Original Study

Sunitinib Versus Sorafenib as Initial Targeted Therapy for mCC-RCC With Favorable/Intermediate Risk: Multicenter Randomized Trial CROSS-J-RCC

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Abstract

The aim of the present randomized controlled study was to compare the efficacy of sunitinib and sorafenib as first-line treatment of patients with metastatic clear cell renal cell carcinoma with favorable or intermediate Memorial Sloan Kettering Cancer Center risk. The median first progression-free survival was 8.7 and 7.0 months in the sunitinib and sorafenib groups, respectively (hazard ratio, 0.67; 95% confidence interval, 0.42-1.08).

Purpose: The present study compared the efficacy of sunitinib and sorafenib as first-line treatment of metastatic clear cell renal cell carcinoma (mCC-RCC) with favorable or intermediate Memorial Sloan Kettering Cancer Center (MSKCC) risk. **Patients and Methods:** Treatment-naive patients with mCC-RCC were randomized to receive open-label sunitinib followed by sorafenib (SU/SO) or sorafenib followed by sunitinib (SO/SU). The primary endpoint was first-line progression-free survival (PFS). The secondary endpoints were total PFS and overall survival (OS). **Results:** Of the 124 patients enrolled at 39 institutions from February 2010 to July 2012, 120 were evaluated. The median first-line PFS duration was 8.7 and 7.0 months in the SU/SO and SO/SU groups, respectively (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.42-1.08). The total PFS and OS were not significantly different between the SU/SO and SO/SU groups (27.8 and 22.6 months; HR, 0.73; 95% CI, 0.428-1.246; and 38.4 and 30.9 months; HR, 0.934; 95% CI, 0.588-1.485, respectively). The subgroup analysis revealed that the total PFS with SU/SO was superior to the total PFS with SO/SU in the patients with favorable MSKCC risk and those with < 5 metastatic sites). SO/SU was superior to SU/SO for patients without previous nephrectomy. **Conclusions:** No statistically

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significant differences were found in first-line PFS, total PFS, or OS between the 2 treatment arms (ClinicalTrials.gov identifier, NCT01481870).

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Keywords: PFS, RCT, Renal cell carcinoma, SO/SU, SU/SO

Introduction

Renal cell carcinoma (RCC) with clear cell (CC) histologic features has been demonstrated to exhibit increased angiogenesis in concordance with the upregulation of vascular endothelial growth factor (VEGF), owing to the underlying genetic alteration of von Hippel Lindau[1] or another functionally associated gene.[2] Of the currently approved drugs that target VEGF or its receptors (VEGFRs), sorafenib was the first to be used for metastatic RCC (mRCC) in a second-line setting, followed by interferon (IFN)-α.[3] The median progression-free survival (mPFS) with sorafenib was 5.5 months compared with 2.8 months with placebo, corresponding to a hazard ratio (HR) of 0.44 (95% confidence interval [CI], 0.35-0.55; $P < .001$). In treatment-naive patients with mRCC, sunitinib was associated with longer survival compared with IFN-α (mPFS, 11 months with sunitinib vs. 5 months with IFN-α; HR, 0.42; 95% CI, 0.32-0.54; $P < .001$).[4] The efficacy of pazopanib was also demonstrated to be similar to that of sunitinib in a first-line setting[5] (mPFS, 8.4 months with pazopanib vs. 9.5 months with sunitinib; 95% CI, 8.3-10.9 and 95% CI, 8.3-11.1, respectively). Most of the patients in these trials had had disease categorized as favorable or intermediate risk using the Memorial Sloan Kettering Cancer Center (MSKCC) criteria. In MSKCC poor-risk patients, temsirolimus was shown to achieve longer overall survival (OS) than IFN-α alone.[6] In clinical practice, sunitinib and sorafenib can be chosen as a first-line therapeutic option because of patient status and/or comorbidities that might be unfavorable for treatment with sunitinib, pazopanib, or temsirolimus or because of the healthcare system of the specific country.

The SWITCH study, a prospective, randomized sequential trial to evaluate 2 sequential therapy protocols (sunitinib followed by sorafenib [SU/SO] vs. sorafenib followed by sunitinib [SO/SU]), revealed no differences in first-line PFS (first-PFS), total PFS (T-PFS), or OS.[7] Of the trial subjects, 13% had had a diagnosis of non-CC RCC.[7] However, no direct comparisons were performed between first-line sunitinib and first-line sorafenib for patients with metastatic CC-RCC (mCC-RCC) that had been predefined as favorable or intermediate MSKCC risk groups. Recently, the combination of nivolumab and ipilimumab was associated with a significantly longer median OS than that with sunitinib for patients in the intermediate- and poor-risk groups according to the international mRCC database consortium (IMDC) criteria,[8] which was not observed in the favorable-risk group. The identification of patients who can be expected to benefit more from sunitinib as first-line treatment is warranted.

In the present phase III randomized, open-label trial (ClinicalTrial.gov identifier, NCT01481870; and University Hospital Medical Information Network [Tokyo, Japan] identifier, UMIN00003040), we directly compared the efficacy of sunitinib and sorafenib in treatment-naive patients with a diagnosis of the most frequent type of mCC-RCC with a categorization of favorable- or intermediate-MSKCC risk.

Patients and Methods

Patients

The eligibility criteria included the following: age ≥ 18 but ≤ 80 years; histologically confirmed RCC; metastatic disease; favorable- or intermediate-MSKCC risk group; Eastern Cooperative Oncology Group performance status 0 to 2; and adequate pulmonary, cardiac, renal, hepatic, and hematologic function. Patients who had received previous systemic treatment were excluded; however, those who had received cytokine therapy in a postoperative adjuvant setting and whose disease had not progressed to metastases during cytokine therapy were accepted. Additional criteria included measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[9]

Patients with a diagnosis of cardiovascular disease within 12 months before screening and those with a history of any other malignant tumor were excluded. The presence of brain metastases (BMs) was an exclusion criterion; however, patients with stable BMs for 2 months before screening were enrolled in the present trial.

