Abstract No. 918

Temsirolimus vs Sorafenib as Second-Line Therapy in Metastatic Renal Cell Carcinoma: Phase 3 Results From the INTORSECT Trial

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Disclosures

- Conflict of Interest Disclosure

  Dr. Hutson has served as a remunerated advisor and as a study investigator for Aveo, Bayer, GlaxoSmithKline, Novartis, and Pfizer Inc.

- Research Funding

  This study was sponsored by Pfizer Inc.

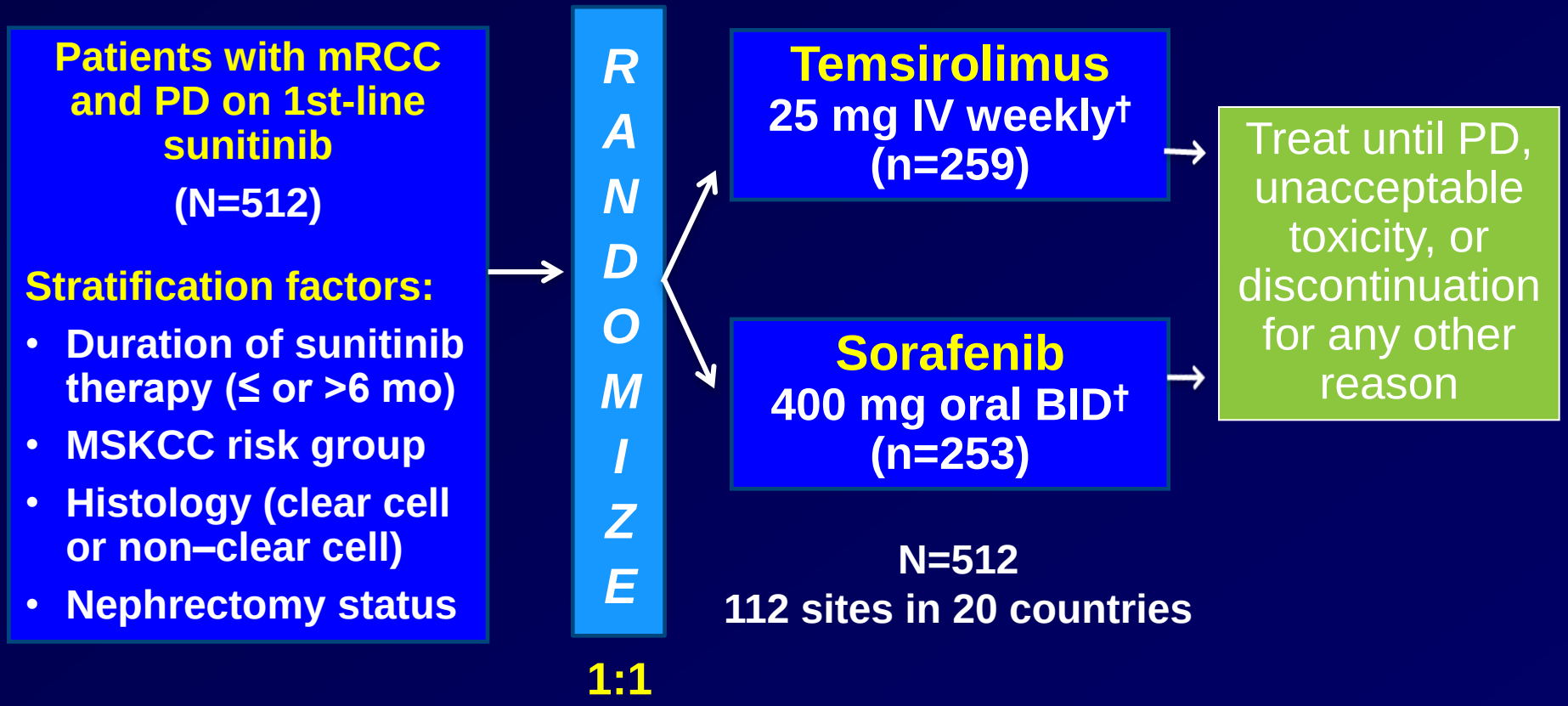
Background

- Inhibitors of VEGF(R) (sunitinib, sorafenib, bevacizumab, pazopanib, axitinib) or mTOR (temsirolimus, everolimus) are the backbone of treatment for mRCC
- Standard of care after sunitinib for 2nd-line RCC treatment may be either a VEGFR inhibitor[1-3] or an mTOR inhibitor[4]
- mTOR inhibitors have not been compared with VEGFR inhibitors in this setting
- This multicenter, randomized, open-label phase 3 trial compared the efficacy and safety of temsirolimus and sorafenib as 2nd-line therapy after failure on sunitinib

mTOR, mammalian target of rapamycin; mRCC, metastatic renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor.

1. Di Lorenzo G, et al. *J Clin Oncol*. 2009;27:4469–4474.
2. Porta C, et al. *BJU Int*. 2011;108(8 Pt 2):E250–E257.
3. Rini BI, et al. *Lancet*. 2011;378:1931–1939.
4. Motzer RJ, et al. *Cancer*. 2010;116:4256–4265.

INTORSECT* Study Design



First patient randomized: September 25, 2007; last patient randomized: January 31, 2012.
Data cutoff: May 4, 2012. At present, 2 patients are on study.

*ClinicalTrials.gov Identifier: NCT00474786.
†Dose reductions were allowed: temsirolimus (to 20 mg then 15 mg); sorafenib (to 400 mg/day then every other day).

BID, twice daily; IRC, independent review committee; IV, intravenous; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center; PD, progressive disease; PFS, progression-free survival.

Study Objectives

- **Primary objective**
