TIVO-3: A Phase 3 Study to Compare Tivozanib to Sorafenib in Subjects with Refractory Advanced Renal Cell Carcinoma (RCC)

Overall Survival 2-Year Update

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Tivozanib: Properties & Clinical Experience in RCC

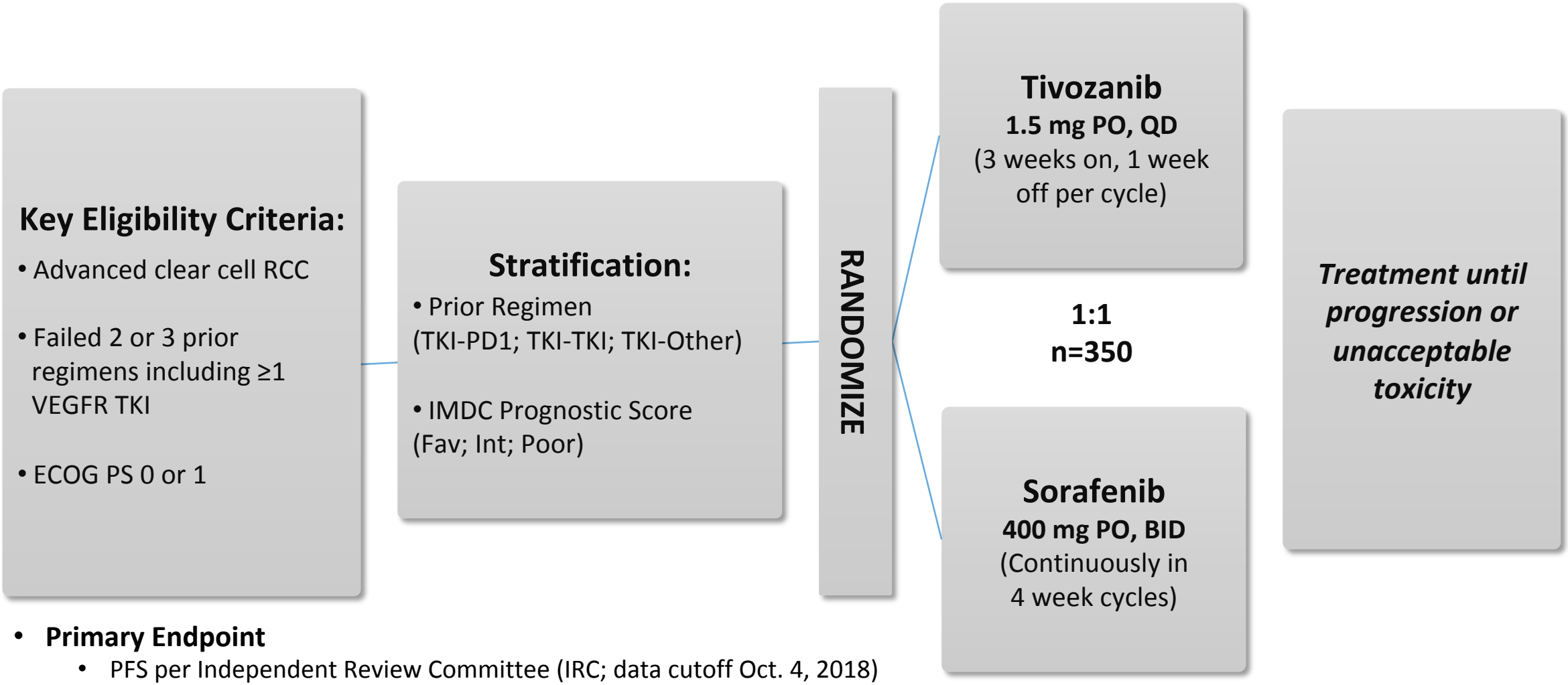
- Tivozanib is a potent, selective inhibitor of VEGFR 1, 2 & 3 with a long half-life designed to optimize VEGFR blockade and minimize off-target toxicities[1,2]

