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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A B S T R A C T

Purpose

This international phase III trial (Investigating Torisel As Second-Line Therapy [INTORSECT]) compared the efficacy of temsirolimus (mammalian target of rapamycin inhibitor) and sorafenib (vascular endothelial growth factor receptor [VEGFR] tyrosine kinase inhibitor) as second-line therapy in patients with metastatic renal cell carcinoma (mRCC) after disease progression on sunitinib.

Patients and Methods

In total, 512 patients were randomly assigned 1:1 to receive intravenous temsirolimus 25 mg once weekly ($n = 259$) or oral sorafenib 400 mg twice per day ($n = 253$), with stratification according to duration of prior sunitinib therapy ($\leq$ or > 180 days), prognostic risk, histology (clear cell or non-clear cell), and nephrectomy status. The primary end point was progression-free survival (PFS) by independent review committee assessment. Safety, objective response rate (ORR), and overall survival (OS) were secondary end points.

Results

Primary analysis revealed no significant difference between treatment arms for PFS (stratified hazard ratio [HR], 0.87; 95% CI, 0.71 to 1.07; two-sided $P = .19$) or ORR. Median PFS in the temsirolimus and sorafenib arms were 4.3 and 3.9 months, respectively. There was a significant OS difference in favor of sorafenib (stratified HR, 1.31; 95% CI, 1.05 to 1.63; two-sided $P = .01$). Median OS in the temsirolimus and sorafenib arms was 12.3 and 16.6 months, respectively. Safety profiles of both agents were consistent with previous studies.

Conclusion

In patients with mRCC and progression on sunitinib, second-line temsirolimus did not demonstrate a PFS advantage compared with sorafenib. The longer OS observed with sorafenib suggests sequenced VEGFR inhibition may benefit patients with mRCC.

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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.¹⁻¹¹

Sunitinib, an oral multitargeted inhibitor of VEGFR and other receptor tyrosine kinases, is ap-

proved 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.^{9,10} After disease progression on sunitinib, multiple second-line options exist, including other types of VEGFR inhibitors and serine-threonine kinase inhibitors targeting mTOR.^{4,7,8,11,12} In this setting, direct comparisons have been conducted between VEGFR inhibitors (axitinib v sorafenib)^{4,11} or mTOR inhibitor (everolimus) versus placebo.^{7,8,11} As second-line therapy, mTOR inhibitors have not been directly compared with VEGFR inhibitors. Temsirolimus demonstrated OS benefit

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versus IFN- α in patients with untreated poor-prognosis advanced RCC.⁶ Retrospective data suggest some efficacy with temsirolimus after progression on VEGFR inhibitors^{13,14}; however, its true benefit in this setting is unknown.

This ongoing, 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^{12,15} at the time of the study design, sorafenib was the only VEGFR inhibitor available for patients who experienced disease progression on sunitinib.

PATIENTS AND METHODS

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.

Key eligibility criteria were at least one measurable (nonbone) 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.

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. Patients receiving temsirolimus were premedicated with 25 to 50 mg diphenhydramine (or comparable IV antihistamine) ~30 minutes before each infusion. Randomization was stratified according to baseline factors: prior nephrectomy (yes or no), duration of sunitinib therapy ($\leq$ or > 180 days), tumor histology (clear or non-clear cell), and Memorial Sloan-Kettering Cancer Center prognostic group (favorable, intermediate, or poor).¹⁷ A computerized, centrally located randomization system was used to assign patient identification and treatment. 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.

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.

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.

Fig 1. CONSORT diagram. ITT, intent-to-treat.

Study Assessments

Efficacy was evaluated by computed tomography with contrast of the chest, abdomen, and pelvis performed at screening (≤ 28 days prerandomization) and week 1 of every 6-week cycle. Magnetic resonance imaging was used if computed tomography scanning was contraindicated or unavailable. Scans underwent local and IRC assessment in accordance with RECIST. Radiographic images were assessed by two independent, board-certified radiologists; an adjudicating radiologist assessed any discrepant results between the primary readers. Confirmation of objective responses was required ≥ 4 weeks after initial documented response. Patients with inadequate data for tumor assessment (eg, no baseline or follow-up assessment) were considered nonevaluable.