  - To compare safety and efficacy (PFS as determined by IRC) of temsirolimus and sorafenib in the 2nd-line setting for patients with mRCC after failure on prior sunitinib
- **Secondary objectives**
  - Overall survival (OS)
  - PFS determined by investigator assessment
  - Objective response rate
  - Proportion of patients with PFS at 12, 24, and 36 weeks
  - Duration of response

IRC, independent review committee; mRCC, metastatic renal cell carcinoma; PFS, progression-free survival.

Statistical Methods

- **Primary end point: PFS (assessed by blinded IRC)**
  - 80% power to detect a 33% improvement in PFS with a stratified 2-sided log-rank test at 0.05 alpha level
  - Sample size of 480 patients required to observe 380 progression events with 15% drop-out rate
  - Analysis based on ITT population, compared using stratified log-rank test
- **Secondary end point: OS**

IRC, independent review committee; ITT, intent to treat; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

Key Eligibility Criteria

- Histologically confirmed mRCC
- Radiologic PD by RECIST[1] or clinical PD (as judged by investigator) while receiving 1st-line sunitinib
  - Must have received ≥1 cycle of sunitinib (≥4 weeks continuously)
  - At time of randomization, ≥2 weeks since prior sunitinib, palliative radiation therapy, and/or surgery
- Measurable disease per RECIST criteria[1]
- ECOG performance status 0 or 1
- Adequate blood counts and organ function

ECOG, Eastern Cooperative Oncology Group; mRCC, metastatic renal cell carcinoma; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Therasse P, et al. *J Natl Cancer Inst*. 2000;92:205-216.

Key Exclusion Criteria

- CNS metastasis from RCC
- Sunitinib discontinuation due specifically to intolerance
- Prior systemic therapy other than sunitinib for mRCC
- Active ketonuria secondary to poorly controlled diabetes mellitus

CNS, central nervous system; mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma.