- TIVO-1: 1st line Phase III RCC study of tivozanib vs. sorafenib[3]
  - Received 1st line EMA approval (Aug 2017) based on superior PFS
  - FDA requested additional Ph3 (PFS Primary and no adverse effect on OS)

- Refractory RCC Landscape
  - No RCC treatments have shown superior benefit over another active therapy in the 3rd /4th line setting
  - Immunotherapy has emerged a standard of care for early lines of treatment for RCC patients, limited prospective data exist to inform sequencing after IO failure

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

TIVO-3: Study Design



- **Primary Endpoint**
  - PFS per Independent Review Committee (IRC; data cutoff Oct. 4, 2018)
- **Secondary Endpoints**
  - ORR, OS, Inv PFS, DOR, Safety

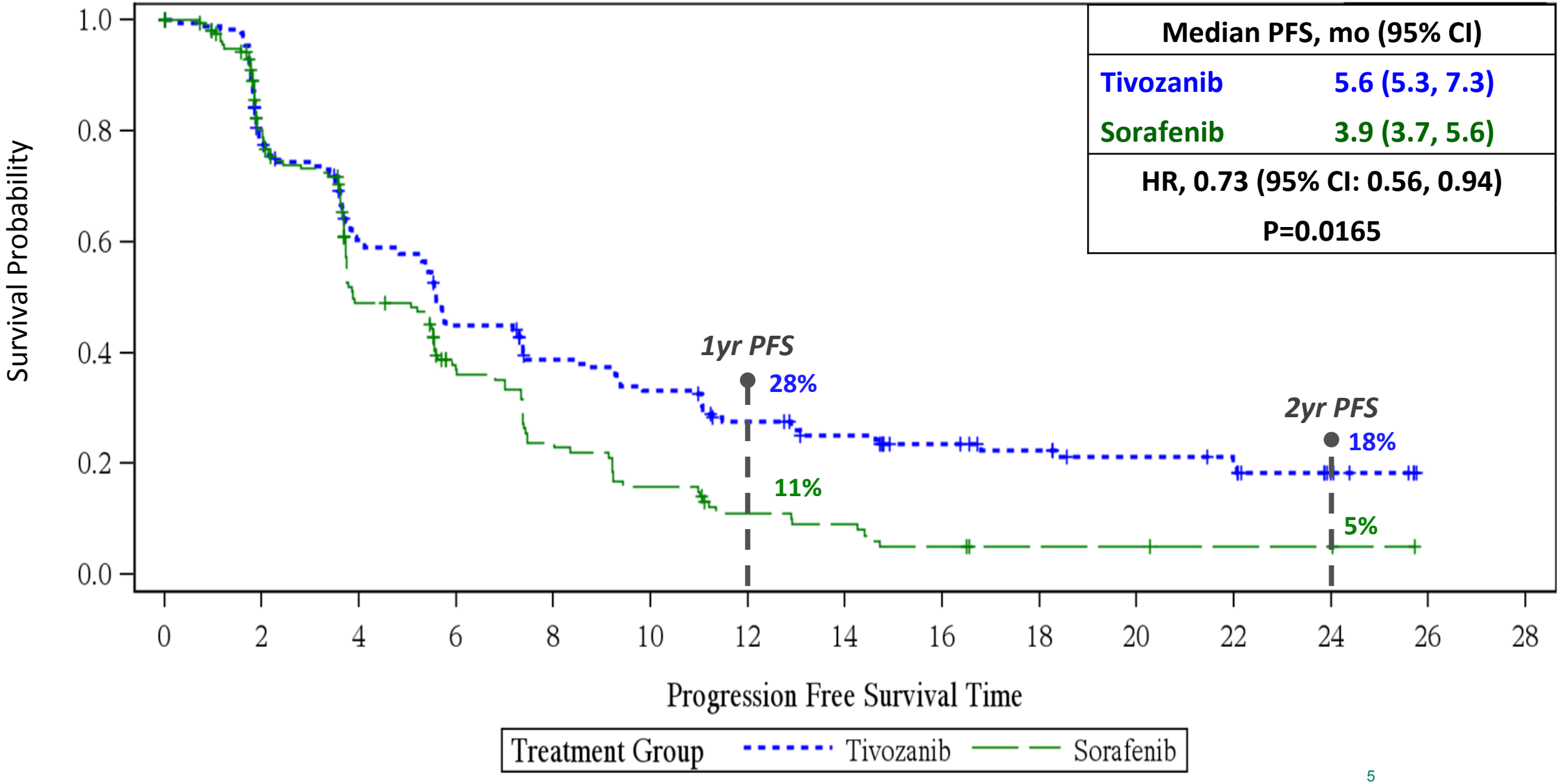
IMDC, International Metastatic RCC Database Consortium; **QD,** once per day**; BID,** twice per day; **PO**, oral administration

