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SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer

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Abstract

Background: Understanding how to sequence targeted therapies for metastatic renal cell carcinoma (mRCC) is important for maximisation of clinical benefit.
Objectives: To prospectively evaluate sequential use of the multikinase inhibitors sorafenib followed by sunitinib (So-Su) versus sunitinib followed by sorafenib (Su-So) in patients with mRCC.
Design, setting, and participants: The multicentre, randomised, open-label, phase 3 SWITCH study assessed So-Su versus Su-So in patients with mRCC without prior systemic therapy, and stratified by Memorial Sloan Kettering Cancer Center risk score (favourable or intermediate).
Intervention: Patients were randomised to sorafenib 400 mg twice daily followed, on progression or intolerable toxicity, by sunitinib 50 mg once daily (4 wk on, 2 wk off) (So-Su), or vice versa (Su-So).
Outcome measurements and statistical analysis: The primary endpoint was improvement in progression-free survival (PFS) with So-Su versus Su-So, assessed from randomisation to progression or death during second-line therapy. Secondary endpoints included overall survival (OS) and safety.

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Results and limitations: In total, 365 patients were randomised (So-Su, $n = 182$; Su-So, $n = 183$). There was no significant difference in total PFS between So-Su and Su-So (median 12.5 vs 14.9 mo; hazard ratio [HR] 1.01; 90% confidence interval [CI] 0.81–1.27; $p = 0.5$ for superiority). OS was similar for So-Su and Su-So (median 31.5 and 30.2 mo; HR 1.00, 90% CI 0.77–1.30; $p = 0.5$ for superiority). More So-Su patients than Su-So patients reached protocol-defined second-line therapy (57% vs 42%). Overall, adverse event rates were generally similar between the treatment arms. The most frequent any-grade treatment-emergent first-line adverse events were diarrhoea (54%) and hand-foot skin reaction (39%) for sorafenib; and diarrhoea (40%) and fatigue (40%) for sunitinib.
Conclusions: Total PFS was not superior with So-Su versus Su-So. These results demonstrate that sorafenib followed by sunitinib and vice versa provide similar clinical benefit in mRCC.
Patient summary: We investigated if total progression-free survival (PFS) is improved in patients with advanced/metastatic kidney cancer who are treated with sorafenib and then with sunitinib (So-Su), compared with sunitinib and then sorafenib (Su-So). We found that total PFS was not improved with So-Su compared with Su-So, but both treatment options were similarly effective in patients with advanced/metastatic kidney cancer.
Trial registration: ClinicalTrials.gov identifier NCT00732914, www.clinicaltrials.gov

1. Introduction

Treatment of metastatic renal cell carcinoma (mRCC) has greatly improved over the past decade with the introduction of targeted therapies acting on vascular endothelial growth factor receptor (VEGFR) or mammalian target of rapamycin (mTOR) [1]. However, as most patients experience disease progression during treatment with targeted therapy, sequential treatment with different agents has become standard practice [2,3]. Choosing the sequence of agents to optimise outcomes remains a key clinical challenge [3,4]. Sorafenib and sunitinib are multikinase inhibitors with overlapping but not identical kinase inhibition profiles. They target VEGFR 1–3, platelet-derived growth factor receptor, and c-Kit [5,6]; sorafenib also targets BRAF and RET [6]. Both are approved for the treatment of mRCC in first-line (sunitinib) and cytokine-unsuitable (sorafenib) settings; sorafenib has shown efficacy in multiple treatment lines [2,7–11].

In retrospective studies, sequential use of sorafenib and sunitinib in mRCC was well tolerated and provided additional clinical benefit beyond the use of either agent alone; these retrospective studies suggested that outcomes could be better with sorafenib followed by sunitinib (So-Su) compared with sunitinib followed by sorafenib (Su-So) [3,12–16]. The largest retrospective analysis at the time when the present study was designed ($n = 189$) revealed a numerically longer progression-free survival (PFS) for So-Su than for Su-So (17.2 vs 11.7 mo) [15,17]. SWITCH was the first prospective, randomised, phase 3 study to test the hypothesis that sequential therapy with So-Su is superior to Su-So in prolonging total PFS (defined as time from randomisation to confirmed progression or death during second-line therapy) in advanced/metastatic RCC.

2. Patients and methods

2.1. Study design and patients

SWITCH was a prospective, open-label, multicenter, randomised (1:1) phase 3 study (NCT00732914). Eligibility criteria included age 18–85 yr; advanced/metastatic RCC (all histologies); unsuitable for cytokine therapy (established by the investigator according to patient characteristics); no prior systemic therapy; Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1; one or more measurable lesions by computed tomography (CT) or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumours (RECIST 1.0); favourable or intermediate Memorial Sloan Kettering Cancer Center (MSKCC) risk score [18]; and adequate bone marrow, liver, and renal function. Exclusion criteria included unstable or severe cardiac disease; active, clinically serious infections; and symptomatic metastatic brain tumours. All patients gave written informed consent. The study complied with local legal and regulatory requirements and the Declaration of Helsinki/Good Clinical Practice guidelines.

Patients were randomised to sorafenib 400 mg twice daily followed by sunitinib 50 mg once daily (4 wk on, 2 wk off) (So-Su) or vice versa (Su-So). The treatment cycle length was 6 wk for both sorafenib and sunitinib. Dose modifications to manage adverse events (AEs) were permitted at the discretion of the investigator; the protocol included recommendations on when and how to implement dose reductions, interruptions, and permanent discontinuations. The sorafenib dose could be reduced to 400 mg once daily and then 400 mg every other day. The sunitinib dose could be reduced to 37.5 mg once daily and then 25 mg once daily. Randomisation was stratified by MSKCC score (favourable vs intermediate). Centralised randomisation via fax was coordinated by iOMEDICO AG (Germany). The randomisation list was generated by ICRC Weyer GmbH using an SAS program. The person who generated the randomisation list was not involved in the study project management, monitoring, or data management.