Study Design

The present study was a phase III randomized, open-label trial of sunitinib (Sutent; Pfizer) followed by sorafenib (Nexavar; Bayer) and vice versa. Treatment-naive patients with mRCC were randomly assigned at a 1:1 ratio to either SU/SO or SO/SU treatment. Randomization was performed according to the presence of previous nephrectomy (yes vs. no), MSKCC risk group (favorable vs. intermediate risk), and institution.

Sunitinib was orally administered for a 6-week cycle at a once-daily dose of 50 mg for 4 weeks, followed by 2 weeks without treatment. Sorafenib was orally administered at a dosage of 400 mg twice daily without a break. Patients continued to receive the study drug until disease progression, unacceptable toxicity, death, or another reason for discontinuation of the study drug. A dose reduction of sunitinib (from 50 mg to first, 37.5 mg and then, 25 mg) and sorafenib (from 400 mg twice daily to first, 400 mg once daily and then, 400 mg every other day) was determined according to the severity of the adverse events (AEs).

The institutional review board or ethics committee at each institution approved the present study, which was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Table 1 Baseline Demographics and Clinical Characteristics

Characteristic[a]	All Patients	Arm A (Sunitinib to Sorafenib)	Arm B (Sorafenib to Sunitinib)	*P* Value[b]
Patients	120	57	63	
Sex				.622
Male	99	46	53	
Female	21	11	10	
Age, y				.510
Median	67	67	66	
Range	41-79	41-79	44-79	
MSKCC risk group				.877
Favorable	26	12	14	
Intermediate	94	45	49	
Histologic grade				.236
1	15	8	7	
2	57	22	35	
3	38	21	17	
cT at initial visit				.639
1a	13	4	9	
1b	21	12	9	
2	24	12	12	
3a	26	14	12	
3b	20	8	12	
3c	0	0	0	
4	7	3	4	
cN at initial visit				.822
0	108	50	58	
1	10	5	5	
M at initial visit				
0	56	25	31	
1	64	32	32	
Metastatic sites, n				.210
1	9	7	2	
2	16	9	7	
3	24	8	16	
4	14	6	8	
>4	57	27	30	
Lung metastasis				.588
Yes	87	40	47	
No	33	17	16	
Lymph node metastasis				.248
Yes	34	19	15	
No	86	38	48	
Bone metastasis				.201
Yes	34	13	21	
No	86	44	42	
Brain metastasis				.071
Yes	6	5	1	
No	114	63	62	
Liver metastasis				.620
Yes	10	4	6	
No	110	53	57	

Table 1 Continued

Characteristic[a]	All Patients	Arm A (Sunitinib to Sorafenib)	Arm B (Sorafenib to Sunitinib)	*P* Value[b]
Local and/or renal recurrence (or metastasis)				.220
Yes	20	12	8	
No	100	45	55	
Metastases at other sites				.894
Yes	33	16	17	
No	87	41	46	
Surgery for primary lesion				.842
Yes	106	50	56	
No	14	7	7	
Metastasectomy				.228
Yes	22	13	9	
No	98	44	54	
Adjuvant interferon-α treatment				.620
Yes	10	4	6	
No	110	53	57	
Irradiation for brain metastases				.137
Yes	5	4	1	
No	115	53	62	
Irradiation for osseous metastases				.900
Yes	6	3	3	
No	114	54	60	

Abbreviation: MSKCC = Memorial Sloan Kettering Cancer Center.
[a]Characteristics were measured at baseline, except for cT, cN, and M; TNM stage was estimated at the first renal cell carcinoma diagnosis using the 2009 Union Internationale Contre le Cancer/American Joint Cancer Committee TNM classification; histologic grade was determined using the General Rules of Clinical and Pathological Studies on Renal Cell Carcinoma in Japan (histologic grade classified as grade 1-3).
[b]Calculated using the χ^2 test, except for age, which was calculated using the Welch *t* test.

Endpoints and Assessments

The primary endpoint was first-PFS, which was defined as the interval from the date of randomization to the date of disease progression or death from any cause. The secondary endpoints included the objective response rate (ORR), safety, OS, and T-PFS of first and second treatment (SU/SO vs. SO/SU). Laboratory tests were performed at least every 4 weeks. Tumor assessments using computed tomography was performed at baseline, week 8, and every 8 weeks thereafter until disease progression. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[10]

Statistical Analysis

The present randomized trial tested the null hypothesis that the mPFS with sunitinib was 11 months versus the alternative hypothesis that mPFS with sorafenib was 5.5 months, with an mPFS increase of 5.5 months or 100% improvement with sunitinib, corresponding to a HR of 0.5 (overall 1-sided α of 0.01). To yield a 90% power for detecting a statistically significant difference ($P < .05$) between the treatment arms, an estimated total of 116 patients were required for enrollment. Randomization and registration were performed by an independent organization, University Hospital Medical Information Network Clinical Trial Registry (Tokyo, Japan). The assignment was obtained at enrollment by the investigator via the Internet, and the patients and investigator were not blinded to the treatment.

Efficacies were analyzed in the intent-to-treat population (all treatment-naive patients randomly assigned to 1 of the 2 groups). Safety analyses were performed in the safety population, which included all randomly assigned patients who had received ≥ 1 dose of the drug. An interim futility analysis was planned for when 60 patients were evaluable (ie, ∼50% of those required for the final analysis), and the data monitoring committee could consider early trial discontinuation. The data in the present report were based on the secondary interim analysis with a significance level set as $P = .0151$ using the O'Brien-Fleming method. The final analysis was planned for August 2015, with $P = .0471$.

