Abstract No. 4501

Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a Phase III randomized, open-label, multicenter trial

R. Motzer, D. Nosov, T. Eisen, I. Bondarenko, V. Lesovoy, O. Lipatov, P. Tomczak, O. Lyulko, A. Alyasova, M. Harza, M. Kogan, B.Y. Alexeev, C.N. Sternberg, C. Szczylik, J. Zhang, A. Strahs, B. Esteves, W. Slichenmyer, A. Berkenblit, T.E. Hutson, and the TIVO-1 Study Group

Background

- **Tivozanib is a potent, selective inhibitor of VEGFRs 1, 2, and 3 with a long half-life that is designed to optimize blockade while minimizing off-target toxicities[1,2]**
- **Favorable pharmacokinetic profile:**
  - **$t_{1/2}$ of 3.7–4.7 days allows once-daily dosing (1.5 mg) with consistent serum concentration[2,3]**
  - **No interaction with CYP3A4 inhibitors[4]**
- **Phase II trial conducted in 272 advanced RCC patients[5]**
  - **Median PFS was 11.7 months**
  - **Hypertension was the predominant toxicity**
  - **Low incidence of 'off-target' AEs**

AEs, adverse events; CYP3A4, cytochrome P450 3A4; PFS, progression-free survival; RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.

1. Nakamura K *et al*. *Cancer Res* 2006;66:9134–9142. 2. Eskens FA *et al*. *Clin Cancer Res* 2011;17:7156–7163. 3. Cotreau M *et al*. ASCO-NCI-EORTC; San Francisco, CA; November 12–16, 2011. 4. Data on file. 5. Nosov D *et al*. *J Clin Oncol* 2012;30:1678–1685.