TIVO-3: Patient Demographics at Entry (ITT)

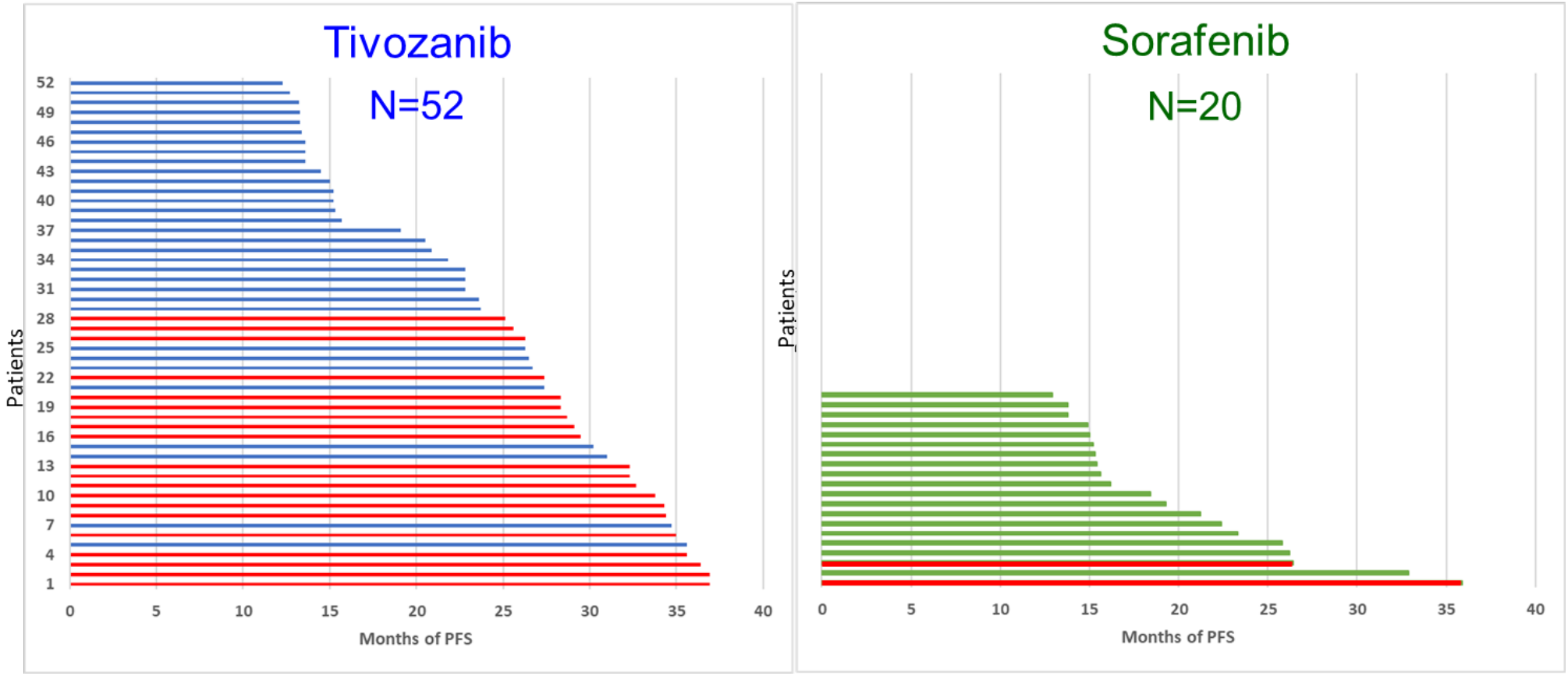
Characteristic	Tivozanib (N=175)	Sorafenib (N=175)
Median age, years	62	64
Male, %	72	73
IMDC prognostic risk,		
Favorable	19%	21%
Intermediate	62%	60%
Poor	18%	19%
ECOG performance status, % (0/1)	(49/50)	(47/48)
Region, % (NA/EU)	(18/82)	(15/85)
Prior Lines of Therapy, % (2/3)	(62/38)	(59/41)
Prior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