The Kaplan-Meier method was used to estimate the mPFS, and 2-sided 95% CIs were calculated. The PFS rates between the 2 treatment arms were compared using the log-rank test. The Cox proportional hazards model was used to estimate the HRs with 2-sided 95% CIs, with a significance level of $P = .05$. The PFS rates between the treatment arms were also compared on the basis of baseline patient characteristics, including clinical T and M stage at

the initial diagnosis; histologic grade of primary RCC; MSKCC risk group; previous nephrectomy; cerebral, hepatic, pulmonary, or osseous metastasis; leukocytopenia, neutropenia, lymphopenia, and thrombocytopenia; serum C-reactive protein (CRP) level; number of metastatic lesions; and overall diameter of the lesions using the RECIST. The Kaplan-Meier method was used to estimate the median duration of the response with a 2-sided 95% CI, and the dose intensity was evaluated using the Mann-Whitney *U* test.

Results

Patients

From February 18, 2010 to July 15, 2012, 124 patients with treatment-naive mCC-RCC were enrolled at 39 sites in Japan (Supplemental Appendix in the online version). The demographic and clinical characteristics of the enrolled patients at baseline were balanced between the 2 treatment groups (Table 1), except for the number of patients with stable BMs. More patients with BMs had been included in the SU/SO arm than in the SO/SU arm (5 vs. 1), which was not a statistically significant difference ($P = .071$). Of the 124 patients, 60 and 64 were randomly assigned to the SU/SO and SO/SU arms, respectively. Four patients withdrew their consent (3 and 1 in the SU/SO and SO/SU arms, respectively), and the remaining 57 patients in the SU/SO arm and 63 patients in the SO/SU arm received the assigned first-line treatment. At the data cutoff date of June 30, 2015, 95% and 98% of the patients in the SU/SO and the SO/SU arms, respectively, had discontinued the first-line treatment, most frequently because of disease progression (Figure 1). The median first-line treatment duration was relatively longer (6.7 vs. 5.9 months; $P = .097$) and the median relative dose intensity (total dose administered/total dose assigned dose × 100) was greater (65.8% [range, 7.1%-100%] vs. 61.2% [range, 10.7%-100%]; $P = .333$) with sunitinib than sorafenib. Subsequently, 30 of the 54 patients (56%) were administered sorafenib after sunitinib, and 47 of the 62 patients (76%) were administered sunitinib after sorafenib ($P = .030$). At the data cutoff date, 1 of the 30 patients (3%) and 7 of the 47 patients (15%) had continued treatment to receive sorafenib and sunitinib, respectively.

PFS and OS

The median first-PFS was longer with sunitinib than that with sorafenib (8.7 months; 95% CI, 5.5-21.1 months; and 7.0 months; 95% CI, 6.1-12.2 months, respectively; Table 2 and Figure 2A). The difference was not statistically significant (HR, 0.67; 95% CI, 0.42-1.08; 2-sided $P = .128$). No statistically significant differences were found between the sunitinib and sorafenib groups in T-PFS (27.8 and 22.6 months, respectively; HR, 0.73; 95% CI, 0.428-1.246; $P = .247$; Figure 2E) or OS (38.4 and 30.9 months, respectively; HR, 0.934; 95% CI, 0.588-1.485; $P = .773$; Figure 2F).

The subgroup HR analyses for first-PFS of patients with serum creatinine greater than the normal limit (n = 61; HR, 0.525; 95% CI, 0.277-0.995; $P = .04937$); favorable MSKCC risk (n = 26; HR, 0.245; 95% CI, 0.082-0.734; $P = .012$); histopathologic grade 1 or 2 primary tumors (n = 72; HR, 0.397; 95% CI, 0.213-0.742; $P = .003$); previous nephrectomy (n = 106; HR, 0.602; 95% CI, 0.378-0.960; $P = .032$); clinical stage T1 or T2 (n = 58; HR, 0.283; 95% CI, 0.137-0.588; $P < .001$); stage M0 versus M1 at the initial RCC diagnosis (n = 56; HR, 0.411; 95% CI, 0.203-0.834; $P = .012$) and ≤ 4 metastatic lesions (n = 63; HR, 0.406; 95% CI, 0.207-0.797; $P = .007$) revealed that sunitinib was superior to sorafenib. In contrast, sorafenib was superior to sunitinib for patients without previous nephrectomy (n = 14; HR, 3.359; 95% CI, 1.016-11.100; $P = .046$).

The T-PFS of the SU/SO arm was superior to that of the SO/SU arm in the subgroup of patients with favorable MSKCC risk (HR, 0.164; 95% CI, 0.035-0.766; $P = .008$) and those with < 5 metastatic sites (HR, 0.406; 95% CI, 0.207-0.797; $P = .009$). In contrast, the HR was lower in the SO/SU arm in the patients without previous nephrectomy (HR, 11.816; 95% CI, 1.355-103; $P = .007$). No statistically significant differences were found in the OS rates between the treatment groups in any of the subgroup analyses (Figure 3).

Objective Response

The ORR was evaluated using RECIST, version 1.1. A complete response (CR) determined by the assessment of the treating physician, was observed in 2 patients treated with sunitinib (4.3%) and 1 patient treated with sorafenib (2.1%) in first-line treatment (Table 2). A partial response (PR) was observed in 12 patients treated with sunitinib (25.5%) and 9 patients treated with sorafenib (19.1%). The ORR (CR plus PR), although the difference was not significant, was greater with sunitinib than with sorafenib (29.8% vs. 21.2%; $P = .390$). The median response duration was 32.0 months with sunitinib and 14.9 months with sorafenib. At the data cutoff date, 3 of the 57 patients (5.0%) and 1 of the 63 patients (1.6%) had continued to receive sunitinib and sorafenib, respectively, as first-line treatment.

