Randomized Phase III Trial of Temsirolimus Versus Sorafenib As Second-Line Therapy After Sunitinib in Patients With Metastatic Renal Cell Carcinoma

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Introduction

Therapeutic options for metastatic renal cell carcinoma (mRCC) have changed during recent years owing to availability of targeted therapies with efficacy in this chemotherapy-refractory disease. Previously, treatment was predominantly with cytokines. Today, inhibitors of vascular endothelial growth factor (VEGF) or VEGFR (vascular endothelial growth factor receptor)—sunitinib, sorafenib, bevacizumab, axitinib, and pazopanib—or mammalian target of rapamycin (mTOR) temsirolimus and everolimus—comprise standard therapy.

Introduction

Sunitinib, an oral multitargeted inhibitor of VEGFR and other receptor tyrosine kinases, is approved for patients with advanced RCC. Sunitinib has superior efficacy versus **interferon-α** (IFN-α) as first-line therapy for mRCC, with median progression-free survival (PFS) of 11 months and median overall survival (OS) of more than 2 years. After disease progression on sunitinib, multiple second-line options exist, including other types of VEGFR as well as mTOR inhibitors.

Introduction

As **second-line therapy**, mTOR inhibitors have not been directly compared with VEGFR inhibitors. Temsirolimus demonstrated OS benefit versus IFN-a in patients with untreated poor-prognosis advanced RCC. Retrospective data suggest some efficacy with temsirolimus after progression on VEGFR inhibitors; however, its true benefit in this setting is unknown.

Introduction

This is an international, multicenter, randomized, open-label, phase III trial (Investigating Torisel As Second-Line Therapy [INTORSECT]) compared efficacy and safety of second-line temsirolimus versus sorafenib after disease progression with sunitinib in patients with mRCC. Based on efficacy data from phase II trials at the time of the study design, sorafenib was the only VEGFR inhibitor available for patients who experienced disease progression on sunitinib.

Patients and Methds

Patients: Eligible patients, age more than 18 years, had histologically confirmed mRCC (any histology) with documentation of radiologic progressive disease (PD) according to Response Evaluation Criteria for Solid Tumors (RECIST, version 1.0)16 or clinical PD, as judged by investigator, while receiving first-line sunitinib. Patients must have received at least one 4-week cycle of continuous sunitinib, regardless of dose; discontinuation because of intolerance alone was unacceptable for inclusion. Patients must have completed sunitinib, palliative radiation therapy, or surgery ≥ 2 weeks before randomization.

Patients and Methds

Key eligibility criteria were at least one measurable (non-bone) target lesion per RECIST; Eastern Cooperative Oncology Group performance status 0 or 1; life expectancy 12 weeks; and adequate hematologic, hepatic, renal, and cardiac function. Patients were excluded if they had brain metastases, unstable coronary artery disease or myocardial infarction during preceding 6 months, hypertension uncontrolled by medication, active ketonuria secondary to poorly controlled diabetes mellitus, history of pulmonary hypertension or interstitial lung disease, or prior systemic therapy other than sunitinib for mRCC. All patients provided written informed consent.

Patients and Methds

Study Design and Treatment: This international, randomized, open-label, multicenter, phase III trial randomly assigned (1:1) eligible patients to receive intravenous (IV) temsirolimus 25 mg once weekly or oral sorafenib 400 mg twice per day. Randomization was stratified according to baseline factors: prior nephrectomy (yes or no), duration of sunitinib therapy (≤ or >180 days), tumor histology (clear or non–clear cell), and Memorial Sloan- Kettering Cancer Center prognostic group (favorable, intermediate, or poor)

Patients and Methods

Patients received treatment in 6-week cycles for up to 2 years or until disease progression, significant toxicity, or consent withdrawal. Toxicity-related dose reductions were allowed for temsirolimus (20 mg, then 15 mg weekly) and sorafenib (400 mg daily, then 400 mg every other day). All patients were followed for survival.

Patients and Methods

The primary end point was **PFS**, defined as time from randomization date to first documented PD (evaluated by a centralized independent review committee [IRC]) or death for any reason. **Secondary end points** were PFS by investigator assessment, objective response rate (**ORR**), **OS**, and **safety**. Exploratory analyses of PFS and OS by baseline characteristic factors were conducted if appropriate.

Patients and Methods

The trial was approved by the institutional review board or independent ethics committee of each center and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice, and applicable local regulatory requirements. An independent data safety monitoring board with access to safety data throughout the study and final efficacy data oversaw study conduct.