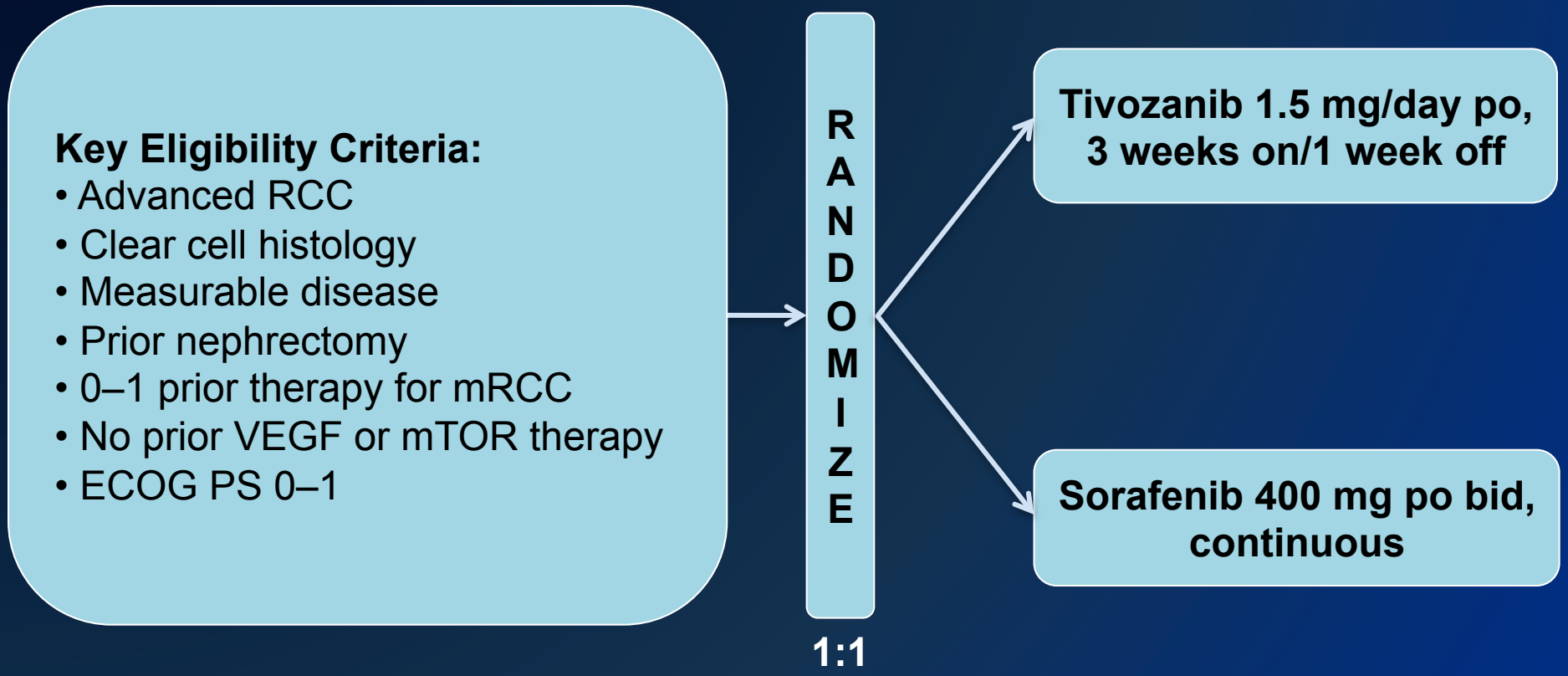
Study objectives

- **Primary objective:**
  - **To demonstrate PFS superiority in patients with mRCC receiving tivozanib vs sorafenib as a first-line targeted therapy**

- **Secondary objectives:**
  - **Objective response rate**
  - **Safety**
  - **Overall survival[a]**
  - **Patient-reported outcomes[a]**
  - **Pharmacokinetics[a]**

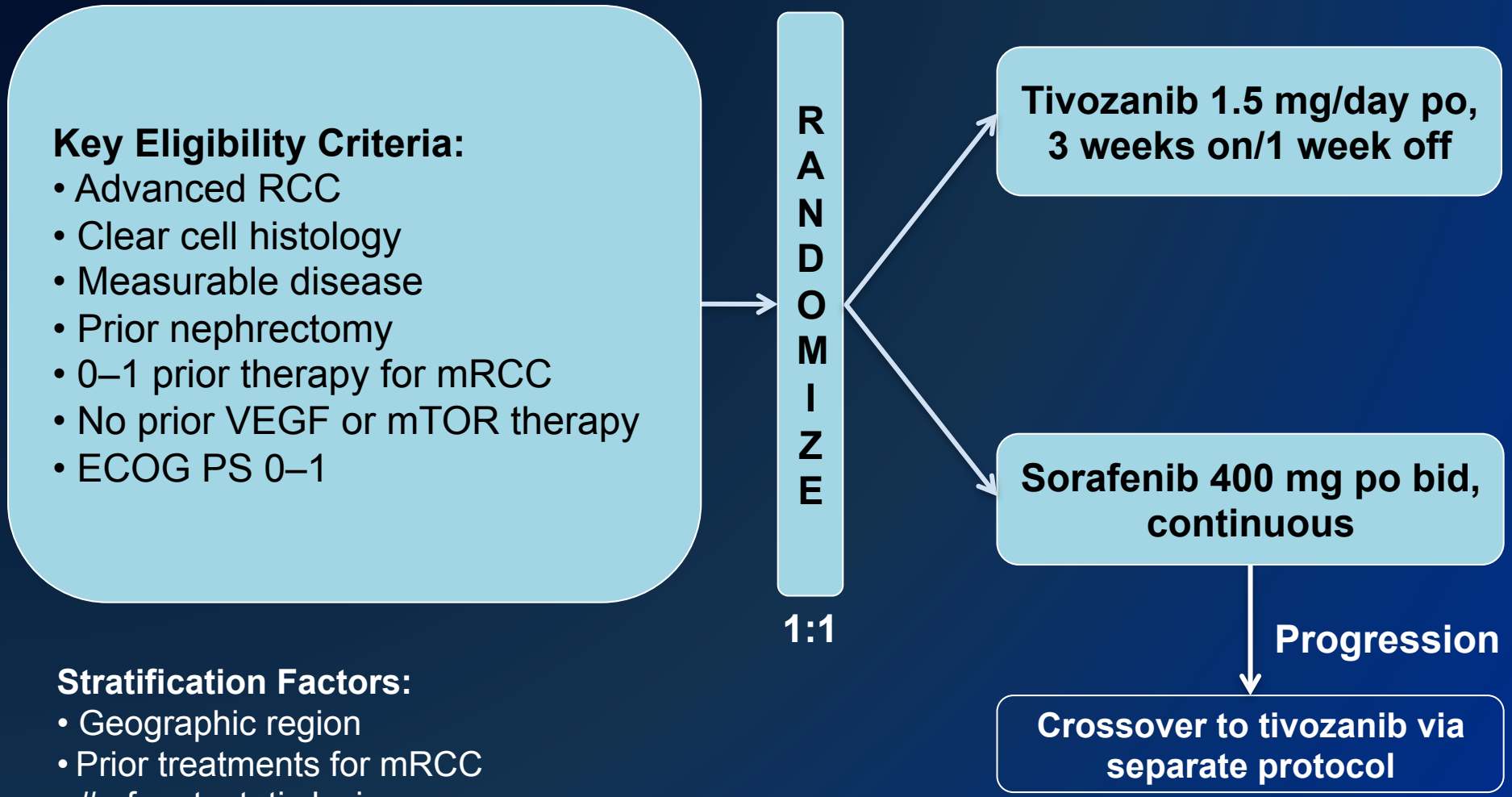
[a]Data not reported.