Patient Characteristics

Characteristic	Temsirolimus (n=259)	Sorafenib (n=253)
Median age, y (range)	60 (19–82)	61 (21–80)
Gender (%)		
Male	75	76
Female	25	24
Race (%)		
White	69	64
Asian	15	20
Other/unspecified	16	16
ECOG PS, n		
0	103	113
1	150	139
Other*	6	1

*In the temsirolimus group, 3 patients had ECOG PS 2, 1 patient had ECOG PS 3, and 2 were missing assessments; in the sorafenib arm, 1 patient was missing assessments.

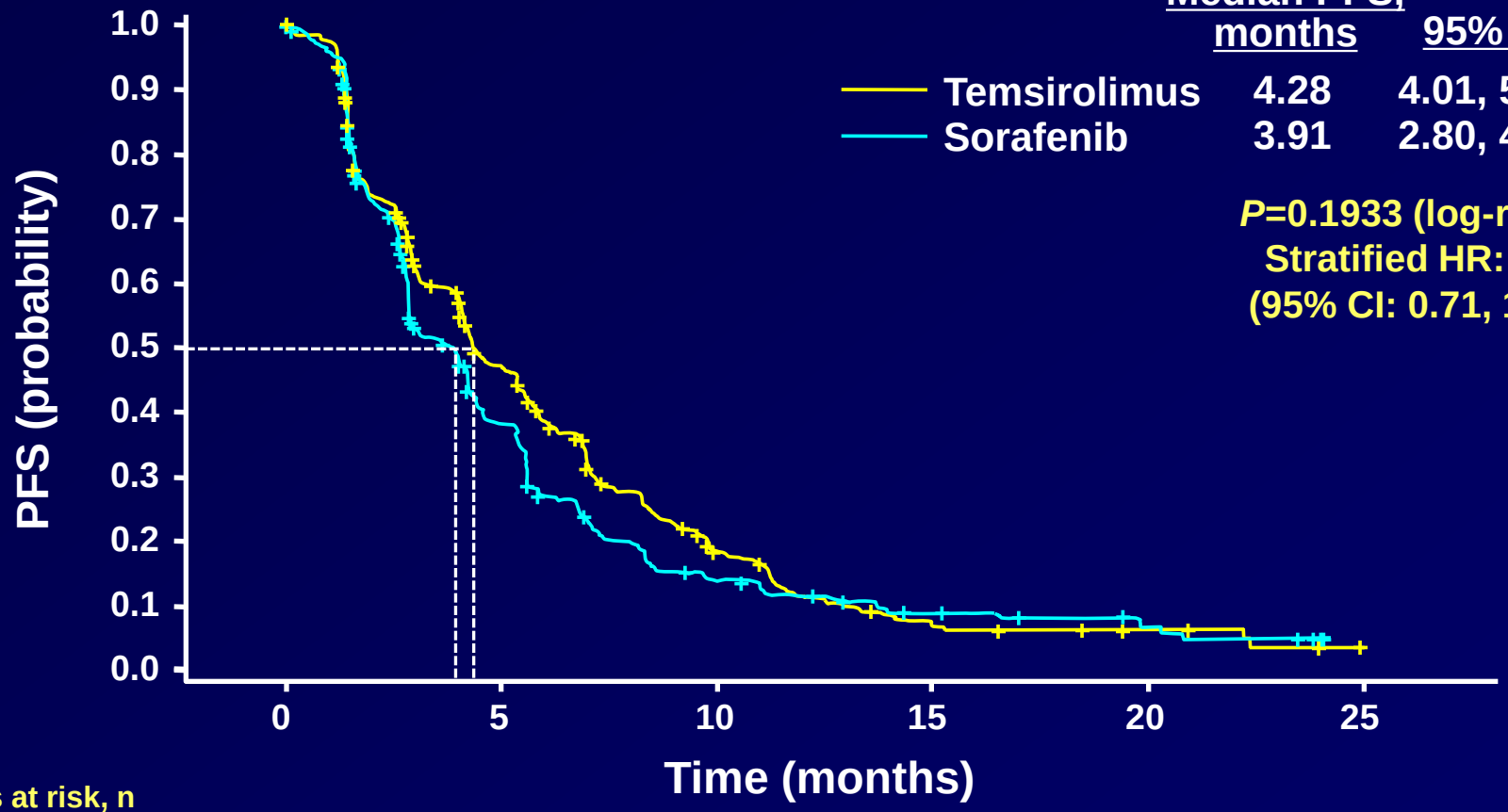
ECOG PS, Eastern Cooperative Oncology Group performance status.