Safety and tolerability were assessed by physical examination, hematology and biochemistry tests, and monitoring adverse events (AEs), graded per Common Terminology Criteria for Adverse Events version 3.0. All patients had ECGs performed at screening and end-of-treatment visits. Additionally, patients had ECGs before and within 1 hour of completing the first temsirolimus infusion; the first ~ 50 patients also had an ECG within 1 hour before the second weekly infusion. Subsequent anticancer therapies were recorded up to 1 month after the last temsirolimus or sorafenib dose.

Statistical Methods

Efficacy end points were analyzed in the intent-to-treat population on the basis of blinded IRC 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).

Between-group comparison of PFS used a stratified, two-sided log-rank test adjusting for stratification factors applied at randomization. Kaplan-Meier methods were used to estimate median PFS, with corresponding 95% CIs. In patients without PD who were still alive, PFS was censored on date of last study tumor assessment or on initiation of subsequent cancer therapy. For patients whose PD or death occurred immediately after two or more consecutive missing or nonevaluable tumor assessments, PFS was censored on the last valid assessment before the missing assessments. Patients with inadequate baseline or no postbaseline tumor assessment had PFS time censored on date of randomization, with 1-day duration. OS (time from randomization to death from any cause) was analyzed using the same statistical methods as for PFS. Patients without a date of death were censored at last date known alive.

RESULTS

Patients

Patients were screened at 112 sites in 20 countries; 104 sites enrolled 512 patients between September 19, 2007, and April 18, 2011. Patients 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. These patients were evaluable for efficacy by intent-to-treat, but not included in the safety population ($n = 501$; Fig 1). At the data cutoff date (January 31, 2012), 14 patients (3%) were still on treatment, and 102 (20%) were being followed for survival. Baseline demographics and clinical characteristics were largely representative of the target population^{4,12,18} and generally well balanced between arms (Table 1).

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

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

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MSKCC, Memorial Sloan-Kettering Cancer Center.

*In the temsirolimus group, three patients had ECOG PS 2, one patient had ECOG PS 3, and two were missing assessments; in the sorafenib group, one patient was missing assessment.

†Includes low serum hemoglobin level, increased corrected serum calcium level, increased serum lactate dehydrogenase level, poor performance status, and interval of < 1 year between diagnosis and treatment.¹⁷

mus 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.

Efficacy

At the data cutoff date for primary end point analysis, 389 patients (76%) had IRC-assessed PFS events. Median follow-up for all patients was 9.2 months. The IRC-assessed 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 $P = .19$). Similar results were observed for investigator-assessed PFS (stratified HR, 0.87; 95% CI, 0.70 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. Median PFS did not differ significantly between arms according to the duration of prior sunitinib exposure (conversely to OS as reported further). Confirmed IRC-assessed objective tumor response was achieved in 20 patients in each arm (ORR, 8%; Table 2).

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.

During the study drug treatment period (within 30 days of last dose), 48 patients died (temsirolimus, 25 [10%]; sorafenib, 23 [9%]). At the time of primary analysis, including deaths in follow-up, 187 temsirolimus-treated patients (72%) and 164 sorafenib-treated

patients (65%) had died. 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

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.

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.

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 (unstratified log-rank $P = .002$), longer duration of prior sunitinib (> 180 days, $P = .02$), clear-cell histology ($P = .01$), and Memorial Sloan-Kettering Cancer Center intermediate risk ($P = .002$). Median OS was longer with sorafenib versus temsirolimus in patients receiving more than 180 days of sunitinib (17.8 v 14.4 months; $P = .02$), but not those receiving ≤ 180 days of sunitinib (11.4 v 10.1 months; $P = .11$). The OS benefit in favor of sorafenib was significant with respect to other baseline variables (ie, age < 65 years [$P = .0005$], male sex [$P = .02$], and normal hepatic function [$P = .007$]), but not geographic region or defined racial subgroups. In a post hoc exploratory analysis, OS remained significantly longer with sorafenib versus temsirolimus in patients with normal baseline lactate dehydrogenase (LDH; 18.7 v 16.0 months; HR, 1.39; 95% CI, 1.07 to 1.70; $P = .01$), but not those with high ($> 1 \times$ upper limit of normal) LDH (7.8 v 8.9 months; HR, 1.05; 95% CI, 0.72 to 1.53; $P = .78$).