First-line treatment in both arms continued until disease progression according to RECIST or intolerable toxicity (after unsuccessful dose reduction/interruption). There was a treatment-free crossover period of 1–4 wk after first-line treatment to avoid additive toxicity. Patients who discontinued first-line treatment because of toxicity began second-line treatment only after nonhaematological toxicity had resolved to grade $\leq$1 and haematological toxicity to grade $\leq$2. Patients who refused further first-line treatment because of toxicity could begin second-line treatment if they consented and were in general compliance with the study protocol.

2.2. Study endpoints and assessments

Supplementary Table 1 summarises the key endpoints. The primary endpoint was total PFS (time from randomisation to confirmed progression or death during second-line therapy). First-line events

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were used for patients who did not switch to per-protocol second-line therapy. Patients without tumour progression or death were censored at their last date for tumour evaluation. Secondary endpoints included overall survival (OS; time from randomisation to time of death from any cause); first-line PFS (time from randomisation to confirmed progression or death during first-line therapy); second-line PFS (time from first day of second-line therapy to confirmed progression or death during second-line therapy); objective response rate (ORR; complete or partial responses) and disease control rate (DCR; complete or partial responses or stable disease for ≥8 wk) during first-line and second-line therapy; total time to progression (TTP; time from randomisation to confirmed progression during second-line therapy); and time to first-line treatment failure (time from randomisation to progression, death, or discontinuation due to toxicity). The tumour response was assessed according to RECIST by CT/MRI after every second cycle (ie, every 12 wk). Responses were confirmed by repeat CT/MRI at least 4 wk after being first recorded. Crossover from first-line to second-line treatment required a CT scan, which was the baseline scan for second-line treatment. Safety was assessed for each treatment line using National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 at 0, 3, 6, 9, and 12 wk, and then every 6 wk and at treatment end. Cardiotoxicity was assessed by monitoring left ventricular ejection fraction (LVEF) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. LVEF was determined by echocardiography at baseline, then every 12 wk, on the last day of first-line treatment, and treatment end. NT-proBNP was measured at baseline, on day 1 of each cycle, on the last day of first-line treatment, and at treatment end.

2.3. Statistical analysis

SWITCH was planned as a noninferiority study based on data available in 2008, with a planned sample size of 540 patients to observe 381 events. However, with the emergence of considerable retrospective data suggesting that So-Su might provide longer combined PFS and OS than Su-So (particularly the large retrospective study by Porta et al [15]), SWITCH was amended in June 2010 to a superiority design; 138 patients had already been randomised. The sample size for the superiority design was originally based on the following assumptions: overall PFS of 17.2 versus 11.7 mo for So-Su versus Su-So [17]; accrual period of 36 mo; total treatment duration of 54 mo; 231 events; and 10% of patients not evaluable for statistical analysis. A sample size of 346 would provide 90% power to show a 47% increase in total PFS. A protocol amendment in August 2013, after all planned patients had been randomised, reduced the power from 90% to 85%, and thus reduced the required sample size to 272 patients to show 194 events. This amendment was made because of a slower than expected rate of events.

Efficacy was assessed in the intention-to-treat (ITT) population, which included all randomised patients; for ORR and DCR, only patients who received at least one dose of study drug in the respective treatment line were included. Missing values were not imputed. For time-to-event analysis, missing values were censored. Details of event handling with respect to the primary endpoint are given in Supplementary Table 2. In particular, patients were censored if they received unauthorised cancer treatment (without progressive disease or other status counted as an event), which included patients who received off-protocol second-line therapy instead of per-protocol second-line therapy. It also included patients who ultimately received the correct sequence but not per protocol; for example, a patient who received second-line sorafenib >4 wk after stopping first-line sunitinib would be recorded as receiving off-protocol second-line therapy. Time-to-event endpoints were assessed using a one-sided log-rank test with a significance level of $\alpha = 0.05$. The log-rank test is symmetric: the calculated p values are the same whether the test is one- or two-sided, although the significance level for the two-sided test would be halved to 0.025. For PFS, OS, TTP, and time to first-line treatment failure, hazard ratios (HRs) and two-sided 90% confidence intervals (CIs) were derived from a Cox proportional hazard model. ORR and DCR were assessed using Fisher's exact test. Post hoc analysis assessed differences between treatment arms for total PFS, OS, and first-line PFS in subgroups for age (>65 vs ≤65 yr), sex, MSKCC score (favourable vs intermediate), and ECOG PS (0 vs 1). A further post hoc analysis evaluated updated OS, with a data cutoff of January 14, 2014, using 172 events. No corrections were made for multiple hypothesis testing. Safety was assessed in all patients receiving at least one dose of study treatment and was summarised using descriptive statistics.

