**
  - PFS per Independent Review Committee (IRC; data cutoff Oct. 4th 2018)
  - 90% power to detect PFS improvement of 4 vs 6 months

- **Secondary Endpoints**
  - ORR per IRC
  - OS: Preliminary analysis at Oct. 4th 2018 PFS cutoff date.
    Final analysis cutoff date Aug. 2019 (2 years after last patient enrolled)
  - Investigator-Assessed PFS
  - Duration of Response
  - Safety

Baseline Patient Characteristics (ITT)

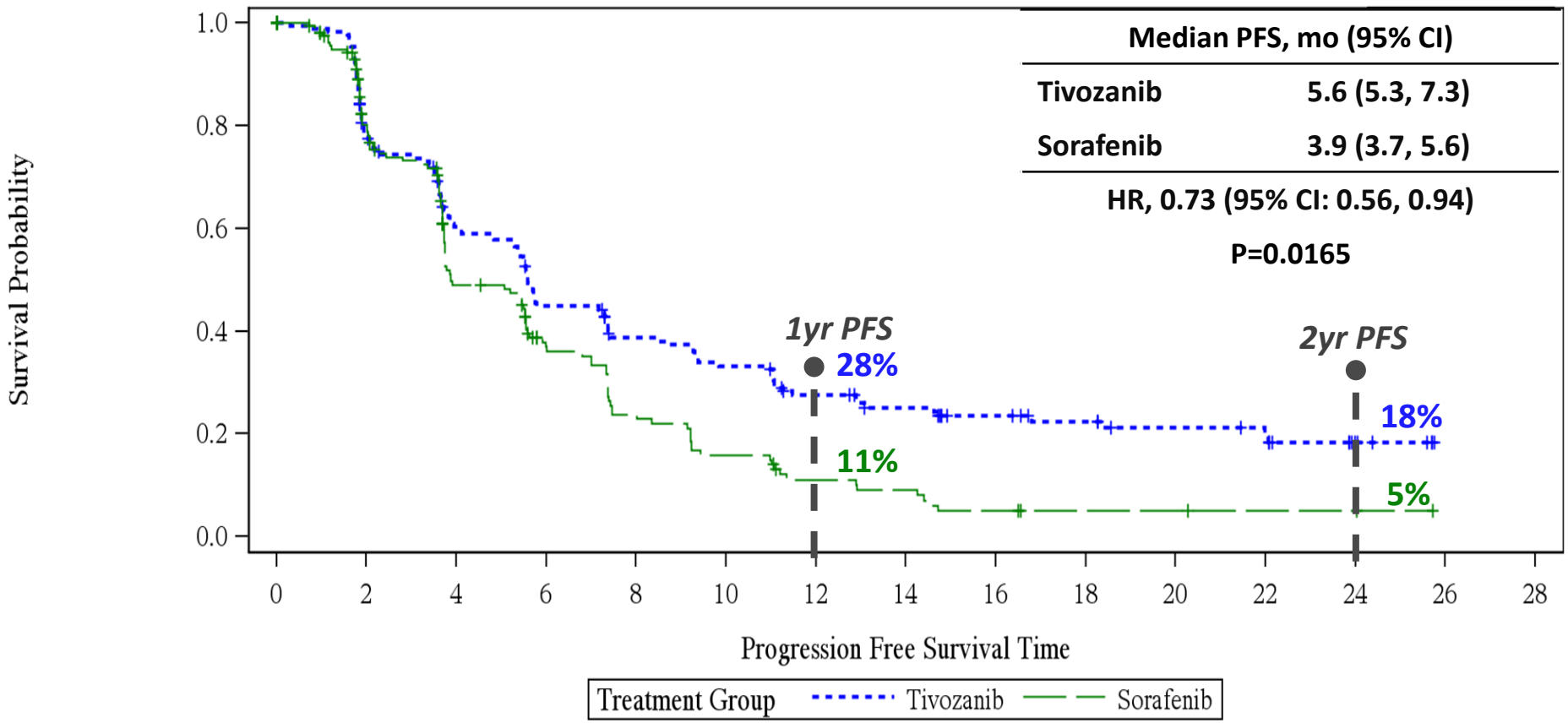
Characteristics	Tivozanib (N=175)	Sorafenib (N=175)
Median age, years	62	64
Male, %	72	73
IMDC Prognostic Risk, %		
Favorable	19	21
Intermediate	62	60
Poor	18	19
ECOG Performance Status, % (0/1)	(49/50)	(47/48)
Region, % (NA/EU)	(18/82)	(15/85)
Prior Lines of Therapy, % (2/3)	(62/38)	(59/41)
Prior Treatment Regimen, %		
TKI-PD1	27	25
TKI-TKI	45	46
TKI-Other	28	29