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). Common AEs (all grade) occurring with more than 10% increased incidence with temsirolimus compared with sorafenib were cough, anemia, mucosal inflammation, dyspnea, peripheral edema, stomatitis, hypertriglyceridemia, hypercholesterolemia, epistaxis, and hyperglycemia. With sorafenib, AEs that occurred more than 10% more frequently compared with temsirolimus were diarrhea, PPE, alopecia, hypertension, and dysphonia.

A similar proportion of patients experienced at least one grade ≥ 3 AE with temsirolimus (70%) and sorafenib (69%). Grade ≥ 3 AEs that were more than 5% more frequent with temsirolimus versus sorafenib, respectively, were anemia (9% v 3%) and hyperglycemia (8% v 2%), whereas PPE was more than 5% more frequent with sorafenib (0 v 15%). The incidence of serious AEs (SAEs) was higher with temsirolimus (41%) versus

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

Adverse Event	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	
	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.

sorafenib (34%), but the incidence of the most common SAEs, that is, general physical health deterioration (3% v 3%), dyspnea (3% v 3%), pneumonia (3% v 2%), and pleural effusion (3% v 2%), was similar between arms. The incidence of fatal AEs (8%) was similar for temsirolimus and sorafenib. Three deaths were considered temsirolimus-related (infusion-related reaction, pneumonia *Legionella*, respiratory failure), and two were sorafenib-related (myocardial infarction, cardiorespiratory arrest).

Two sudden deaths (one in each arm), one cardiac arrest with temsirolimus, and two cardiopulmonary arrests (one in each arm) were reported. In all, 54 and six patients in the temsirolimus and sorafenib arms, respectively, had baseline glycosylated hemoglobin < 7% that shifted to $\geq 7\%$ as a maximum value. All-causality, all-grade interstitial lung disease, eosinophilic pneumonia, pneumonitis, or pulmonary fibrosis was reported in 31 patients (12%) receiving temsirolimus and none receiving sorafenib.

AEs resulted in dose reductions in 16% and 33% of patients in the temsirolimus and sorafenib arms, respectively. For temsirolimus, the most common AEs (% patients) requiring at least one dose reduction were pneumonitis (2%) and fatigue, asthenia, mucosal inflammation, and anemia (1% each); for sorafenib, these were PPE (14%) and diarrhea and fatigue (4% each). The only AEs leading to discontinuation in more than two patients occurred with sorafenib: PPE (n = 4) and pneumonia, pain in extremity, and rash (n = 3 each).

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 IRC-assessed 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.

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- α in patients with poor prognostic features.⁶ 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.^{4,11} 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.¹¹ 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.^{19,20}

The reasons for lack of correlation between PFS and OS in the present trial are not fully understood. Although more patients in the temsirolimus arm died compared with the sorafenib arm, respectively (72% v 65%), this difference was mostly due to the greater number of patients dying more than 30 days from the last dose (62% v 56%). Given the nonsignificant trend toward improved PFS in favor of temsirolimus with the confounding substantial OS improvement with sorafenib, the most likely explanation relates to use of poststudy anticancer therapy, which was not prespecified in the protocol. Unfortunately, information on poststudy therapy was not systematically collected; treatments received more than 1 month after the last dose of study drug were not recorded. Within 1 month of study treatment discontinuation, few patients (6%) in each arm received poststudy therapy. Among participating countries, access to other therapies used in third-line settings varied. Another possible explanation is that sorafenib did provide an OS benefit over temsirolimus in the second-line setting despite no statistical difference in PFS between the agents.

High ($> 1 \times$ upper limit of normal) baseline LDH may be predictive of OS benefit with first-line temsirolimus versus IFN- α .²¹ In the present trial, OS benefit with sorafenib versus temsirolimus was observed in patients with normal LDH but not those with high LDH. Further analyses are needed in future trials to determine whether LDH is a useful biomarker.

Although both arms were balanced among known prognostic factors, patient selection could have influenced the efficacy end points and trial outcomes. The target enrollment period was 18 months, but actual accrual lasted 43 months. This could have been due to wider availability of more agents for RCC starting in 2006 and longer than anticipated duration of first-line therapy. These factors were probably balanced among treatment arms and therefore not likely to influence OS.