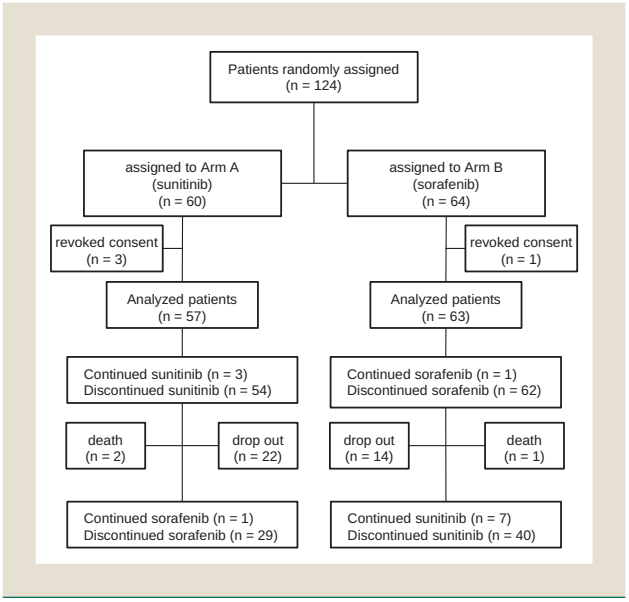
With second-line treatment, 3 patients (7.3%) had achieved a CR with sunitinib; however, none of the patients had achieved CR with sorafenib. A PR was observed in 6 patients with sunitinib (14.6%) and 5 patients with sorafenib (21.7%). The ORR was not significantly different between the 2 groups (21.9% and 21.7% with sunitinib and sorafenib, respectively; $P = .984$; Supplemental Table 1 in the online version). The median response duration was 30.1 and 19.3 months with sunitinib and sorafenib, respectively. At the data cutoff date, 1 of the 30 patients (3.3%) and 7 of the 47 patients (14.9%) had continued to receive sunitinib and sorafenib, respectively, as second-line treatment.

Safety

The study patients had received sunitinib and sorafenib for a median duration of 6.7 months (range, 0.1-45.3 months) and 6.1 months (range, 0.3-46.1 months), respectively, at the data cutoff date (March 30, 2013; $P = .097$). The most frequent all-grade, all-causality AEs (ie, those detected in > 40% of patients) were hand-foot syndrome (HFS), anorexia, fatigue, hypertension and stomatitis with sunitinib and HFS, rash, hypertension, fatigue, and diarrhea with sorafenib. The laboratory abnormalities included thrombocytopenia, neutropenia, proteinuria, hypothyroidism, increased lipase, and decreased serum albumin with sunitinib and increased lipase, proteinuria, increased aspartate transaminase, increased alanine transaminase, and thrombocytopenia with sorafenib (Table 3).

The AEs that occurred more frequently (≥ 15% difference) with sunitinib than with sorafenib were anorexia, nausea, vomiting,

Figure 1 Consolidated Standards of Reporting Trials Diagram



stomatitis, fatigue, fever, neutropenia, thrombocytopenia, hypothyroidism, low hemoglobin, increased creatinine, and decreased serum albumin. In contrast, those that occurred more frequently with sorafenib than with sunitinib were rash, diarrhea, and HFS (Table 3).

Grade ≥ 3 AEs were reported in 98 patients (81.7%) in the entire study, including 50 (79.4%) and 48 (84.2%) patients treated with sunitinib and sorafenib, respectively. The grade ≥ 3 AEs that occurred more frequently (≥ 5% difference) in patients treated with sunitinib were anorexia, nausea, fatigue, low hemoglobin, neutropenia, thrombocytopenia, and hyponatremia. In contrast, increased aspartate transaminase, increased alanine transaminase, diarrhea, rash, and HFS occurred more frequently in those treated with sorafenib. A total of 13 (22.8%) and 12 (19.0%) patients in the sunitinib and sorafenib groups, respectively, discontinued therapy because of treatment-related AEs. One grade 5 AE, gastrointestinal perforation, was reported during sorafenib treatment.

For second-line treatment, the patients had received sunitinib and sorafenib for a median duration of 4.1 months (range, 0.6-46.4 months) and 3.3 months (range, 0.2-35.6 months), respectively ($P = .361$). The most frequent all-grade, all-causality AEs (AEs detected in > 40% of patients) were HFS, anorexia, hypothyroidism, and fatigue with sunitinib and HFS, hypothyroidism, and rash with sorafenib. Although the rate of patients with fatigue was almost identical between the first-line and second-line sunitinib groups (58% and 51%, respectively), the rate of patients with fatigue was lower among those with second-line sorafenib (23%) compared with those with first-line sorafenib (44%). The incidence of HFS was lower in both second-line sunitinib and sorafenib groups. The changes in the rates of other AEs and laboratory abnormalities were comparable, albeit occurring at lower frequencies (Supplemental Table 2 in the online version).

Grade ≥ 3 AEs were reported in 30 patients (39.0%) during second-line treatment, including 15 (51.7%) and 15 (31.3%) patients treated with sunitinib and sorafenib, respectively. The grade ≥ 3 AEs that occurred more frequently (≥ 5%) in patients treated with sunitinib were anorexia and fatigue. A total of 5 patients (10.6%) treated with sunitinib and 8 (26.7%) treated with sorafenib discontinued therapy because of treatment-related AEs. One grade 5 AE, pneumonitis, was reported during sorafenib treatment (Supplemental Table 2 in the online version).