Patient Characteristics

Characteristic	Temsirolimus (n=259)	Sorafenib (n=253)
Prior nephrectomy, n (%)	223 (86)	219 (87)
Tumor histologic type, n (%)		
Clear cell	214 (83)	208 (82)
Non–clear cell	45 (17)	45 (18)
MSKCC risk factors,[1] n (%)		
0 (favorable)	50 (19)	44 (17)
1–2 (intermediate)	178 (69)	177 (70)
≥3 (poor)	31 (12)	32 (13)
Duration of prior sunitinib, n (%)		
≤6 months	97 (37)	92 (36)
>6 months	162 (63)	161 (64)

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

Progression-Free Survival
(IRC Assessment)



Patients at risk, n

Sorafenib	252	72	22	11	6	0
Temsirolimus	259	96	28	9	5	0

CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; PFS, progression-free survival.

Progression-Free Survival

Median PFS, mo (95% CI)	Temsirolimus (n=259)	Sorafenib (n=253)	HR (95% CI)	*P* value†
IRC assessment*	4.28 (4.01, 5.43)	3.91 (2.80, 4.21)	0.87 (0.71, 1.07)	0.193
Investigator assessment	5.43 (4.24, 5.86)	4.14 (3.26, 5.36)	0.87 (0.70, 1.07)	0.189

*389 patients had PFS events, defined as disease progression or death due to any cause.
†2-sided log-rank test stratified by prior nephrectomy status, duration of sunitinib therapy, tumor histology, and MSKCC risk group.

CI, confidence interval; HR, hazard ratio; IRC, independent review committee; MSKCC, Memorial Sloan-Kettering Cancer Center; PFS, progression-free survival.