TIVO-1: Phase III superiority study of tivozanib vs sorafenib as first-line targeted therapy for mRCC



Stratification Factors:
- Geographic region
- Prior treatments for mRCC
- # of metastatic lesions

TIVO-1: Phase III superiority study of tivozanib vs sorafenib as first-line targeted therapy for mRCC



Study assessments

- Safety data collected from consent to 30 days after last dose
- Assessment of response every 2 cycles (8 weeks)
- Treatment continued until progression or intolerance
  - 'Real-time' blinded third-party review to confirm progression
  - Radiographic progression required for sorafenib patients to cross over to tivozanib
- Independent blinded review for primary endpoint by core imaging laboratory

Statistical analysis

- **Primary endpoint**
  - **PFS, assessed by independent review**
  - **Stratified log-rank test with two-sided significance level of α=0.05**
- **Planned trial size**
  - **N=500 powered for PFS (310 events)**
  - **90% power to detect a ≥45% improvement in median PFS from 6.7 months for sorafenib to 9.7 months for tivozanib**

Baseline characteristics

Characteristic	Tivozanib	Sorafenib
No. of patients	260	257
Median age (range)	59 (23–83)	59 (23–85)
Gender, male, %	71	74
ECOG score,[a] %		
0	45	54
1	55	46
Number of organs involved, %		
1	29	34
≥2	71	66
Sites of metastases, %		
Lung	82	79
Liver	26	19
Bone	24	20

[a]Imbalance between arms. $P<0.05$ by Fisher exact test.