Discussion

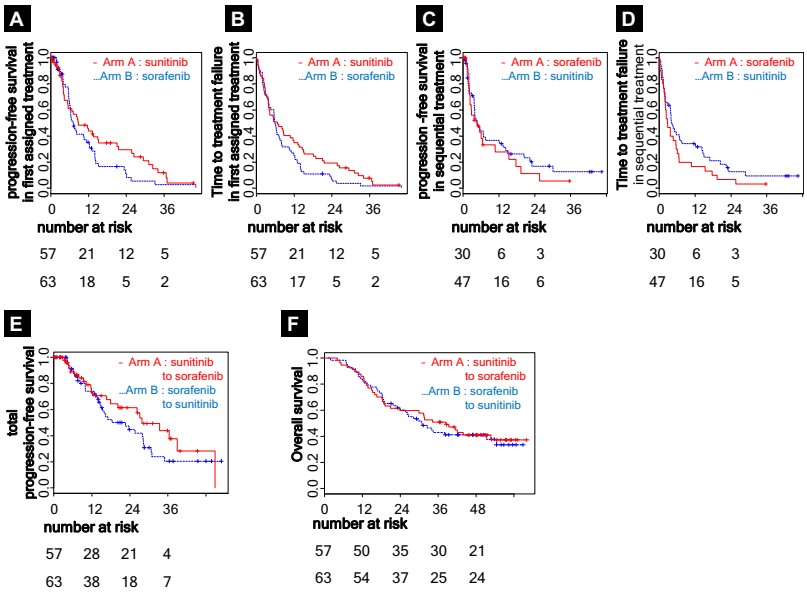
The present randomized trial was designed to elucidate the previously unreported comparison of 2 active compounds, sunitinib and sorafenib, as first-line treatment of mRCC. Because temsirolimus was demonstrated to prolong OS for patients with poor MSKCC risk,[6] the present trial was prespecified to patients with favorable and intermediate MSKCC risk. Thus, all patients with a diagnosis of CC-RCC were enrolled, and no patient with non-CC histologic features was enrolled. The trial was determined on the hypothesis of a 5.5-month improvement in mPFS with sunitinib compared with sorafenib.[4,11] In the present study, no significant difference in mPFS was found between the patients treated with sunitinib and sorafenib, although the survival duration was numerically longer with sunitinib. Sorafenib, chosen as the active comparator, was originally reported to prolong PFS as second-line treatment in patients pretreated with cytokines. The mPFS of sorafenib, 5.5 months, was used to design the present study. In the present study, the mPFS of sorafenib was 7.0 months, which was longer than expected. A randomized trial of tivozanib versus sorafenib as first-line therapy (TIVO-1) also reported a longer mPFS

Table 2 Best Tumor Response[a] and Progression-free Survival With First Assigned Treatment

Variable	Sunitinib (n = 57)	Sorafenib (n = 63)	*P* Value[b]
Objective response	14 (29.8)	10 (21.3)	.390
Complete response	2 (4.3)	1 (2.1)	
Partial response	12 (25.5)	9 (19.1)	
Stable disease	14 (30.0)	22 (46.8)	
Progressive disease	19 (40.4)	15 (31.9)	
Disease could not be evaluated or data missing	10 (17.5)	16 (25.3)	
Progression-free survival			.128
Patients in analysis, n	57	63	
Median, mo	8.7	7.0	
95% CI, mo	5.5-21.1	6.1-12.2	

Abbreviation: CI = confidence interval.
[a]Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1.
[b]Calculated using the χ^2 test for the objective response and log-rank test for progression-free survival.

Figure 2 Kaplan-Meier Curve Estimated (A) Progression-free Survival (PFS) in First Assigned Treatment (Sunitinib or Sorafenib), (B) Time to Treatment Failure in First Assigned Treatment, (C) PFS in Sequential Treatment (Sorafenib After Sunitinib Treatment or Sunitinib After Sorafenib Treatment), (D) Time to Treatment Failure in Sequential Treatment, (E) Total PFS (Sunitinib to Sorafenib or Sorafenib to Sunitinib), and (F) Overall Survival



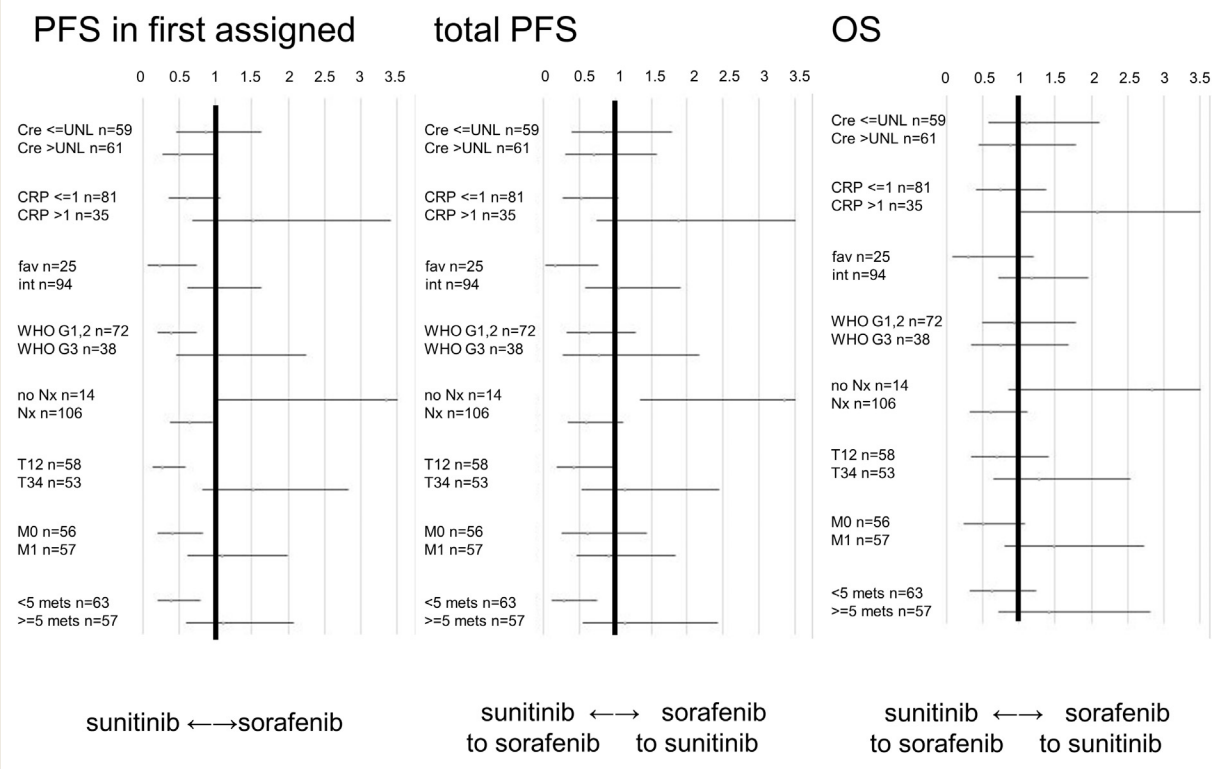
(9.1 months; 95% CI, 7.3-9.5 months) in the sorafenib arm.[12] In another randomized trial comparing axitinib with sorafenib in treatment-naive patients, sorafenib was also associated with a longer mPFS of 6.5 months (95% CI, 4.7-8.3 months).[13] Another single-arm trial assessing sorafenib as first-line treatment also found mPFS longer than 5.5 months with the treatment.[14,15] In the present study, the mPFS with first-line sorafenib was 7.0 months (95% CI, 6.3-7.7 months), comparable with previously reported results.