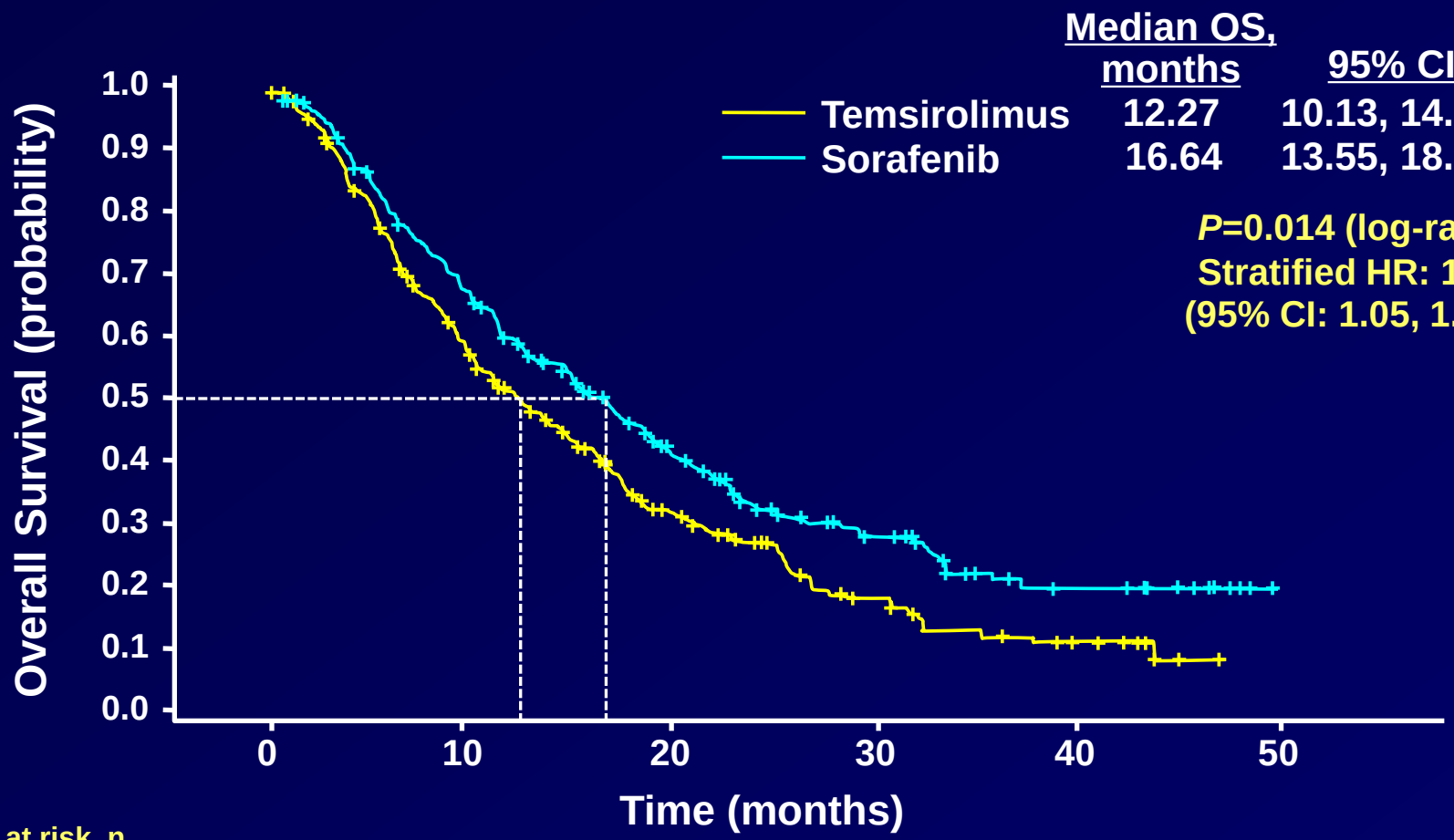
Objective Response by RECIST (IRC Assessment)

Response Parameter, n (%)	Temsirolimus (n=259)	Sorafenib (n=253)
Overall confirmed ORR*	20 (8)	20 (8)
Complete response	0	1
Partial response	20 (8)	19 (8)
Stable disease	151 (61)	153 (61)
Progressive disease	59 (23)	61 (24)
Median duration of response, months (95% CI)	8.26 (6.71, 10.36)	6.96 (4.18, 17.50)

*Stratified 1-sided Cochran-Mantel-Haenszel test of treatment.

CI, confidence interval; IRC, independent review committee; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Overall Survival



Patients at risk, n

Sorafenib	253	158	74	34	13	0
Temsirolimus	259	132	54	22	8	0

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Follow-up Treatments
(Safety Population; n=501)

Antineoplastic Agent, n (%)	Temsirolimus (n=249)	Sorafenib (n=252)
Surgery	0 (0)	6 (2.4)
Radiation therapy	5 (2.0)	12 (4.8)
Any nonstudy medication*	14 (5.6)	16 (6.3)
Bevacizumab	0	1 (0.4)
Everolimus	2 (0.8)	12 (4.8)
Interferon alfa	3 (1.2)	1 (0.4)
Sorafenib	9 (3.6)	1 (0.4)
Temsirolimus	0	2 (0.8)

*Includes medications started after the last dose of randomized study medication. Information collected up to 30 days after study completion. Patients may have received 2 or more different agents.