Patient Disposition

Disposition	Tivozanib (N=175)	Sorafenib (N=175)
Active Follow Up, %	42	47
Lost to Follow Up, %	2	5
Remain on Study Therapy, %	19	5
Never Treated, %	1	3
Treatment Discontinuation, %	79	92
Reasons for Treatment Discontinuation, %		
Disease progression	48	52
Adverse event	13	23
Clinical deterioration	11	8
Other	8	9

Progression-Free Survival per IRC (ITT)

Primary endpoint

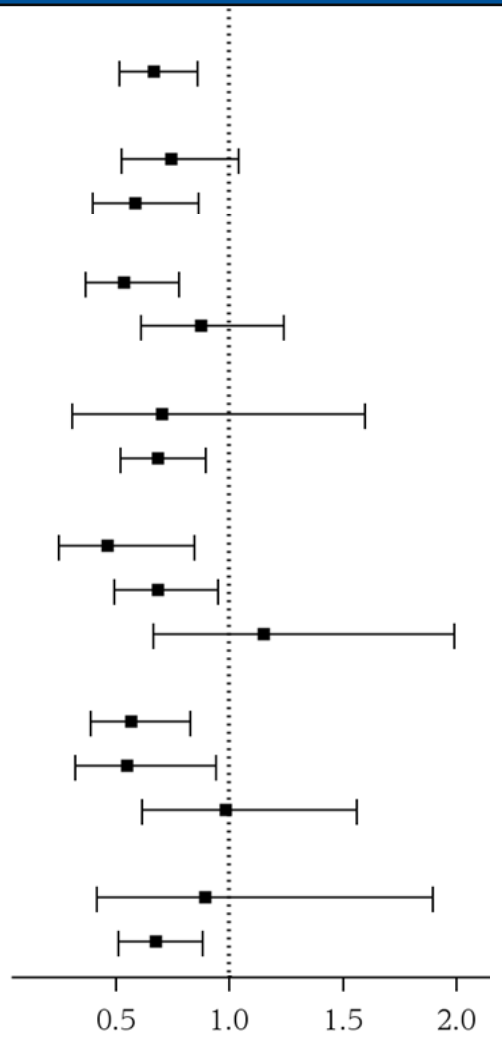


Subjects at risk

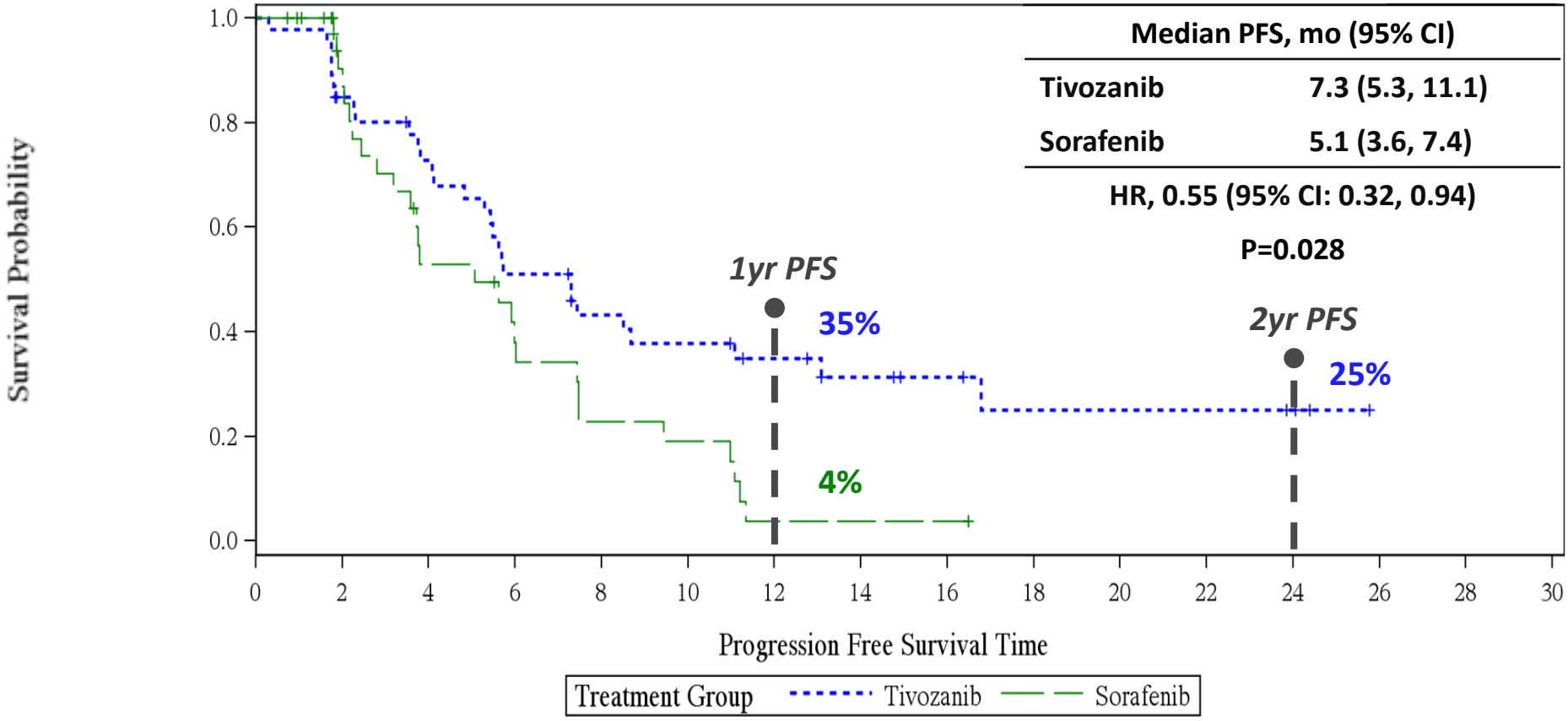
Survival Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Tivozanib	170	128	94	69	56	48	37	31	24	20	16	14	6	0	0
Sorafenib	159	116	65	42	27	18	11	9	5	3	3	2	2	0	0