Whether 1 of the clones in primary RCC develops into metastatic lesions has been a focus of intense debate, and the characteristics of primary RCC cells are not identical to those of the metastatic lesions. Systematic comprehensive investigation of primary and metastatic lesions revealed several common genetic alterations, at least partially,[16] and key genetic and molecular alterations might be retained throughout the targeted therapy.[17,18] In the present study, of the factors predicting for longer PFS with first-line sunitinib treatment, clinical stage T1 or T2 and/or lower primary tumor grade reflected the less aggressive features of the tumor cells. An elevated CRP, which corresponds to aggressiveness in RCC, is associated with a predisposition to a worse prognosis.[19] Correspondingly, the patients with lower CRP levels achieved longer PFS with sunitinib in the present study.

As a more direct clinical implication, significantly longer PFS was observed with sunitinib among patients with favorable risk than those with intermediate risk. In previous studies comparing PFS of more specific tyrosine kinase inhibitors (TKIs) targeted against VEGFR, tivozanib and axitinib, with sorafenib as first-line therapy,[12,15] the selective TKIs led to longer PFS for patients with favorable risk than that for those with intermediate risk. In the first clinical trial of sorafenib,[11] the HR for PFS for patients with intermediate risk was lower than that for those with favorable risk. Thus, selective TKIs with more specificity for VEGFR are expected to provide more benefit for patients with less aggressive mRCC.[12,20] The patients with intermediate risk comprise a heterogeneous population, with associated differences in clinical outcomes[21]; thus, a detailed examination of patients with intermediate risk is necessary to determine the susceptibility toward specific drugs. In the context of risk factors, the efficacy of the combination of the immune checkpoint inhibitors ipilimumab and nivolumab as first-line therapy was associated with a longer median OS compared with that with sunitinib for patients with intermediate and poor prognoses using the IMDC criteria.[22] A randomized controlled trial that compared cabozantinib, a broad TKI against c-Met and VEGFR2, which also inhibits AXL and RET, and sunitinib in 167 patients with treatment-naive mRCC with intermediate or poor IMDC risk revealed that the mPFS duration was 8.6 months (95% CI, 6.8-14.0 months) with cabozantinib and 5.3 months (95% CI, 3.0-8.2 months) with sunitinib (HR, 0.48; 95% CI, 0.31-0.74; $P = .0008$).[23] The results of these 2 clinical trials, albeit evaluating different drugs, suggest that the benefit of sunitinib treatment can be expected in patients with mRCC and relatively fewer poor prognostic factors. In addition to the data regarding sorafenib as first-line treatment in the present study, it might be worthwhile to compare sorafenib with the new TKIs, such as cabozantinib, or a combination of nivolumab and ipilimumab, as first-line therapy specifically for patients with intermediate or poor MSKCC risk.

No statistically significant differences were found in the secondary outcome measures of the present study, including

Figure 3 Cox Progression Hazards Analysis of Progression-free Survival (PFS) With First-Line Therapy and Total Protocol Treatment and Overall Survival (OS) Stratified by Various Patient Baseline Factors (Extracts)



Abbreviations: Cre = creatinine; CRP = C-reactive protein; fav = favorable (risk); G = grade; int = intermediate (risk); mets = metastasis; Nx = any node stage; UNL = upper normal limit.

T-PFS and OS. Targeted drugs for mRCC have been approved by the positive (ie, statistically significant) results of, not OS, but PFS, in randomized trials, except for a trial comparing temsirolimus with IFN-α[6] and a phase II trial comparing lenvatinib plus everolimus with everolimus alone in a second-line treatment setting.[24] In contrast, recent studies evaluating the immune checkpoint inhibitor nivolumab alone in a sequential treatment setting[25] and nivolumab and ipilimumab in a first-line setting[22] demonstrated significant differences, not in PFS, but in OS rates. At the cutoff date for the present study, no patients had received treatment with an immune checkpoint inhibitor; therefore, the data in the present study should be assessed with other studies conducted in the pre-immune checkpoint inhibitor era.

Conclusions

The primary endpoint of first-PFS for sunitinib compared with sorafenib was not met. Sunitinib appeared to be more active than sorafenib for patients with mCC-RCC and the following clinicopathologic characteristics: favorable MSKCC risk, no BMs, primary cT1 or T2 but not $\geq$ T3, lower histologic grade, and CRP $\leq$ 1 mg/mL.

Clinical Practice Points

- The median first-PFS was 8.7 and 7.0 months in the SU/SO and SO/SU groups, respectively; however, the primary endpoint of first-PFS was not met.
- The T-PFS and OS were similar between the SU/SO and SO/SU groups (27.8 and 22.6 months; HR, 0.73; 95% CI, 0.428-1.246; and 38.4 and 30.9 months; HR, 0.934; 95% CI, 0.588-1.485, respectively).
- Sunitinib appeared to be more active than sorafenib in patients with mCC-RCC and the following clinicopathologic characteristics: favorable MSKCC risk, no BMs, primary cT1 or cT2 but not $\geq$cT3, lower histologic grade, and CRP $\leq$ 1 mg/mL.