PFS by Duration of Prior Sunitinib
(ITT Population; IRC Assessment)

Prior Sunitinib Use	Temsirolimus (n=259)	Sorafenib (n=253)	HR (95% CI)	*P* value*
≤180 days, n (%)	97 (38%)	92 (36%)		
Median PFS, mo	4.1	3.5	0.8	0.228
(95% CI)	(3.0, 5.5)	(2.8, 5.5)	(0.59, 1.13)	
>180 days, n (%)	162 (62%)	161 (64%)		
Median PFS, mo	5.8	4.2	0.9	0.414
(95% CI)	(5.3, 6.9)	(3.9, 5.6)	(0.69, 1.2)	

*Unstratified log-rank test.

CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ITT, intent to treat; PFS, progression-free survival.

OS by Duration of Prior Sunitinib (ITT Population)

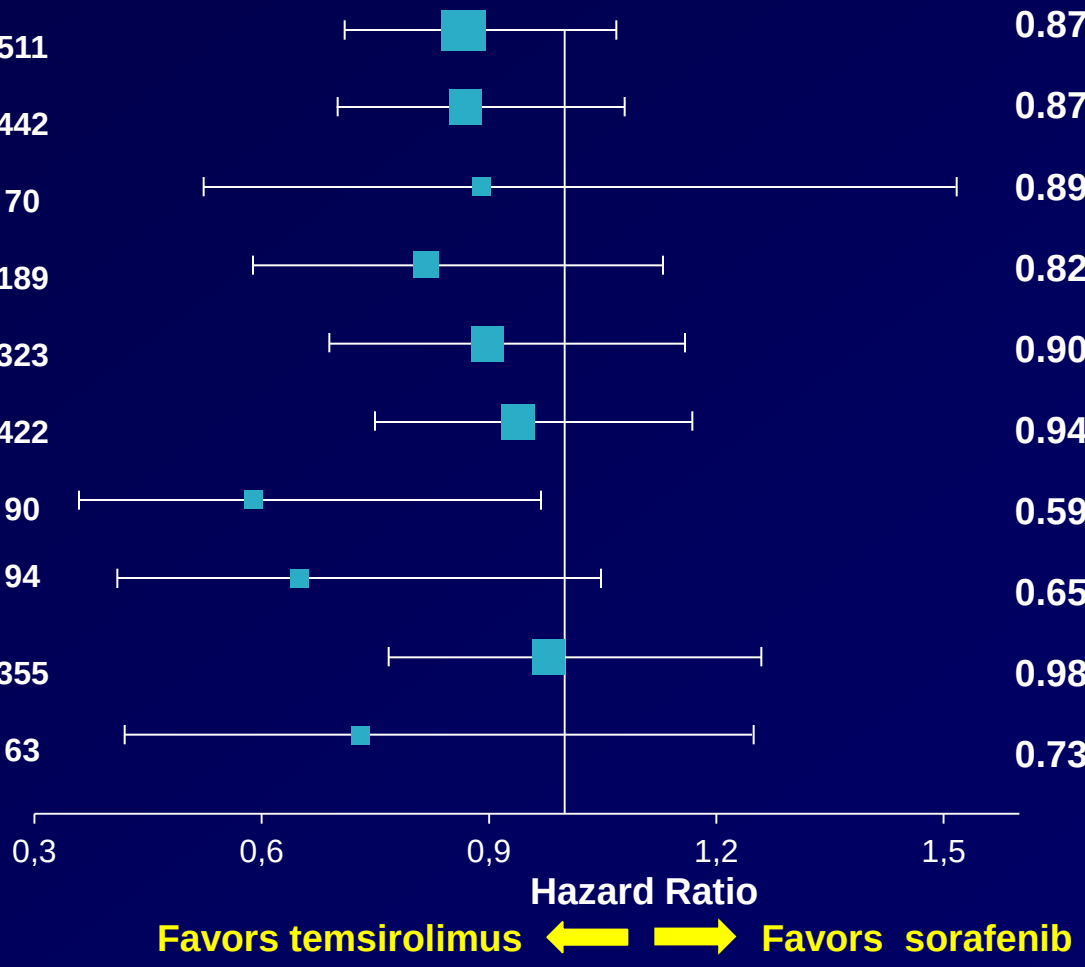
Prior Sunitinib Use	Temsirolimus (n=259)	Sorafenib (n=253)	HR (95% CI)	*P* value*
≤180 days, n (%)	97 (38%)	92 (36%)		
Median OS, mo	10.1	11.4	1.30	0.111
(95% CI)	(8.5, 13.4)	(8.9, 16.8)	(0.94, 1.81)	
>180 days, n (%)	162 (62%)	161 (64%)		
Median OS, mo	14.4	17.8	1.37	0.025
(95% CI)	(11.3, 16.9)	(15.4, 22.9)	(1.04, 1.80)	