Patients and Methods

Study Assessments: Efficacy was evaluated by CT-CAP with contrast performed at screening (≤ 28 days pre-randomization) and week 1 of every 6-week cycle. Magnetic resonance imaging was used if computed tomography scanning was contraindicated or unavailable. Confirmation of ORs was required ≥ 4 weeks after initial documented response. Safety and tolerability were assessed by physical ex., hematology and biochemistry tests, and monitoring adverse events (AEs), graded per CTCAEs v. 3.0.

Patients and Methods

Statistical Analysis: Efficacy end points were analyzed in the ITT population on the basis of blinded assessments. This study was designed to test the **hypothesis** that median PFS would improve from 4 months with sorafenib to 5.3 months with temsirolimus. Target sample size was calculated based on 80% power to detect 33% improvement in median PFS using a two-sided stratified log-rank test at a significance level of .05. The required sample size was estimated to be 480 patients (240 per arm) to observe 380 PFS events, assuming an 18-month accrual period with a 15% dropout rate. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

Results: Patients

512 patients between September 19, 2007, and April 18, 2011 were randomly assigned to receive temsirolimus 25 mg IV weekly (n = 259) or sorafenib 400 mg orally twice per day (n = 253). Ten patients in the temsirolimus arm and one in the sorafenib arm were randomly assigned but not treated. Baseline demographics and clinical characteristics were largely representative of the target population and generally well balanced between arms (Table 1).

Table 1. Demographic and Baseline Characteristics of Randomly Assigned Patients

Characteristic	Temsirolimus 25 mg IV Once per Week (n = 259)		Sorafenib 400 mg Orally Twice per Day (n = 253)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	60		61	
Range	19-82		21-80	
Sex				
Male	193	75	192	76
Female	66	25	61	24
Race				
White	178	69	163	64
Asian	38	15	50	20
Other	43	17	40	16
ECOG PS				
0	103	40	113	45
1	150	58	139	55
Other*	6	2	1	< 1
Previous nephrectomy	223	86	219	87
Tumor histologic type				
Clear cell	214	83	208	82
Non–clear cell	45	17	45	18
No. of MSKCC risk factors†				
0 (favorable)	50	19	44	17
1-2 (intermediate)	178	69	177	70
≥ 3 (poor)	31	12	32	13
Duration of prior sunitinib, days				
≤ 180	97	37	92	36
> 180	162	63	161	64

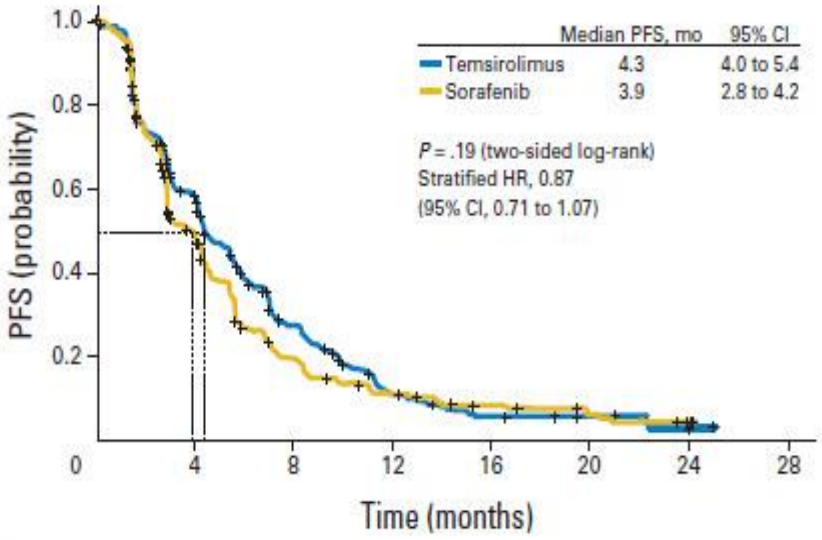
Results: Study Treatment

Median treatment duration was 4.4 months (range, 0.5 to 25.2 months) and 3.6 months (range, 0.2 to 24.2 months) with temsirolimus and sorafenib, respectively. A similar proportion of patients had dose interruptions with temsirolimus (69%) and sorafenib (63%). Overall, the median relative dose intensity (percentage of actual/intended) was 88% for temsirolimus and 96% for sorafenib.