Baseline characteristics

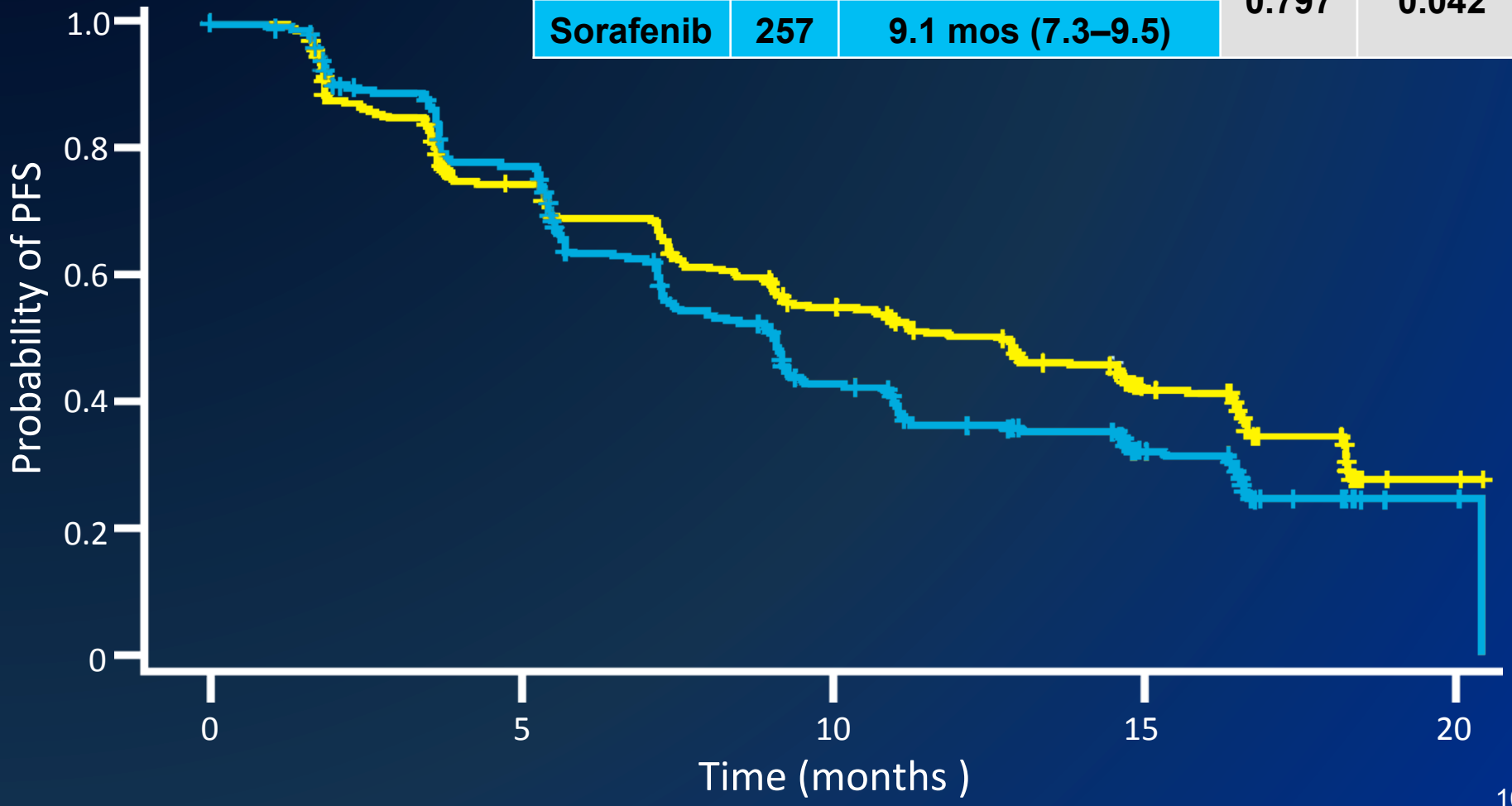
Characteristic	Tivozanib (N=260)	Sorafenib (N=257)
MSKCC prognostic group,[1] %		
Favorable	27	34
Intermediate	67	62
Poor	7	4
Prior systemic therapy for metastatic RCC, %		
0	70	70
1	30	30

MSKCC, Memorial Sloan-Kettering Cancer Center.