Lancet Oncology, In Press

TIVO-3: Primary Endpoint Progression-Free Survival per IRC (ITT)



TIVO-3: Swimmers Plot of Patients Progression Free >1 Year

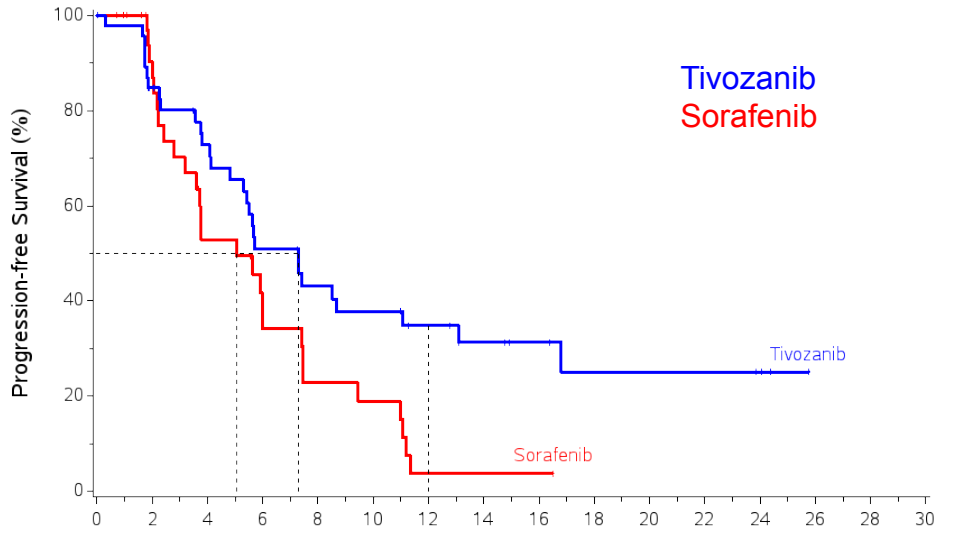


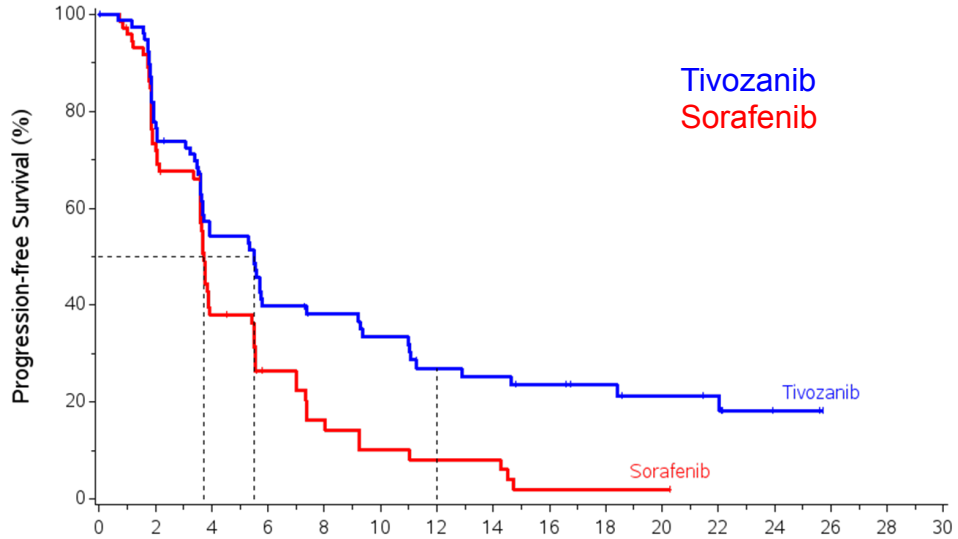
RED = Patients Progression Free* and Still on Therapy (Tivozanib n=20 / Sorafenib n=2)

Overall Response Rate: 18% tivozanib vs 8% sorafenib, p=0.02

*Investigator assessed PFS

TIVO-3: PFS & ORR in Key Subgroups*