Results: Study Treatment

At the data cutoff for primary end-point analysis, **PFS** was assessed in 389 patients (76%). Median follow-up was 9.2 months. PFS (primary end-point) showed no significant difference between treatments (Fig 2A). **Median PFS** was **4.3** months for temsirolimus and **3.9** months for sorafenib (stratified hazard ratio [HR], 0.87; 95% CI, 0.71 to 1.07; two-sided*P* = .19). No other secondary or exploratory end-point, including prespecified subset analyses (Fig 2B), showed significant PFS favoring temsirolimus. **Confirmed objective tumor response** was achieved in 20 patients in each arm (ORR, 8%; Table 2).

A



No. at risk								
Temsirolimus	259	123	48	17	8	5	1	0
Sorafenib	252	96	34	18	10	6	1	0

B

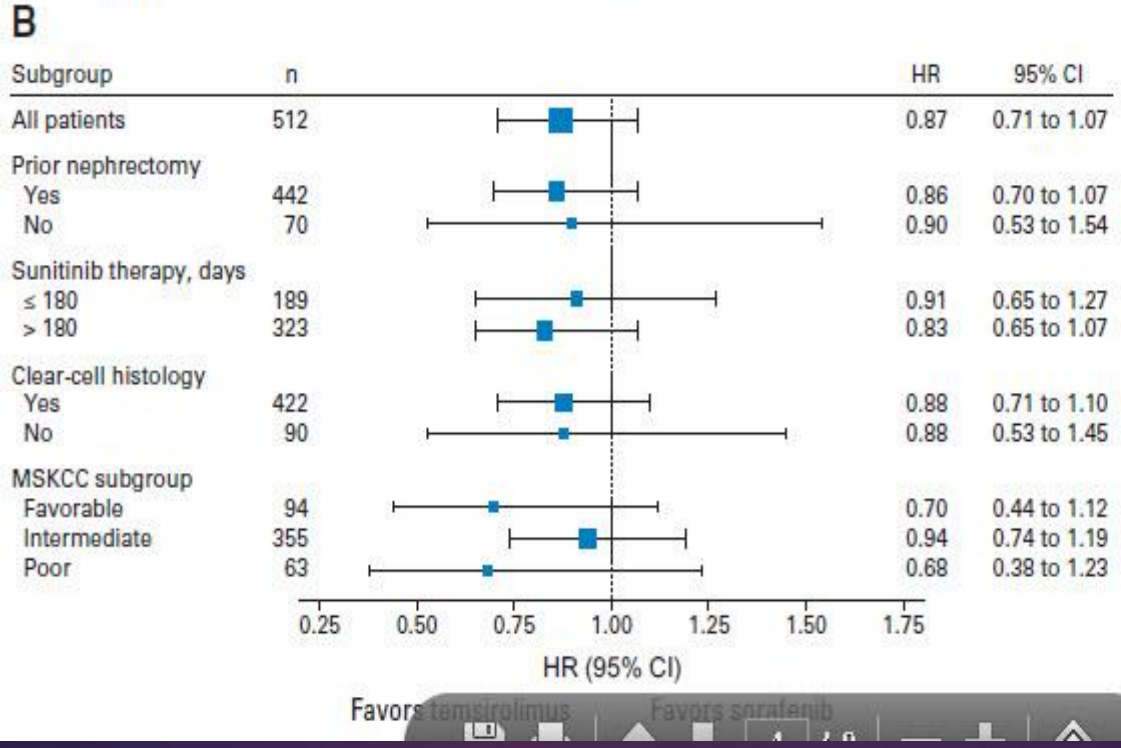


Fig 2. (A) Kaplan-Meier curves of IRC-assessed progression-free survival (PFS). (B) Subgroup analysis of IRC-assessed PFS with respect to stratification factors. HR, hazard ratio; IRC, independent review committee; mo, months; MSKCC, Memorial Sloan-Kettering Cancer Center.

Table 2. Best Objective Response by RECIST

Response	Temsirolimus 25 mg IV Once per Week (n = 259)		Sorafenib 400 mg Orally Twice per Day (n = 253)	
	No. of Patients	%	No. of Patients	%
Overall confirmed response*	20	8	20	8
CR	0	0	1	< 1
PR	20	8	19	8
Stable disease	157	61	153	60
Progressive disease	59	23	61	24
Unknown	3	1	2	1
Not assessed	1	< 1	0	0
Missing†	19	7	17	7

Abbreviations: CR, complete response; IV, intravenous; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.[18]
*Independent review committee assessment.
†No valid postbaseline assessment by the end of treatment.