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Table 3 Adverse Events and Laboratory Abnormalities With First Assigned Treatment

Variable	Sunitinib			Sorafenib			*P* Value
	All Grades	Grade 3-4	Grade 5	All Grades	Grade 3-4	Grade 5	
AEs							
Hand-foot syndrome	40 (70)	7 (12)	0 (0)	54 (86)	16 (25)	0 (0)	.077
Anorexia	37 (65)	6 (11)	0 (0)	26 (41)	0 (0)	0 (0)	.001
Hypothyroidism	37 (65)	0 (0)	0 (0)	19 (30)	2 (3)	0 (0)	<.001
Fatigue	33 (58)	9 (16)	0 (0)	28 (44)	1 (2)	0 (0)	.026
Hypertension	32 (56)	10 (18)	0 (0)	28 (44)	12 (19)	0 (0)	.474
Stomatitis	26 (46)	2 (4)	0 (0)	14 (22)	0 (0)	0 (0)	.022
Nausea	19 (33)	3 (5)	0 (0)	7 (11)	0 (0)	0 (0)	.011
Rash	14 (25)	1 (2)	0 (0)	31 (49)	9 (14)	0 (0)	.022
Diarrhea	14 (25)	0 (0)	0 (0)	28 (44)	4 (6)	0 (0)	.084
Vomiting	13 (23)	1 (2)	0 (0)	2 (3)	0 (0)	0 (0)	.012
Fever	9 (16)	0 (0)	0 (0)	3 (5)	0 (0)	0 (0)	.045
Hemorrhage, GI	2 (4)	2 (4)	0 (0)	1 (2)	0 (0)	0 (0)	.709
LV systolic dysfunction	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	.157
Cardiac ischemia	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Perforation, GI	0 (0)	0 (0)	0 (0)	1 (0)	1 (2)	1 (2)	NA
Edema, limb	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	NA
Infection (lung)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	NA
Joint function	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	NA
Urinary retention	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	NA
Laboratory abnormalities							
Thrombocytopenia	51/57 (89)	19/57 (33)	0 (0)	27/62 (44)	1/62 (2)	0 (0)	<.001
Leukopenia	48/57 (84)	5/57 (9)	0 (0)	11/62 (18)	0/62 (0)	0 (0)	<.001
Neutropenia	42/53 (79)	15/53 (28)	0 (0)	10/56 (18)	0/62 (0)	0 (0)	<.001
Lymphopenia	41/53 (77)	10/53 (19)	0 (0)	32/55 (58)	5/55 (9)	0 (0)	.123
Proteinuria	34/47 (72)	2/47 (4)	0 (0)	31/54 (57)	4/54 (7)	0 (0)	.074
Lipase	23/35 (66)	4/35 (11)	0 (0)	24/39 (62)	8/39 (21)	0 (0)	.475
Albumin serum, low	37/56 (66)	4/56 (7)	0 (0)	24/61 (39)	2/61 (3)	0 (0)	.021
Anemia	35/57 (61)	7/57 (12)	0 (0)	15/62 (24)	3/62 (5)	0 (0)	.001
AST elevation	35/57 (61)	4/57 (7)	0 (0)	32/62 (52)	8/62 (13)	0 (0)	.244
Creatinine	30/57 (53)	0/57 (0)	0 (0)	13/63 (21)	1/63 (2)	0 (0)	.001
ALT elevation	29/57 (51)	6/57 (11)	0 (0)	30/62 (48)	10/62 (16)	0 (0)	.030
Amylase	21/48 (44)	3/48 (6)	0 (0)	23/55 (42)	3/55 (5)	0 (0)	.867
Hyponatremia	24/56 (43)	8/56 (14)	0 (0)	20/62 (32)	3/62 (5)	0 (0)	.187
ALP elevation	23/55 (42)	1/55 (2)	0 (0)	24/62 (39)	0/62 (0)	0 (0)	.753
Hyperkalemia	19/56 (34)	2/56 (4)	0 (0)	21/62 (34)	0/62 (0)	0 (0)	.413
Hyperuricemia	18/56 (32)	2/56 (4)	0 (0)	13/59 (22)	0/50 (0)	0 (0)	.224
Bilirubin	10/56 (18)	1/56 (2)	0 (0)	8/62 (13)	1/62 (2)	0 (0)	.153

Data presented as n (%) or n/N (%).
Abbreviations: AEs = adverse events; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; LV = left ventricular; NA = not applicable.

Disclosure

Y.T. has received grants and lecture and advisory fees from Novartis, Japan; Ono, and Astellas, grants and lecture fees from Astellas and Pfizer, Japan lecture fees from Bristol-Myers Squibb, Japan and grants from Takeda, Japan. T. Kondo has received lecture fees from Intuitive Surgical, Novartis, Ono, and Pfizer. W.O. has received grants form Nipuro and Takeda and lecture fees from Astellas, Bristol-Myers Squibb, Ono, and Pfizer. J.T. has received lecture fees from Pfizer. M.T. has received lecture fees from Pfizer. H.M. has received grants and lecture fees from Janssen, grants from

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Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2020.01.001.

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Supplemental Appendix

In addition to the authors, the following investigators participated in the present study: Hidehiro Kakizaki, Asahikawa Medical University; Naoya Masumori, Sapporo Medical University; Shintaro Narita, Yohei Horikawa, and Norihiko Tsuchiya, Akita University; Akihiro Ito, Tohoku University; Makoto Morozumi, Saitama Medical University; Akio Horiguchi and Tomohiko Asano, National Medical Defense College; Tetsuo Fujita, Shiro Baba, and Masatsugu Iwamura, Kitasato University; Haruki Kume, Tokyo University; Noboru Nakaigawa, Yokohama City University; Hidenori Zakouji, Yamanashi University; Yasuhide Kitagawa, Yoshihui Kadono, Hiroyuki Konaka, and Atsushi Mizokami, Kanazawa University; Toru Kimura, Social Insurance Chukyo Hospital; Tomomi Kamba, Kyoto University; Hiroaki Kawanishi, Tenri Hospital; Takehiro Sejima, Tottori University; Satoshi Honda, Shimane University; Hiroyuki Tsunemori and Yoshiyuki Kakehi, Kagawa University, Ooba Kojiro, Yasushi Mochizuki, and Hideki Sakai, Nagasaki University; Katsuyoshi Hashine and Kensuke Shinomori, Shikoku Cancer Center; Yasutoshi Yamada and Kenryu Nishiyama, Kagoshima University; Shouichiro Mukai and Toshiyuki Kamoto, Miyazaki University; and Yoshinori Oshiro, University of the Ryukyus.