*Unstratified log-rank test.

CI, confidence interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival.

PFS by Subgroup

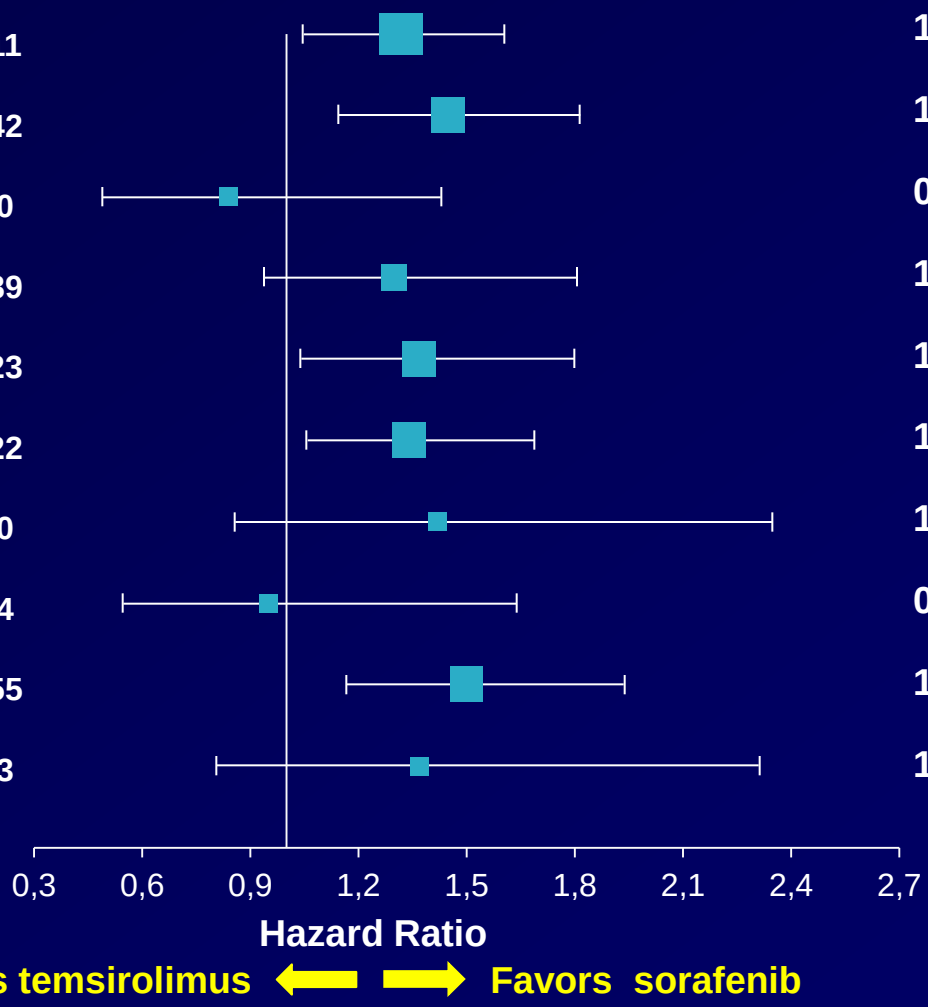
Subgroup	N	HR	95% CI
All patients	511	0.87	0.71, 1.07
Prior nephrectomy	442	0.87	0.70, 1.08
No prior nephrectomy	70	0.89	0.52, 1.52
≤180 days sunitinib therapy	189	0.82	0.59, 1.13
>180 days sunitinib therapy	323	0.90	0.69, 1.16
Clear cell histology	422	0.94	0.75, 1.17
Non–clear cell histology	90	0.59	0.36, 0.97
MSKCC favorable subgroup	94	0.65	0.41, 1.05
MSKCC intermediate subgroup	355	0.98	0.77, 1.26
MSKCC poor subgroup	63	0.73	0.42, 1.25