Results: Study Treatment

At the time of primary analysis, a significant difference in **OS** was observed in favor of sorafenib (stratified HR, 1.31; 95% CI, 1.05 to 1.63; two-sided *P* = .01; **Fig 3A**). **Median OS** was **12.3** months (95% CI, 10.1 to 14.8 months) with temsirolimus and **16.6** months (95% CI, 13.6 to 18.7 months) with sorafenib. Exploratory **subgroup analyses** of prespecified factors identified differential OS benefit with sorafenib versus temsirolimus for multiple patient characteristics (**Fig 3B**). These included prior nephrectomy, longer duration of prior sunitinib (> 180 days, *P* = .02), clear-cell histology (*P* = .01), and MSKCC intermediate risk (*P* = .002).

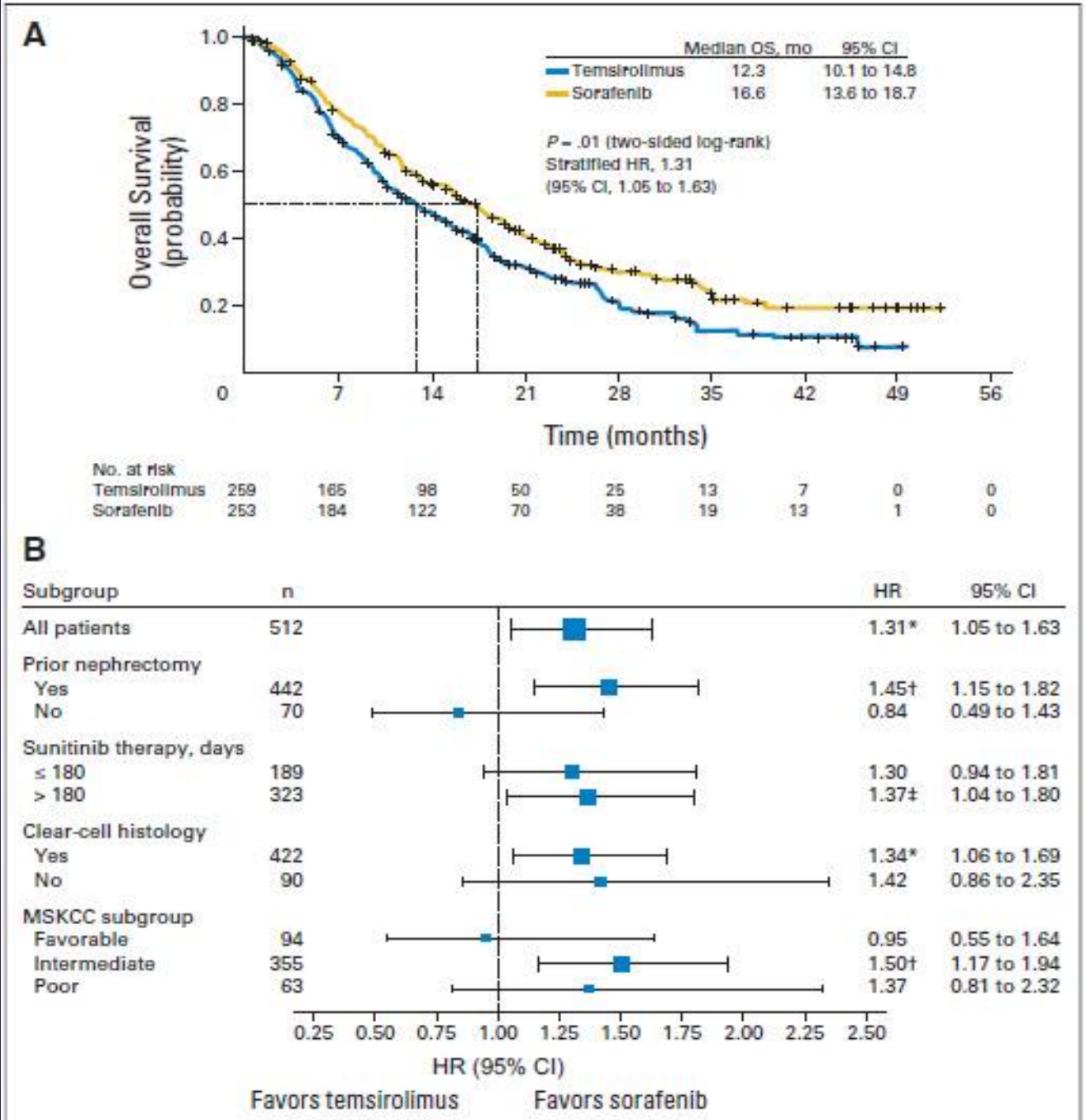


Fig 3. (A) Kaplan-Meier curves of overall survival (OS). (B) Subgroup analysis of OS with respect to stratification factors. *P = .01; †P = .002; ‡P = .02. HR, hazard ratio; mo, months; MSKCC, Memorial Sloan-Kettering Cancer Center.