3. Results

3.1. Patients

From February 2009 to December 2011, 365 patients were randomised (182 to So-Su; 183 to Su-So) at 72 centres in Germany, Austria, and the Netherlands (Fig. 1). Patient demographics and baseline characteristics were well balanced between the treatment groups (Table 1). Although the study protocol mandated that patients should not have received prior treatment and should be unsuitable for cytokines, seven patients had prior interferon-α and four patients had prior interleukin-2. These patients were included in the analyses under the intention-to-treat principle. At data cutoff for all analyses (August 15, 2013), the mean follow-up (from last treatment to end of follow-up) was 10.3 mo. Overall, 353 (97%) patients received first-line treatment and 179 (49%) patients received second-line treatment. More patients reached protocol-defined second-line therapy in the So-Su arm ($n = 103$, 57%) than in the Su-So arm ($n = 76$, 42%; $p < 0.01$; Fig. 1). When the 13 So-Su and 24 Su-So patients receiving documented, non–protocol-defined second-line therapy were included, the difference was no longer statistically significant ($n = 116$ [64%] vs $n = 100$ [55%]; $p = 0.09$). Of the 103 So-Su patients and 76 Su-So patients who received per-protocol first- and second-line therapy, 52 and 36 patients, respectively, went on to receive further treatment. Subsequent therapy for patients who discontinued the study after first-line therapy and for those who received both first- and second-line therapy is detailed in Supplementary Table 3, and typically included mTOR inhibitors (everolimus and temsirolimus) and VEGF(R) inhibitors (bevacizumab/interferon, pazopanib, sunitinib, sorafenib). Some patients received second-line sorafenib or sunitinib outside of the study protocol, mostly because of a treatment break longer than the protocol-specified 28 d.

In both groups, the most common reason for stopping first-line therapy was disease progression. The most frequent reasons for not initiating protocol-defined second-line treatment after stopping first-line treatment were death (So-Su $n = 16$ [8.8%]; Su-So $n = 19$ [10%]) and adverse events (So-Su $n = 8$ [4.4%]; Su-So $n = 17$ [9.3%]; Fig. 1). Demographic and baseline characteristics were generally similar between patients who received first-line therapy only and those who received both first- and second-line therapy, although patients not progressing to second-line therapy typically had a less favourable MSKCC score and ECOG PS and more previous treatment; in addition, fewer patients had

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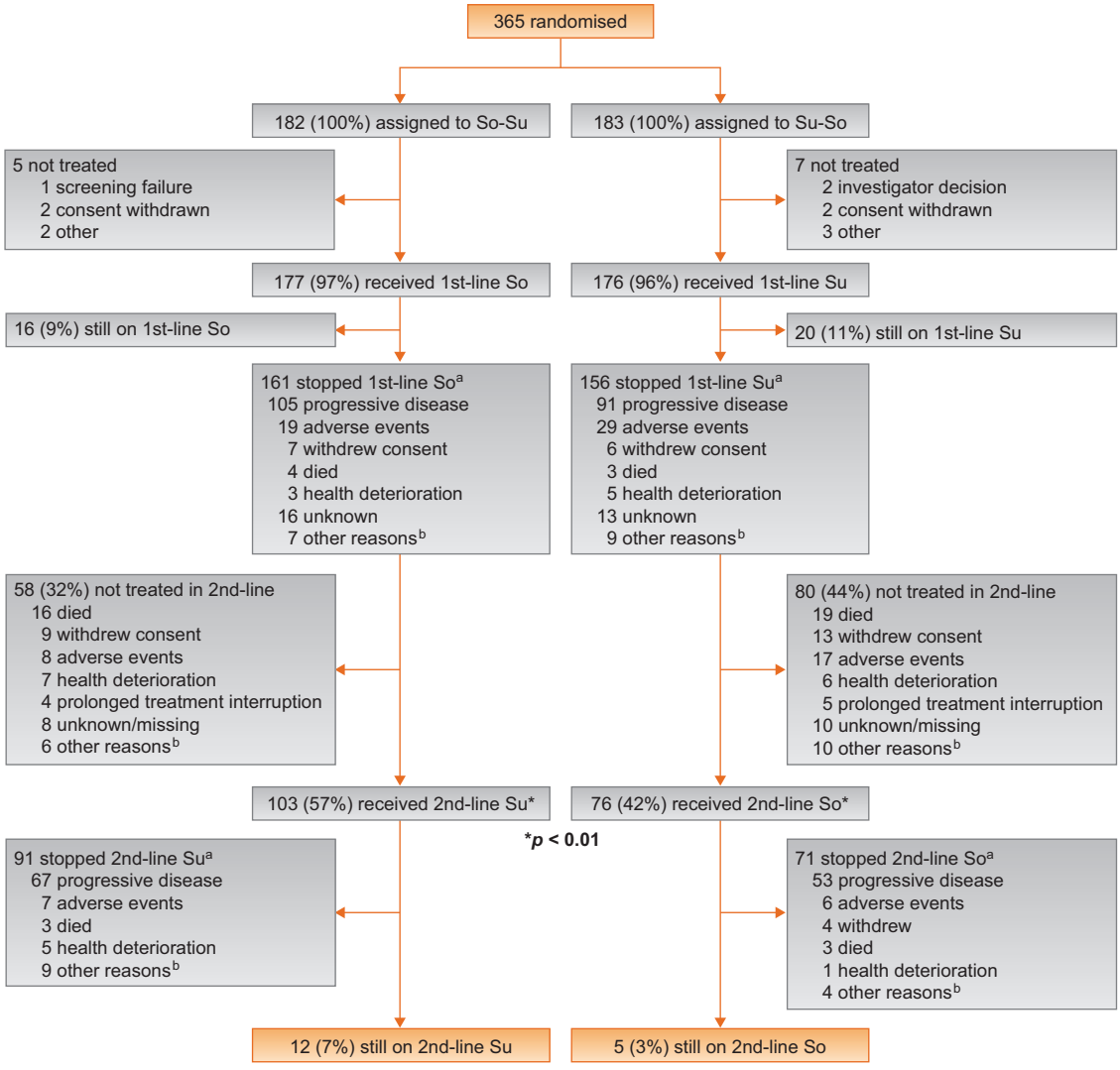

Fig. 1 – Patient disposition.
[a] Reasons for stopping treatment as reported by the investigator.
[b] Other reasons included investigator decision, lost to follow-up, and noncompliance.
So = sorafenib; Su = sunitinib.

undergone nephrectomy and more had non–clear-cell histology (Supplementary Table 4).