1. Motzer RJ *et al. J Clin Oncol* 1999;17:2530–2540.

Primary endpoint: Progression-free survival (independent review)

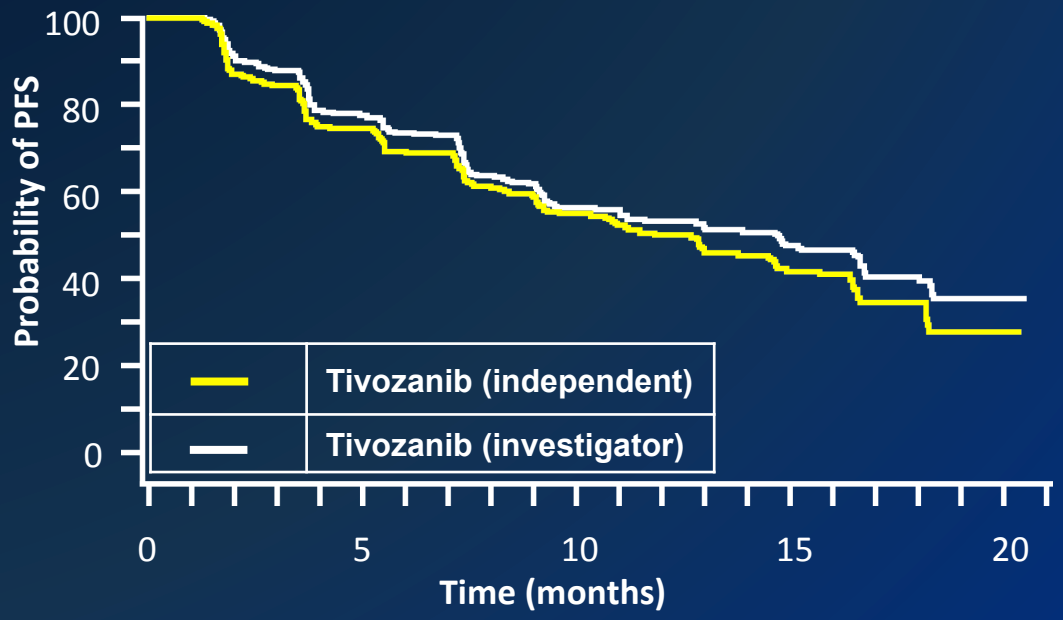
	N	Median PFS (95% CI)	HR	*P* value
Tivozanib	260	11.9 mos (9.3–14.7)	0.797	0.042
Sorafenib	257	9.1 mos (7.3–9.5)		