*Final analysis, as of Oct 4, 2018

Porta et al. ASCO 2019

Prior Checkpoint Inhibitor + VEGFR TKI

	Tivozanib (n=47)	Sorafenib (n=44)
Median PFS, months (95% CI)	7.3 (4.8, 11.1)	5.1 (3.2, 7.4)
HR (95% CI)	0.55 (0.32, 0.94)	
P Value	0.028	
ORR	24.4%	6.8%

Two Prior VEGFR TKIs

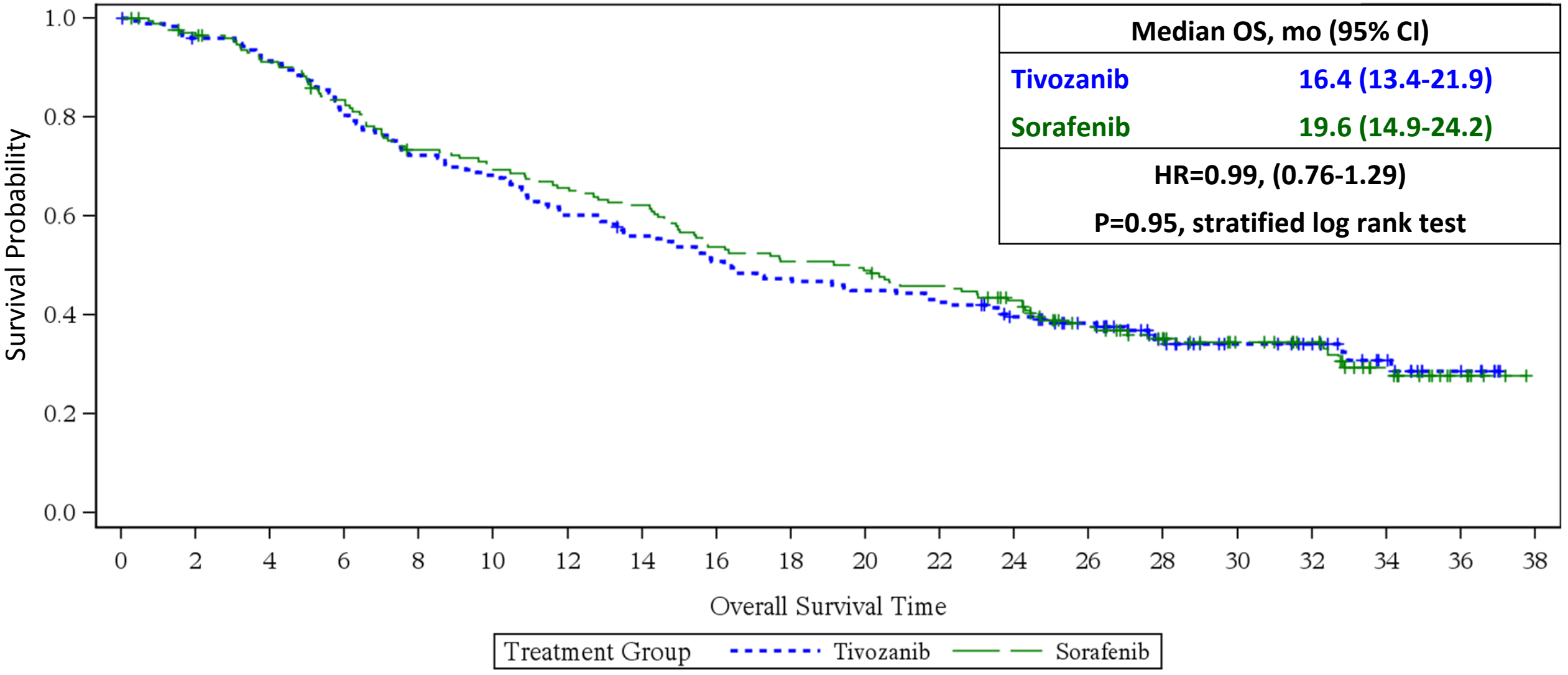
	Tivozanib (n=79)	Sorafenib (n=80)
Median PFS, months (95% CI)	5.5 (3.6, 7.4)	3.7 (3.6, 3.9)
HR (95% CI)	0.57 (0.39, 0.83)	
P Value	0.003	
ORR	15.2%	7.5%