3.2. *Efficacy*

At data cutoff (August 15, 2013), the primary objective was not met: So-Su was not superior to Su-So in terms of PFS (median 12.5 vs 14.9 mo; HR 1.01, 90% CI 0.81–1.27; $p = 0.5$ for superiority; Fig. 2A). OS was similar in both arms (median 31.5 mo for So-Su and 30.2 mo for Su-So; HR 1.00, 90% CI 0.77–1.30; $p = 0.5$ for superiority; Fig. 2B). Median follow-up for patients without an OS event was 1.4 mo for So-Su and 3.0 mo for Su-So. Median first-line PFS was also similar between the two groups (5.9 mo for So-Su vs 8.5 mo for Su-So; HR 1.19, 90% CI 0.97–1.47; $p = 0.9$ for superiority; Fig. 3a). Median second-line PFS was longer for So-Su than for Su-So (5.4 vs 2.8 mo; HR 0.55, 90% CI 0.41–0.74; $p < 0.001$ for superiority; Fig. 3B). ORR and DCR were similar during first-line treatment with sorafenib and sunitinib. During second-line treatment, ORR and DCR were higher for sunitinib than for sorafenib ($p = 0.03$ for DCR; Table 2). Median time to first-line treatment failure (6.0 vs 9.0 mo; HR 1.15, 90% CI 0.93–1.42; $p = 0.9$ for superiority) and median total TTP (15.2 vs 17.2 mo; HR 1.01, 90% CI 0.79–1.30; $p = 0.5$ for superiority) were comparable between the So-Su and Su-So groups.

Updated survival analysis (data cutoff January 14, 2014) revealed median OS of 30.0 mo for So-Su and 27.4 mo for Su-So (HR 0.99, 90% CI 0.77–1.27; $p = 0.5$ for superiority; Supplementary Fig. 1) [19].

Efficacy findings in the per-protocol population were generally consistent with those in the ITT population (data not shown), except for the interim OS analysis (31.5 mo for So-Su vs 35.6 mo for Su-So; HR 1.06, 90% CI 0.80–1.42;

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Table 1 – Patient demographics and baseline characteristics (intention-to-treat population)

Variable	So-Su (*n* = 182)	Su-So (*n* = 183)	Total (*n* = 365)
Median age, yr (range)	64 (39–84)	65 (40–83)	65 (39–84)
Sex, *n* (%)			
Female	43 (24)	48 (26)	91 (25)
Male	139 (76)	135 (74)	274 (75)
Clear cell histology, *n* (%)	164 (90)	154 (84)	318 (87)
Nephrectomy (total or partial), *n* (%)	167 (92)	168 (92)	335 (92)
MSKCC risk score [a], *n* (%)			
High	1 (0.5)	1 (0.5)	2 (0.5)
Intermediate	108 (59)	94 (51)	202 (55)
Favourable	71 (39)	82 (45)	153 (42)
Unknown	2 (1.1)	4 (2.2)	6 (1.6)
Missing	0 (0)	2 (1.1)	2 (0.5)
ECOG PS, [b] *n* (%)			
0	116 (66)	106 (60)	222 (63)
1	55 (31)	66 (38)	121 (34)
2	0 (0)	1 (0.6)	1 (0.3)
Missing	6 (3.4)	3 (1.7)	9 (2.5)
Metastatic sites, [b] *n* (%)			
Lung	139 (79)	126 (72)	265 (75)
Lymph nodes	85 (48)	71 (40)	156 (44)
Liver	36 (20)	42 (24)	78 (22)
Bone	22 (12)	30 (17)	52 (15)
Brain	6 (3.4)	4 (2.3)	10 (2.8)
Number of metastatic sites, [b] *n* (%)			
1	38 (21)	51 (29)	89 (25)
2	68 (38)	59 (34)	127 (36)
3	51 (29)	36 (20)	87 (25)
≥4	19 (11)	28 (16)	47 (13)
Previous cancer therapies, [c] *n* (%)			
Interferon-α	2 (1.1)	5 (2.7)	7 (1.9)
Interleukin-2	1 (0.5)	3 (1.6)	4 (1.1)
Other	13 (7.1)	13 (7.1)	26 (7.1)
Radiotherapy	16 (8.8)	23 (13)	39 (11)
Total	26 (14)	31 (17)	57 (16)

ECOG PS = Eastern Cooperative Oncology Group performance status; MSKCC = Memorial Sloan Kettering Cancer Center; So = sorafenib; Su = sunitinib.
[a] Based on central assessment post-randomisation. Imbalance in MSKCC risk score distribution occurred because of incorrect site entries at randomisation.
[b] Presented for the safety population, So-Su *n* = 177, Su-So *n* = 176, total *n* = 353.
[c] Some patients received more than one previous cancer treatment. For two of the patients assigned to the Su-So group, the information was missing.

$p = 0.6$ for superiority). In the updated analysis, median OS in the per-protocol population (31.5 mo for So-Su vs 30.2 mo for Su-So; HR 1.06, 90% CI 0.81–1.40; $p = 0.6$ for superiority) was again consistent with that in the ITT population.