CI, confidence interval; HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; PFS, progression-free survival.

OS by Subgroup

Subgroup	N	HR	95% CI
All patients	511	1.31	1.05, 1.63
Prior nephrectomy	442	1.45	1.15, 1.82
No prior nephrectomy	70	0.84	0.49, 1.43
≤180 days sunitinib therapy	189	1.30	0.94, 1.81
>180 days sunitinib therapy	323	1.37	1.04, 1.80
Clear cell histology	422	1.34	1.06, 1.69
Non–clear cell histology	90	1.42	0.86, 2.35
MSKCC favorable subgroup	94	0.95	0.55, 1.64
MSKCC intermediate subgroup	355	1.50	1.17, 1.94
MSKCC poor subgroup	63	1.37	0.81, 2.32



CI, confidence interval; HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Center; OS, overall survival.

Drug Delivery
(Safety Population)

	Temsirolimus (n=249)	Sorafenib (n=252)
Dose interruptions, %	67	63
Due to AEs, %	15	33
Median relative dose intensity, %	88	96
Discontinuations due to treatment-related AEs,* %	17	14

*Adverse events related to treatment as determined by investigators.

AE, adverse event.

All-Grade Adverse Events*

Event, %	Temsirolimus (n=249)	Sorafenib (n=252)
Rash	42	35
Fatigue	40	34
Cough	35	23
Anemia	34	14
Nausea	33	28
Diarrhea	31	63
Decreased appetite	31	37
Mucosal inflammation	30	14
Dyspnea	29	18
Asthenia	26	26
Pruritus	26	26
Hand-foot syndrome	4	52
Alopecia	2	31

*All-causality; experienced by >25% of patients in either treatment arm.

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Event, %	Temsirolimus (n=249)	Sorafenib (n=252)
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Dyspnea	29	18
Asthenia	26	26
Pruritus	26	26
Hand-foot syndrome	4	52
Alopecia	2	31

*All-causality; experienced by >25% of patients in either treatment arm.

Grade ≥3 Adverse Events*

	Temsirolimus (n=249)		Sorafenib (n=252)	
Event, %	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Hand-foot syndrome	4	0	52	15
Fatigue	40	6	34	7
Anemia	34	9	14	3
Hypophosphatemia	11	5	12	7
Hyperglycemia	19	8	6	2
Diarrhea	31	2	63	6

*Incidence ≥5% in either treatment arm.

Conclusions

- Temsirolimus was not superior to sorafenib in the primary (PFS) or secondary end point (OS)
  - Median PFS was slightly longer with temsirolimus compared with sorafenib (4.28 months vs 3.91 months), but this difference was not statistically significant
  - The sorafenib arm had a longer median OS than did the temsirolimus arm (16.64 months vs 12.27 months; *P*=0.014)
- Safety data were as expected for both agents
- Further evaluation is needed to define the optimum treatment sequence after sunitinib in patients with advanced RCC, given axitinib and everolimus data

OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

Acknowledgments

We thank the patients, their families, and the clinical personnel and investigators who participated in this study.

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