TIVO-3: Overall Survival Update

	Oct 4, 2018	Aug 15, 2019
OS HR	**1.12**	**0.99**
95% CI; p value	**0.84-1.51; p=0.44**	**0.76-1.29; p=0.95**
OS Events	**183 (52%)**	**227 (65%)**

- 44 additional events since Oct. 4, 2018 data cut
  - 16 tivozanib events and 28 sorafenib events
  - OS events 114 tivozanib and 113 sorafenib
- Median follow up duration of 33 months, 24 months from last patient enrolled

TIVO-3: Overall Survival – ITT (August 15, 2019)



TIVO-3: OS Data by Subgroup

	Oct 4, 2018		Aug 15, 2019	
Group (n)	% of Events	OS HR	% of Events	OS HR
ITT (350)	52%	1.12	65%	0.99
VEGF/IO (91)	43%	1.14	58%	0.88
VEGF/VEGF (159)	58%	1.05	66%	0.98
VEGF/Other (100)	54%	1.42	69%	1.10

**PFS assessment by investigator*

TIVO-3: Treatment-Related Adverse Events

Fewer adverse events observed for tivozanib

Preferred Term	Tivozanib (N=173)		Sorafenib (N=170)	
	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
PPE*	16	1	38	10
Rash	4	0	24	8

>5% difference between arms

TIVO-3: Patient Disposition and Drug Exposure (ITT)

	Tivozanib (N=173)		Sorafenib (N=170)
Mean Number of Cycles Initiated	11.9		6.7
AEs Leading to Dose Reductions (%)	**24**	P=0.005	**38**
AEs Leading to Dose Interruption (%)	**48**	P=0.007	**63**
Treatment Related SAEs (%)	12		11
Treatment Related Deaths (%)	0		0

TIVO-3: Conclusions

- Tivozanib significantly improves PFS and ORR compared to sorafenib in 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
- Updated Overall Survival HR 0.99
- Tivozanib was well tolerated with lower overall rates of adverse events
  - Fewer dose interruptions and reductions required on tivozanib

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TIVO-3: Overall Survival by Quartile

OS Quartiles (95% CI)	Tivozanib	Sorafenib
25%	7.4 (6.0, 10.2)	7.3 (6.4, 10.9)
50%	16.4 (13.4, 21.9)	19.6 (14.9, 24.2)
75%	NR (32.8, NR)	NR (32.4, NR)