3.3. Safety

The safety population included 177 So-Su patients and 176 Su-So patients who received at least one dose of first-line study treatment. The safety results are summarised in Table 3. The mean duration of first-line therapy was not significantly different between sorafenib and sunitinib (log rank test $p = 0.1$). During second-line treatment, the mean duration of therapy was shorter for sorafenib (Su-So arm) than for sunitinib (So-Su arm; log rank test $p < 0.001$). The mean (± standard deviation) treatment break between first- and second-line therapy (excluding the regular 2-wk interval after sunitinib) was 21 ± 16 d for So-Su and 17 ± 14 d for Su-So ($p = 0.1$). The most common treatment-emergent AEs were diarrhoea, hand-foot skin reaction, hypertension, and fatigue for first-line sorafenib, and diarrhoea, fatigue, hypertension, and nausea for first-line sunitinib. Withdrawal because of AEs during first-line treatment was significantly more frequent in the Su-So arm (*n* = 52, 30%) than in the So-Su arm (*n* = 33, 19%; $p = 0.02$). Cardiac safety parameters (LVEF and NT-proBNP) were similar between the groups at all three assessment visits (Supplementary Table 5).

3.4. Post hoc subgroup analyses

Median total PFS and median first-line PFS were generally similar between the treatment arms across patient subgroups categorised according to age, sex, ECOG PS, and MSKCC score. Differences in median OS reached statistical significance in subgroups split according to age, with greater benefits observed for So-Su in patients aged >65 yr (HR 0.60, 95% CI 0.37–0.97) and for Su-So in patients aged ≤65 yr (HR 1.57, 95% CI 1.01–2.44). No other significant differences in OS were observed between subgroups (Fig. 4). In the updated OS analysis (cutoff January 14, 2014), the only significant difference between post hoc subgroups was that patients aged >65 yr experienced a greater benefit with So-Su than Su-So (median OS 31.5 vs 19.8 mo; $p = 0.04$; Supplementary Table 6) [19]. To explore possible reasons for the apparent improved OS in older patients who received So-Su compared with Su-So, the number of patients aged ≤65 or >65 yr who received each treatment line, the duration of treatment for each line, and the incidence of grade 3/4 AEs were determined (Supplementary Table 7). In patients aged >65 yr, the mean duration of first-line treatment was similar in each treatment arm (35.7 wk So-Su vs 39.8 wk Su-So, $p = 0.6$); the mean duration of second-line treatment was 36.0 wk with So-Su and 12.9 wk with Su-So ($p < 0.0001$). Rates of grade 3/4 AEs tended to be higher with sunitinib than with sorafenib in both the first and second lines of treatment (first line, Su-So 67% vs So-Su 55%, $p = 0.1$; second line, So-Su 55% vs Su-So 26%, $p = 0.02$).

4. Discussion

Initiated in 2008, SWITCH was the first prospective, randomised phase 3 study of sequential tyrosine kinase inhibitor (TKI) therapy (So-Su vs Su-So) for advanced/metastatic RCC. Both drugs provided overall clinical benefit, regardless of treatment sequence. The primary objective was not met: total PFS was not superior with So-Su versus Su-So (median 12.5 vs 14.9 mo; HR 1.01). OS was similar in both arms: median 31.5 and 30.2 months with So-Su and Su-So, respectively (HR 1.00). Likewise, total TTP was comparable between So-Su and Su-So (15.2 and 17.2 mo; HR 1.01). In both arms, total TTP was approximately 2.5 mo longer than total PFS. This may have

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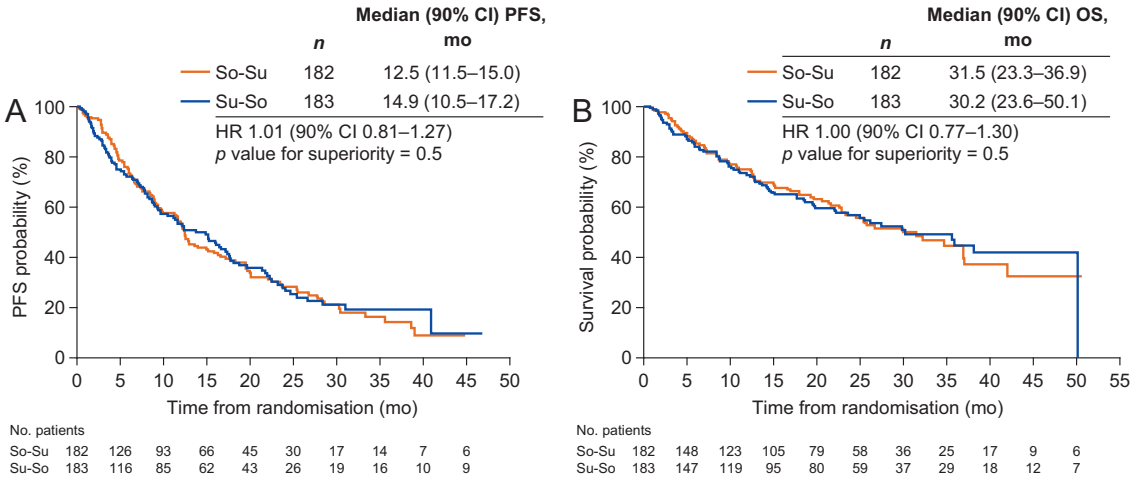

Fig. 2 – Kaplan-Meier plots of (A) total progression-free survival and (B) overall survival (intention-to-treat population).
CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; OS = overall survival; So = sorafenib; Su = sunitinib.

methodological reasons as, unlike PFS, calculation of TTP did not include deaths. Further prospective randomised studies investigating the optimal sequencing of targeted agents are ongoing, e.g. the SWITCH-II study (NCT01613846) assessing sorafenib and pazopanib in sequence [20].