AEs were consistent with the known safety profiles of temsirolimus and sorafenib and considered acceptable in this setting. Compared with sorafenib, temsirolimus-treated patients had a higher incidence of SAEs, but a lower incidence of AEs that led to dose reduction. Differences in certain types of AEs were observed between temsirolimus and sorafenib, but were consistent with the distinct toxicities of mTOR and VEGFR

inhibitors.²² Toxicities commonly associated with mTOR inhibition include anemia, mucosal inflammation, hyperlipidemia, and hyperglycemia, whereas toxicities commonly associated with VEGFR inhibition include diarrhea, PPE, and hypertension. In this study, no new safety signals were observed for either agent.

Findings from this randomized trial add to the growing body of evidence regarding sequential use of targeted agents in mRCC.^{23,24} Efficacy and safety data from three randomized phase III trials may aid oncologists with their choice of second-line treatment. The present study compared two drugs with distinct targeting profiles and mechanisms of action: mTOR inhibitor (temsirolimus) versus VEGFR inhibitor (sorafenib). Two other randomized phase III trials have evaluated targeted agents in previously treated patients. The AXIS trial⁴ compared second-line VEGFR inhibitors (axitinib v sorafenib) in patients pretreated with targeted agents or cytokines. Renal Cell Cancer Treatment With Oral RAD001 Given Daily (RECORD-1)⁸ was a placebo-controlled trial of an mTOR inhibitor (everolimus) after failure of one or two VEGFR inhibitor(s). Because everolimus and axitinib are approved agents for refractory mRCC, both may be acceptable control arms for future trials in that setting. Although the OS benefit for sorafenib may be explained by patient selection factors or unrealized subsequent therapy, the data support the hypothesis that sequenced VEGFR inhibition prolongs OS in patients with mRCC. Because we believe clear-cell RCC is an **HIF (hypoxia-inducible factor)/VEGF-driven tumor**, it follows that persistent VEGFR inhibition may be a reasonable treatment option for patients with RCC. Therefore, sustained VEGFR inhibition by sequential **tyrosine kinase inhibitors** may be an important mechanistic explanation for the result in this trial.

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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a

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GLOSSARY TERMS

HIF (hypoxia-inducible factor): HIF is a transcriptional factor that regulates the adaptive responses of mammalian cells to low oxygen (hypoxia). It is composed of HIF-1 α , which is up-regulated in conditions of hypoxia, and HIF-1 β (or, aryl hydrocarbon receptor nuclear translocators), which is expressed constitutively. Dimerization of HIF-1 α with HIF-1 β leads to transcription of genes such as VEGF and PDGF.

mTOR: The mammalian target of rapamycin belongs to a protein complex (along with raptor and G β L) that is used by cells to sense nutrients in the environment. mTOR is a serine/threonine kinase that is activated by Akt and regulates protein synthesis on the basis of nutrient availability. It was discovered when rapamycin, a drug used in transplantation, was shown to block cell growth presumably by blocking the action of mTOR.

Sorafenib: A substance belonging to the family of drugs called raf kinase inhibitors and anti-VEGF that is being studied in the treatment of cancer.

Sunitinib (SU011248, Sutent): An oral small molecular tyrosine kinase inhibitor that exhibits potent anti-angiogenic and anti-tumor activity.

Temsirolimus: Also called CCI-779, temsirolimus is an inhibitor of mTOR, a member of the phosphoinositide kinase-related family proteins.

Tyrosine kinase inhibitors: Molecules that inhibit the activity of tyrosine kinase receptors. They are small molecules developed to inhibit the binding of ATP to the cytoplasmic region of the receptor (eg, gefitinib), thus further blocking the cascade of reactions that is activated by the pathway.

VEGFR (vascular endothelial growth factor receptor): VEGFRs are transmembrane tyrosine kinase receptors to which the VEGF ligand binds. VEGFR-1 (also called Flt-1) and VEGFR-2 (also called KDR/Flk-1 [murine homologue]) are expressed on endothelial cells, while VEGFR-3 (also called Flt-4) is expressed on cells of the lymphatic and vascular endothelium. VEGFR-2 is thought to be principally responsible for angiogenesis and for the proliferation of endothelial cells. Typically, most VEGFRs have seven extracellular immunoglobulin-like domains, responsible for VEGF binding, and an intracellular tyrosine kinase domain.

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Appendix

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