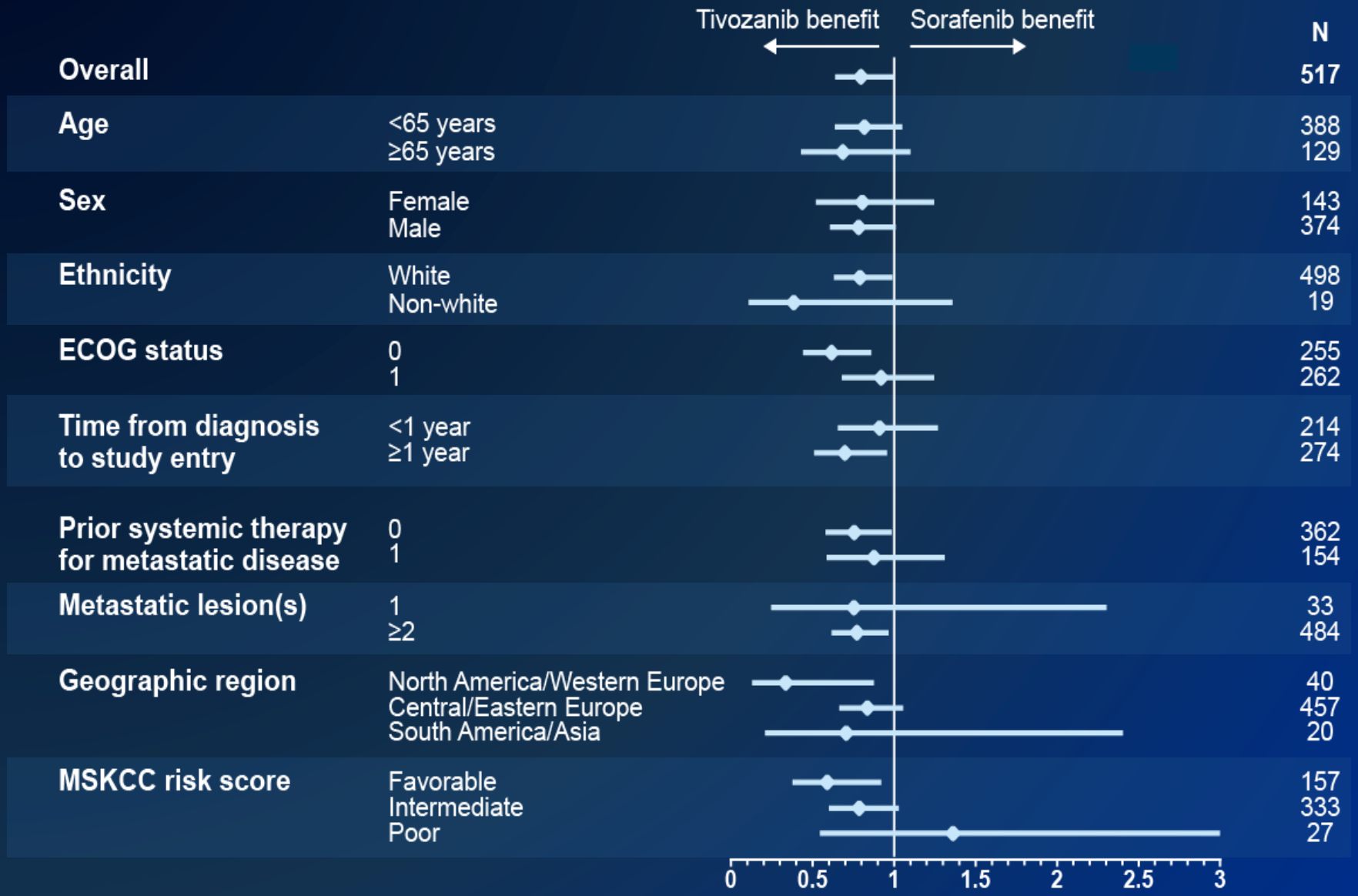
Progression-free survival: Investigator and independent assessment

	Median PFS, months (95% CI)			
	Tivozanib (n=260)	Sorafenib (n=257)	HR	*P* value
Independent	11.9 (9.3–14.7)	9.1 (7.3–9.5)	0.797	0.042
Investigator	14.7 (10.4–16.6)	9.6 (9.0–11.0)	0.722	0.003