First-line PFS for each agent in SWITCH (sorafenib 5.9 mo; sunitinib 8.5 mo) was within the previously reported range (4.4–11.6 mo for sorafenib and 5.1–13.1 mo for sunitinib) [10,15,16,21–23]. Second-line PFS with sorafenib following first-line sunitinib in the phase 3 INTORSECT and AXIS studies (3.9 and 3.4 mo, respectively) [8,11] was also consistent with that seen in SWITCH (2.8 mo). Both first- and second-line PFS in SWITCH were consistent with results from the largest retrospective study reported to date ($n = 2106$ across multiple centres) [24]. In that study, Alimohamed et al reported first-line PFS of 7.3 mo for sorafenib ($n = 412$) and 7.2 mo for sunitinib ($n = 1542$), and second-line PFS of 3.6 mo for sorafenib following sunitinib ($n = 257$), and 5.2 mo for sunitinib following sorafenib ($n = 152$) [24]. In SWITCH, second-line PFS for sunitinib following sorafenib was 5.4 mo. In their large retrospective study, Alimohamed et al concluded that the sequence in which targeted therapies are used does not substantially affect clinical outcome [24]. While our PFS findings confirm this observation, response rates appeared to differ for the treatment sequences. ORR (31% and 29%) and DCR (69% and 64%) were similar for first-line sorafenib and sunitinib, respectively. However, compared with patients receiving Su-So, those receiving So-Su had greater second-line ORR (17% vs 6.6%) and DCR (49% vs 32%). The clinical relevance of these observations remains unclear, particularly in the context of our PFS findings.

To the best of our knowledge, no other phase 3 studies of sequential TKI therapy in RCC have been reported. Findings of a phase 2 study (RECORD-3) investigating sequential everolimus followed by sunitinib (Ev-Su) compared with

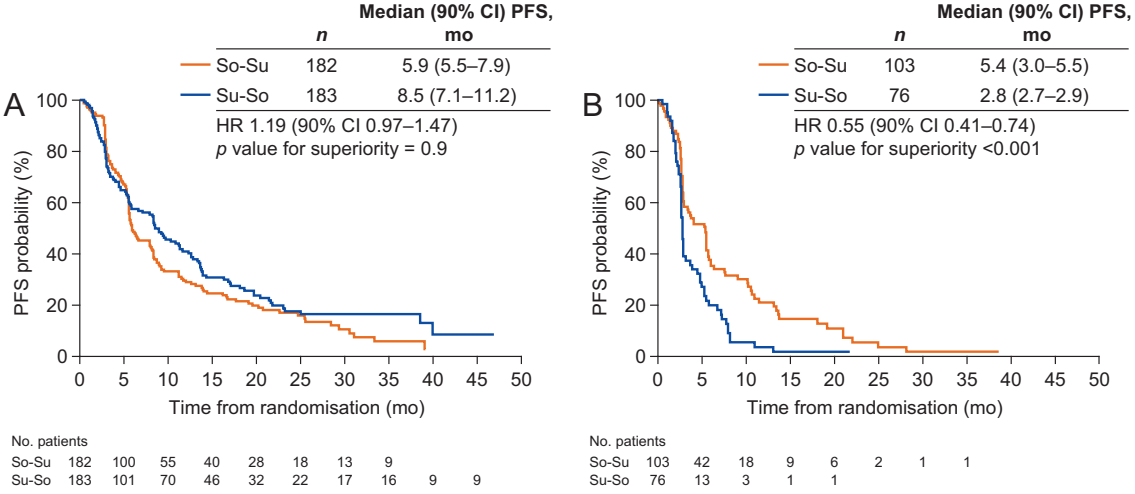

Fig. 3 – Kaplan-Meier plots of (A) first-line progression-free survival and (B) second-line progression-free survival (intention-to-treat population).
CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; So = sorafenib; Su = sunitinib.

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Table 2 – Best overall tumour response and disease control rate (modified intention-to-treat population) [a]

Tumour response, *n* (%)	First-line therapy			Second-line therapy		
	So-Su (*n* = 177)	Su-So (*n* = 176)	*p* value	So-Su (*n* = 103)	Su-So (*n* = 76)	*p* value
Complete response	5 (2.8)	6 (3.4)		1 (1.0)	1 (1.3)	
Partial response	50 (28)	45 (26)		17 (17)	4 (5.3)	
Stable disease	68 (38)	61 (35)		32 (31)	19 (25)	
Objective response rate [b]	55 (31)	51 (29)		18 (17)	5 (6.6)	
Disease control rate [c]	123 (69)	112 (64)	0.7	50 (49)	24 (32)	0.03

So = sorafenib; Su = sunitinib.
[a] Included only patients who received at least one dose of study drug in the respective treatment line. Response evaluation was based on investigator assessment.
[b] Objective response rate = complete response + partial response.
[c] Disease control rate = complete response + partial response + stable disease ≥8 wk.

sunitinib followed by everolimus (Su-Ev) were recently published [25]. Median total PFS was 21.1 mo for Ev-Su and 25.8 mo for Su-Ev (HR 1.3, 95% CI 0.9–1.7) and OS was 22.4 mo for Ev-Su and 32.0 mo for Su-Ev (HR 1.2, 95% CI 0.9–1.6). Notably, 207 patients (44%) overall in RECORD-3 received per-protocol second-line treatment, similar to the proportion of patients who received second-line treatment in our study (179 patients, 49%).