Progression-Free Survival per IRC (Subgroups)

Subgroup	Patients N (%)
All Patients	350 (100.0)
Age Categorization	
< 65 years	193 (55.1)
>= 65 years	157 (44.9)
Baseline ECOG Status	
0	168 (48.0)
1	172 (49.1)
Geographic Region	
North America	58 (16.6)
European Union	292 (83.4)
IMDC Risk Category	
Favorable	70 (20.0)
Intermediate	214 (61.1)
Poor	66 (18.9)
Prior Therapy	
Two Prior VEGFR TKIs	159 (45.4)
Prior Checkpoint Inhibitor Plus VEGFR TKI	91 (26.0)
Prior VEGFR TKI Plus Other Systemic Agent	100 (28.6)
Number of Metastatic Sites	
1	38 (10.9)
>= 2	312 (89.1)



Progression-Free Survival per IRC (Prior IO Subgroup)



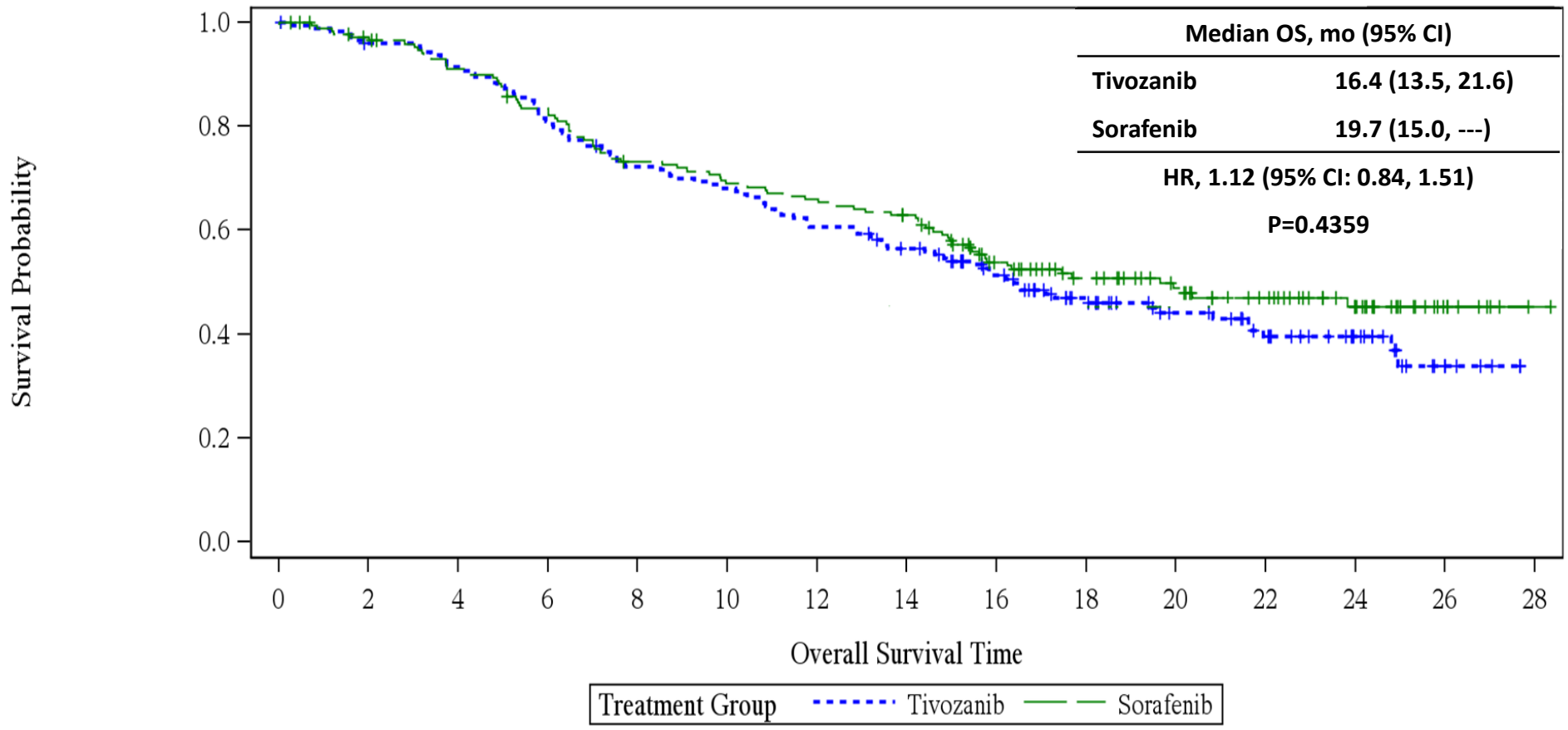
ORR and Duration of Response (ITT)