PFS for tivozanib arm: Investigator vs independent assessment

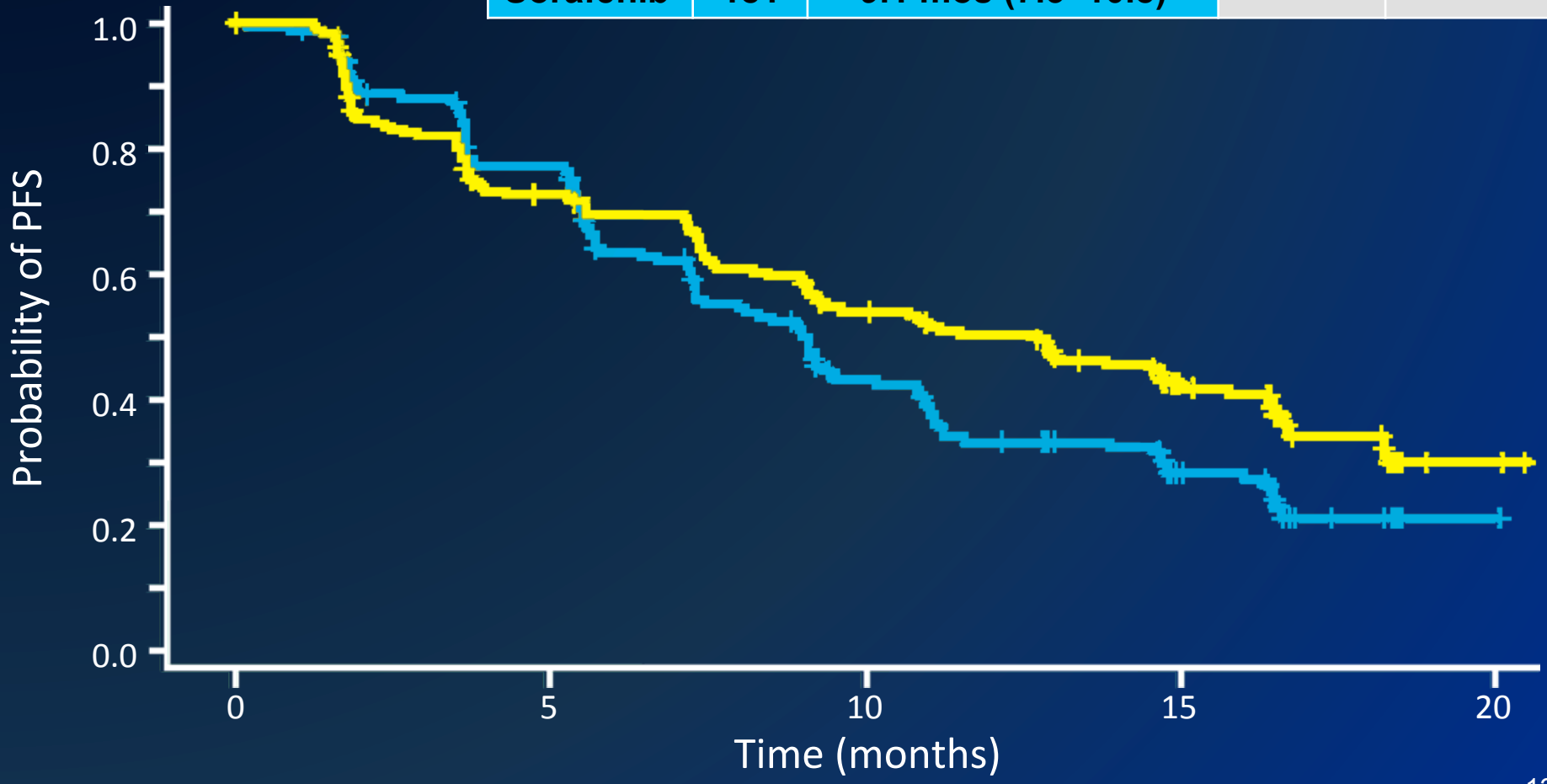


Hazard ratios for PFS by prognostic factors and baseline characteristics



Progression-free survival: Treatment-naïve for metastatic RCC (independent review)

	N	Median PFS (95% CI)	HR	*P* value
Tivozanib	181	12.7 mos (9.1–15.0)	0.756	0.037
Sorafenib	181	9.1 mos (7.3–10.8)		



Best response by RECIST 1.0 (independent review)

	Tivozanib (N=260)	Sorafenib (N=257)
Best overall response, %		
Complete response	1	1
Partial response	32	23
Stable disease	52	65
Progressive disease	13	7
Not evaluable	2	4
Objective response rate, %	**33**	**23**
95% CI	27–39	18–29
P value	0.014	

Dose adjustments due to AEs

	Tivozanib (n=259[a])	Sorafenib (n=257)
Dose interruptions,[b] %	18	35
Dose reductions,[b] %	12	43
Discontinuations,[c] %	4	5

[a]One patient was randomized but never received treatment.
[b]Difference between tivozanib and sorafenib, $P<0.001$ by Fisher exact test.
[c]Due to treatment-related adverse events.