Supplemental Table 1 Best Tumor Response[a] and Progression-free Survival With Sequential Treatment

Variable	Sorafenib (n = 30)	Sunitinib (n = 47)	*P* Value[b]
Objective response	5 (21.7)	9 (21.9	.984
Complete response	0 (0.0)	3 (7.3)	
Partial response	5 (21.7)	6 (14.6)	
Stable disease	6 (26.1)	9 (22.0)	
Progressive disease	12 (52.2)	23 (56.1)	
Disease could not be evaluated or data missing	7 (23.3)	6 (13.6)	
Progression-free survival			.462
Patients in analysis	30	47	
Median, mo	4.7	4.7	
95% CI, mo	2.3-15.4	3.8-13.4	

Abbreviation: CI = confidence interval.
[a]Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1.
[b]Calculated using the χ^2 test for the objective response and log-rank test for progression-free survival.

Supplemental Table 2 Adverse Events[a] and Laboratory Abnormalities With Sequential Treatment

Variable	Sorafenib (n = 30)			Sunitinib (n = 47)			*P* Value
	All Grades	Grade 3-4	Grade 5	All Grades	Grade 3-4	Grade 5	
AEs							
Hand-foot syndrome	14 (47)	1 (3)	0 (0)	21 (45)	2 (4)	0 (0)	.954
Anorexia	6 (20)	0 (0)	0 (0)	19 (40)	3 (6)	0 (0)	.215
Hypothyroidism	9 (65)	0 (0)	0 (0)	22 (47)	1 (2)	0 (0)	.246
Fatigue	7 (23)	1 (3)	0 (0)	24 (51)	6 (13)	0 (0)	.033
Hypertension	7 (23)	3 (10)	0 (0)	16 (34)	3 (6)	0 (0)	.380
Stomatitis	3 (10)	1 (3)	0 (0)	12 (26)	0 (0)	0 (0)	.009
Nausea	4 (13)	0 (0)	0 (0)	12 (26)	0 (0)	0 (0)	.324
Rash	9 (65)	2 (7)	0 (0)	5 (11)	1 (2)	0 (0)	.028
Diarrhea	6 (20)	1 (3)	0 (0)	9 (19)	1 (2)	0 (0)	1.000
Vomiting	3 (30)	0 (0)	0 (0)	7 (15)	0 (0)	0 (0)	.732
Fever	2 (7)	1 (3)	0 (0)	8 (17)	0 (0)	0 (0)	.039
Hemorrhage, GI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Cardiac ischemia	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Edema, limb	2 (7)	2 (7)	0 (0)	3 (6)	0 (0)	0 (0)	.200
Infection (lung)	0 (0)	0 (0)	1 (3)	1 (2)	0 (0)	0 (0)	.026
Joint function	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Urinary retention	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	NA
LV systolic dysfunction	1 (3)	1 (3)	0 (0)	1 (2)	0 (0)	0 (0)	1.000
Perforation, GI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Hiccoughs	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	NA
Laboratory abnormalities							
Thrombocytopenia	6/26 (23)	0/26 (0)	0 (0)	38/44 (86)	14/44 (32)	0 (0)	<.001
Leukopenia	4/23 (17)	0/23 (0)	0 (0)	37/44 (84)	4/44 (9)	0 (0)	<.001
Lymphopenia	13/25 (52)	4/25 (16)	0 (0)	31/42 (74)	7/42 (17)	0 (0)	.374
Neutropenia	1/25 (4)	0/25 (0)	0 (0)	33/42 (79)	15/42 (36)	0 (0)	<.001
Proteinuria	13/22 (59)	2/22 (9)	0 (0)	17/36 (47)	2/36 (6)	0 (0)	.231
Albumin serum, low	8/26 (31)	0/26 (0)	0 (0)	18/41 (44)	3/41 (7)	0 (0)	.470
Lipase	7/16 (44)	2/16 (13)	0 (0)	14/32 (44)	3/32 (9)	0 (0)	.770
AST elevation	6/26 (23)	0/26 (0)	0 (0)	23/44 (52)	2/44 (5)	0 (0)	.088
Anemia	7/24 (29)	3/24 (13)	0 (0)	20/44 (45)	3/44 (7)	0 (0)	.256
Creatinine	7/26 (27)	3/26 (12)	0 (0)	19/44 (43)	2/44 (5)	0 (0)	.160
ALT elevation	6/26 (23)	0/26 (0)	0 (0)	16/44 (36)	2/44 (5)	0 (0)	.667
Amylase	5/24 (21)	1/24 (4)	0 (0)	15/39 (38)	3/39 (8)	0 (0)	.156
Hyponatremia	16/44 (36)	3/44 (7)	0 (0)	9/25 (36)	3/25 (12)	0 (0)	.738
ALP elevation	7/24 (29)	0/24 (0)	0 (0)	12/42 (28)	1/42 (2)	0 (0)	1.000
Hyperkalemia	10/26 (38)	0/26 (0)	0 (0)	15/43 (15)	1/43 (2)	0 (0)	.762
Hyperuricemia	7/24 (29)	2/24 (8)	0 (0)	6/39 (15)	1/39 (3)	0 (0)	.183
Bilirubin	1/25 (4)	0/25 (0)	0 (0)	12/40 (30)	2/40 (5)	0 (0)	.054

Data presented as n (%) or n/N (%).

Abbreviations: AEs = adverse events; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; LV = left ventricular; NA = not applicable.

[a]All AEs occurring in > 10% of sunitinib or sorafenib groups and those with grade 3, 4, or 5; AEs and laboratory abnormalities were determined using the National Cancer Institute Common Terminology Criteria for Adverse Events.