One key challenge in managing mRCC is that only approximately half of patients proceed from first-line to second-line treatment. In the present study, more patients reached second-line therapy on protocol in the So-Su compared with the Su-So arm (57% vs 42%; $p < 0.01$). This is consistent with data from other studies suggesting that patients receiving sorafenib early in the treatment sequence are more likely to receive subsequent therapies than those receiving first-line sunitinib (34–38% for sorafenib vs 16–18% for sunitinib) [26,27]. The reasons for this difference are not clear. Notably, patients in our study who did not progress to second-line therapy happened to have more advanced disease (less favourable MSKCC score and ECOG PS; more prior treatment) or poorer prognosis (fewer patients had undergone nephrectomy; more with non–clear-cell histologies) than those who did progress to second-line therapy. Furthermore, differences in the first-line AE profiles may impact patients' willingness or ability

Table 3 – Safety overview

	So-Su				Su-So			
	First-line So (*n* = 177)		Second-line Su (*n* = 103)		First-line Su (*n* = 176)		Second-line So (*n* = 76)	
Mean therapy duration, wk (SD)	37.5 (37.4) [a,b]		28.2 (29.6) [c]		43.9 (44.3) [b]		16.0 (15.2) [c,d]	
Dose reductions, *n* (%)	65 (37)		24 (23)		65 (37)		35 (46)	
Dose interruptions, *n* (%)	81 (46)		30 (29)		71 (40)		26 (34)	
Any TEAE, *n* (%)	172 (97)		90 (87)		172 (98)		64 (84)	
Grade 3/4 TEAE, *n* (%)	117 (66)		53 (51)		118 (67)		27 (36)	
AEs leading to withdrawal, *n* (%)	33 (19) [e]		20 (19)		52 (30) [e]		15 (20)	
Any serious AE, *n* (%)	88 (50)		43 (42)		81 (46)		19 (25)	
AEs related to deaths, *n* (%)	12 (6.7)		1 (1.0)		16 (9.1)		2 (2.6)	
Most frequent TEAEs [f], *n* (%)	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Diarrhoea	96 (54)	9 (5.1)	16 (16)	2 (1.9)	70 (40)	5 (2.8)	26 (34)	3 (3.9)
Hand-foot skin reaction	69 (39)	21 (12)	14 (14)	5 (4.9)	38 (22)	10 (5.7)	16 (21)	5 (6.6)
Hypertension	57 (32)	16 (9.0)	11 (11)	3 (2.9)	58 (33)	21 (12)	6 (7.9)	2 (2.6)
Fatigue	56 (32)	8 (4.5)	24 (23)	3 (2.9)	70 (40)	13 (7.4)	9 (12)	0
Alopecia	55 (31)	–	2 (1.9)	–	10 (5.7)	–	4 (5.3)	–
Rash	48 (27)	3 (1.7)	8 (7.8)	0	10 (5.7)	0	12 (16)	1 (1.3)
Nausea	39 (22)	2 (1.1)	17 (17)	1 (1.0)	53 (30)	3 (1.7)	6 (7.9)	1 (1.3)
Loss of appetite	37 (21)	2 (1.1)	16 (16)	2 (1.9)	30 (17)	4 (2.3)	12 (16)	0
Pain	33 (19)	6 (3.4)	11 (11)	4 (3.9)	25 (14)	4 (2.3)	4 (5.3)	0
Stomatitis	15 (8.5)	0	9 (8.7)	0	37 (21)	8 (4.5)	5 (6.6)	0
Thrombocytopenia	2 (1.1)	1 (0.6)	1 (1.0)	0	11 (6.3)	9 (5.1)	0	0

SD = standard deviation; So = sorafenib; Su = sunitinib; TEAE = treatment-emergent adverse event.
[a] *n* = 176.
[b] *p* = 0.1.
[c] $p < 0.001$.
[d] *n* = 74.
[e] *p* = 0.02.
[f] Any-grade AE in >20% of patients in either arm, or grade 3/4 AEs in >3% of patients in either arm.

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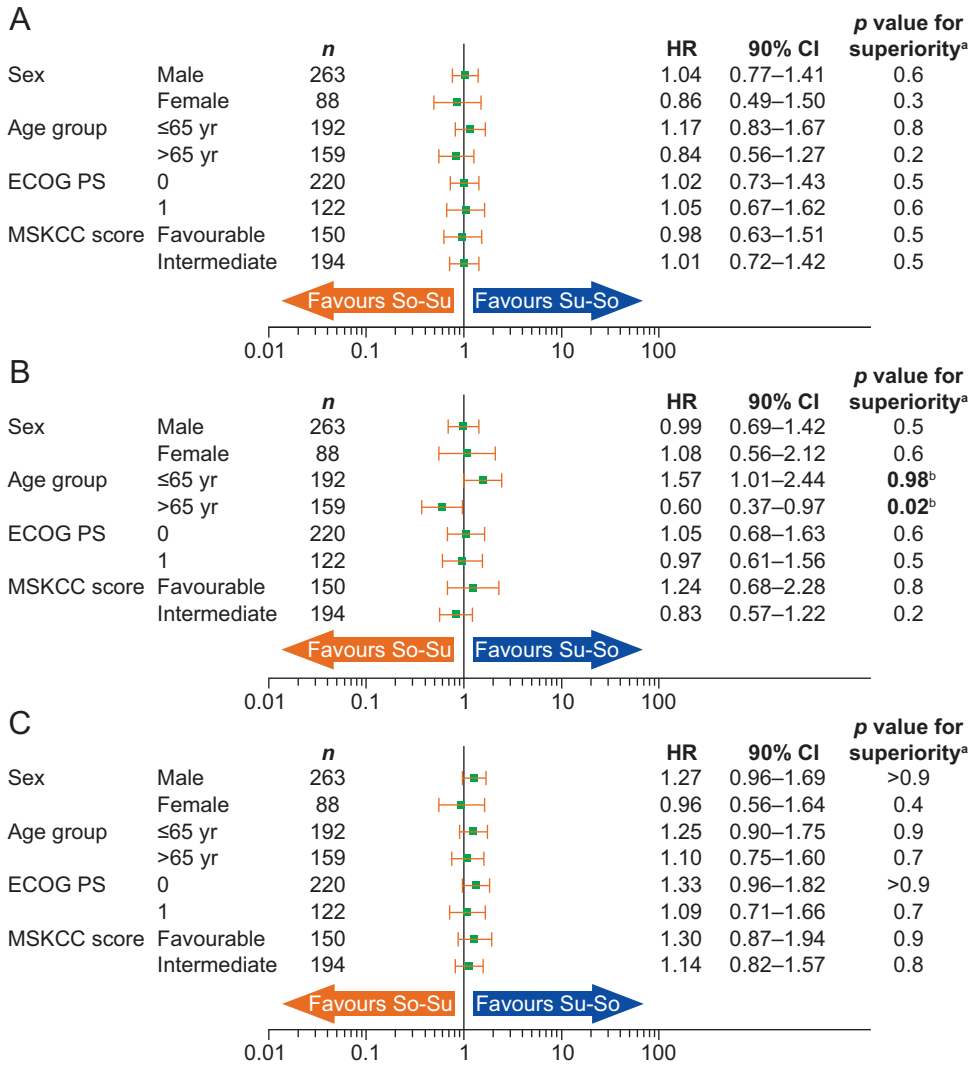