Selected laboratory abnormalities

	Tivozanib (N=259, %)		Sorafenib (N=257, %)	
	All Grade	Grade 3 (4)	All Grade	Grade 3 (4)
Chemistries				
ALT increase	26	<1	34	3 (<1)
AST increase	34	2	49	3 (<1)
Amylase increase	40	4 (<1)	52	6 (<1)
Lipase increase	45	8 (2)	62	20 (4)
Hypophosphatemia	27	4	70	25
Proteinuria	68	3	72	2
Hematology				
Low hemoglobin	36	2 (2)	46	3 (<1)
Neutropenia	10	2 (<1)	9	1 (<1)
Thrombocytopenia	17	0 (<1)	11	0

- Patients with normal TSH levels that increased to >10 mIU/L after treatment: tivozanib, 24%; sorafenib, 6%
  - Few of these patients had low T3 (tivozanib 3%; sorafenib 2%) or low free T4 (tivozanib,2%; sorafenib, <1%) on or after date elevations in TSH were observed

Treatment-emergent AEs[a]

	Tivozanib (N=259, %)		Sorafenib (N=257, %)	
	All Grade	Grade 3 (4)	All Grade	Grade 3 (4)
Hypertension	44	24 (2)	34	17 (<1)
Diarrhea	22	2	32	6
Dysphonia	21	0	5	0
Fatigue	18	5	16	4
Weight decreased	17	<1	20	3
Asthenia	15	4 (<1)	16	3
Palmar-plantar erythrodysesthesia	13	2	54	17
Back pain	14	3	7	2
Nausea	11	<1	8	<1
Dyspnea	10	2[b]	8	2
Decreased appetite	10	<1	9	<1
Alopecia	2	0	21	0

[a]Occurring in ≥10% of patients. [b]One grade 5 dyspnea event was reported.
One death in the tivozanib group (hypertension, possible overdose) and one death in the sorafenib group (cerebrovascular accident) were considered drug-related by the investigator.

Treatment-emergent AEs[a]

	Tivozanib (N=259, %)		Sorafenib (N=257, %)	
	All Grade	Grade 3 (4)	All Grade	Grade 3 (4)
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Diarrhea	**22**	**2**	**32**	**6**
Dysphonia	21	0	5	0
Fatigue	18	5	16	4
Weight decreased	17	<1	20	3
Asthenia	15	4 (<1)	16	3
Palmar-plantar erythrodysesthesia	**13**	**2**	**54**	**17**
Back pain	14	3	7	2
Nausea	11	<1	8	<1
Dyspnea	10	2[b]	8	2
Decreased appetite	10	<1	9	<1
Alopecia	**2**	0	**21**	0

[a]Occurring in ≥10% of patients. [b]One grade 5 dyspnea event was reported.
Numbers highlighted in blue indicate difference between tivozanib and sorafenib, $P<0.05$ by Fisher exact test.

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Diarrhea	22	2	32	6
Dysphonia	**21**	0	**5**	0
Fatigue	18	5	16	4
Weight decreased	17	<1	20	3
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Palmar-plantar erythrodysesthesia	13	2	54	17
Back pain	**14**	3	**7**	2
Nausea	11	<1	8	<1
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Alopecia	2	0	21	0

[a]Occurring in ≥10% of patients. [b]One grade 5 dyspnea event was reported.
Numbers highlighted in yellow indicate difference between tivozanib and sorafenib, $P<0.05$ by Fisher exact test.

Tivozanib progression-free survival[a] by hypertension

	Diastolic BP		Systolic BP	
	>90 mm Hg	≤90 mm Hg	>140 mm Hg	≤140 mm Hg
Patient number	101	158	115	144
Median PFS	**18.3**	**9.1**	**16.7**	**9.0**
Hazard ratio (95% CI)	0.553 (0.391–0.781)		0.543 (0.390–0.756)	
P value	0.001		<0.001	

BP, blood pressure.
[a]Independent assessment.

Conclusions

- **Tivozanib demonstrated superior efficacy compared with sorafenib as treatment for metastatic RCC**
- Tivozanib was well-tolerated, characterized by lower rates of certain off-target AEs and fewer dose adjustments
- This study demonstrated that a more potent, selective VEGFR inhibitor with a long half-life achieved superior efficacy combined with decreased off-target toxicity
- Tivozanib should be considered a first-line treatment option for mRCC

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Acknowledgments

The patients and their families

TIVO-1 Study Group

AVEO Oncology and Astellas Oncology