Results: Safety

In both arms, the same proportion of patients (99.6%) had one or more AE (all-grade; all-cause). The **most common AEs** with **temsirolimus** were rash, fatigue, cough, anemia, and nausea versus diarrhea, palmar-plantar erythrodysesthesia (PPE), decreased appetite, rash, and fatigue with **sorafenib** (**Table 3**). A similar proportion of patients experienced **grade 3 or more** AE with temsirolimus (70%) and sorafenib (69%). AEs resulted in dose reductions in 16% and 33% of patients in the temsirolimus and sorafenib arms, respectively. For temsirolimus, the most common AE requiring at least one dose reduction was pneumonitis (2%), for sorafenib, it was PPE (14%).

Table 3. Common Treatment-Emergent Adverse Events (≥ 20% in either arm)

	Temsirolimus 25 mg IV Once per Week (n = 249)				Sorafenib 400 mg Orally Twice per Day (n = 252)			
	All Grades		Grade ≥ 3		All Grades		Grade ≥ 3	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Rash	104	42	7	3	88	35	8	3
Fatigue	100	40	16	6	85	34	18	7
Cough	86	35	2	< 1	58	23	1	< 1
Anemia	84	34	23	9	35	14	7	3
Nausea	82	33	4	2	71	28	3	1
Diarrhea	78	31	6	2	158	63	14	6
Decreased appetite	77	31	3	1	93	37	8	3
Mucosal inflammation	74	30	3	1	35	14	0	
Dyspnea	71	29	12	5	45	18	11	4
Asthenia	65	26	10	4	65	26	7	3
Pruritus	64	26	2	< 1	65	26	2	< 1
Constipation	57	23	0		57	23	1	< 1
Peripheral edema	57	23	5	2	14	6	0	
Vomiting	56	22	5	2	46	18	7	3
Pyrexia	55	22	2	< 1	29	12	1	< 1
Stomatitis	54	22	5	2	18	7	0	
Hypertriglyceridemia	53	21	8	3	18	7	1	< 1
Hypercholesterolemia	51	20	6	2	16	6	3	1
Epistaxis	51	20	2	< 1	13	5	0	
Weight decreased	35	14	2	< 1	51	20	5	2
PPE	11	4	0		131	52	38	15
Alopecia	5	2	0		78	31	0	

Abbreviations: IV, intravenous; PPE, palmar-plantar erythrodysesthesia.

Discussion

This randomized phase III trial compared temsirolimus to sorafenib as second-line therapy after progression on first-line sunitinib in patients with mRCC. Temsirolimus did not show superiority to sorafenib in the primary end point of **PFS** or secondary end point of **OS**. The median PFS was slightly longer with temsirolimus compared with sorafenib (4.3 v 3.9 months), but this difference was not statistically significant (*P* = .19). The **ORR** was similar between treatments.

Discussion

Overall survival, a secondary end point, was longer in patients treated with sorafenib compared with temsirolimus (*P* = .01). Previously, first-line **temsirolimus** had demonstrated an OS benefit versus **IFN**-ex in patients with poor prognostic features. A phase III trial **Axitinib** Second-Line [AXIS] comparing sorafenib with axitinib as second-line therapy showed shorter PFS with sorafenib and no difference in OS between treatments. The median OS with sorafenib in the present trial (16.6 months) was similar to OS with sorafenib in the AXIS trial (16.5 months) in the subset who received prior sunitinib. **In patients previously untreated** with VEGF or mTOR inhibitors, a phase III trial (TIVO-1) demonstrated a significant PFS benefit with **tivozanib** compared with sorafenib, but no difference in OS.

Discussion

The reasons for lack of correlation between PFS and OS in the present trial are not fully understood. The most likely explanation relates to use of poststudy anticancer therapy, which was not prespecified in the protocol. **AEs** were consistent with the known safety profiles of temsirolimus and sorafenib and considered acceptable in this setting

Discussion

In conclusion, temsirolimus did not demonstrate an efficacy advantage compared with sorafenib as second-line therapy after disease progression on sunitinib in patients with mRCC. Each drug has a differentiated safety profile, consistent with its class and targeting profile. The longer OS with sorafenib is consistent with the hypothesis that sequenced VEGFR inhibition results in improvement in OS in patients with mRCC.

Thank You