Secondary endpoint

Per IRC	Tivozanib (N=175)	Sorafenib (N=175)
Best Overall Response, %		
Complete Response	0	0
Partial Response	18	8
Stable Disease	55	57
Progressive Disease	21	18
Not Evaluable	6	17
Overall Response Rate (ORR), %	**18**	**8**
	P=0.02	
Duration of Response (DOR)		
Median DOR, months (95% CI)	NR (12.9, ---)	5.7 (5.6, ---)
DOR Probability at 1 Year, %	71	46
DOR Probability at 2 Years, %	55	0

Interim Overall Survival (ITT)

Secondary endpoint



Subjects at risk

Survival Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Tivozanib	175	166	158	139	124	117	104	94	75	56	42	33	20	5	0
Sorafenib	175	165	153	139	121	114	109	102	76	62	51	40	26	9	1

Subsequent Systemic Therapy

Treatment, N (%)	Tivozanib (N=175)	Sorafenib (N=175)
Remain on Study Treatment*	34 (19)	9 (5)
Unknown Subsequent Therapy	47 (27)	64 (37)
No Subsequent Therapy	23 (13)	20 (11)
Any Subsequent Therapy	71 (41)	82 (47)
Checkpoint Only	8 (5)	17 (10)
Checkpoint + VEGF or Other	13 (7)	18 (10)
VEGF Only	31 (18)	31 (18)
VEGF + mTOR or Other	9 (5)	4 (2)
mTOR Only	4 (2)	6 (3)
Other	6 (3)	6 (3)

**31 of 43 patients remaining on study treatment have not received prior checkpoint (T=24, S=7)*

Overall Safety Summary

Secondary endpoint

Exposure	Tivozanib (N=173)	Sorafenib (N=170)
Mean Number of Cycles Initiated	10.3	6.3
Mean Dose Intensity, %	89	71
AEs Leading to Dose Reductions, %	24	38
AEs Leading to Dose Interruption, %	48	63
Treatment Related AEs (All Grade), %	84	94
Treatment Related SAEs, %	11	10
Treatment Related Deaths, %	0	0

Treatment-Related Adverse Events (≥10% frequency in either arm)

Secondary endpoint

	Tivozanib (N=173)		Sorafenib (N=170)	
Preferred Term, %	All Grades	Grade 3/4	All Grades	Grade 3/4
Treatment Related AEs	84	44	94	55
Hypertension	36	20	25	14
Diarrhea	33	2	50	9
Fatigue	29	4	19	5
Decreased Appetite	26	4	21	2
Dysphonia	24	1	8	0
Asthenia	21	5	17	4
Stomatitis	19	2	18	2
Nausea	19	0	14	2
PPE*	16	1	38	10
Hypothyroidism	14	1	6	0
Rash	4	0	24	8

*Palmar-plantar erythrodysesthesia syndrome

>5% difference between arms

TIVO-3 Conclusions

- Tivozanib significantly improves PFS and ORR compared to sorafenib in patients with treatment-refractory advanced RCC
  - Tivozanib was superior in patients previously treated with checkpoint inhibitors as well as two VEGFR-TKIs
  - Responses with tivozanib were more durable than sorafenib
- Tivozanib was well tolerated with hypertension as the most common adverse event
  - Lower rates of hand foot syndrome, diarrhea, and rash were observed for tivozanib compared to sorafenib
- OS data are immature with final analysis pending

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