Fig. 4 – Forest plots of (A) total progression-free survival; (B) overall survival, and (C) first-line progression-free survival by subgroups (intention-to-treat population).
[a] *p* values are for superiority of So-Su over Su-So. Significant differences for So-Su over Su-So or Su-So over Su-So are highlighted in bold.
[b] In patients aged ≤65 yr, the *p* value for superiority of So-Su over Su-So was 0.98. When the superiority test is reversed, this gives a significant value of *p* = 0.02 for superiority of Su-So over So-Su. In patients aged >65 yr, *p* = 0.02 for superiority of So-Su over Su-So.
CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; MSKCC = Memorial Sloan Kettering Cancer Center; So = sorafenib; Su = sunitinib.

to continue to second-line treatment, as has been shown elsewhere [28,29]. The most common reasons cited by investigators for not continuing to second-line treatment in SWITCH in the So-Su versus Su-So arms, respectively, were death (16% vs 19%), AEs (8% versus 17%), and withdrawn consent (9% vs 13%).

Safety profiles differed between sorafenib and sunitinib, but were generally as expected and consistent with previous reports for these agents in patients with mRCC [30,31]. AEs were generally less frequent during second-line than first-line therapy. Although the precise reasons are not known, this observation is consistent with previous data showing that AEs tend to occur early in the course of TKI therapy [32,33], and suggests possible cross-tolerance and adaptation to TKI treatment. Prospective assessment of cardiac safety (LVEF and NT-proBNP values) was included in the protocol following previous reports of cardiotoxicity and reduced LVEF, particularly with sunitinib [30,34–38]. For example, a meta-analysis found a higher risk of all-grade and high-grade congestive heart failure, mainly defined as declines in LVEF, in sunitinib-treated compared with placebo-treated renal and nonrenal cancer patients [38]. In addition to monitoring and managing hypertension, which may be associated with cardiac events in patients receiving TKIs [35,37], NT-proBNP represents a more convenient and potentially more reliable early marker of cardiac damage than LVEF [39,40]. Results for LVEF and NT-proBNP monitoring in SWITCH indicated that neither sorafenib nor sunitinib significantly affected cardiac safety. This is consistent with findings from an ongoing phase 3,

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randomised, placebo-controlled study of adjuvant sorafenib or sunitinib in patients with resected, nonmetastatic RCC at high risk of recurrence (NCT00326898). In that study, LVEF declines were negligible, occurring in only 2.3%, 1.8%, and 1.0% of patients receiving sunitinib, sorafenib, and placebo, respectively [41].

Subgroup analyses for age, sex, risk of recurrence, and baseline performance status (ECOG PS 0 vs 1) revealed no differences between So-Su and Su-So in terms of total PFS, OS, or first-line PFS apart from statistically significant differences in OS according to age, with the results favouring So-Su in patients aged >65 yr (Fig. 4B and Supplementary Table 6) [19]. The reasons for this difference are unclear. The study design did not include patient stratification according to age, and our observations should be considered as hypothesis-generating only. Nonetheless, it is interesting that sorafenib appeared to be somewhat better tolerated than sunitinib in elderly patients in our study. Indeed, age was included in our subgroup analyses as previous analyses suggested that sorafenib is effective and well tolerated particularly in elderly patients [33,42–44].

The study has a number of limitations to be considered when interpreting the results. The study was open-label rather than double-blind, introducing a potential for investigator bias; however, the protocol mandated that confirmed radiologic progression was required to stop treatment on the grounds of disease progression, which reduced this potential for bias. The findings for second-line PFS may not be robust because there were low numbers of patients/events; fewer patients received on-study second-line treatment with sunitinib compared with sorafenib; and only selected subsets of patients were able to receive second-line treatment. The results for second-line therapy should therefore be interpreted with caution. OS could have been confounded by subsequent treatments received after patients completed per-protocol therapy. Limited prospective sequential data were available at the time at which the study was designed, so it was not possible to estimate the impact that an imbalance in discontinuation could have on the study findings, particularly in terms of total PFS and second-line PFS. The different safety profiles of sorafenib and sunitinib may have contributed to differences in first-line therapy discontinuation, and thus affected first-line PFS and total PFS. In sequential studies, the decision to end first-line treatment can potentially be influenced by investigator knowledge that a second-line treatment is readily available. In SWITCH, however, confirmed radiologic progression was required to proceed to second-line treatment.

5. Conclusions

SWITCH is the first prospective, randomised, phase 3 study of sequential TKI therapy (So-Su vs Su-So) for advanced/metastatic RCC; 49% of patients received per-protocol second-line therapy. The primary endpoint of total PFS was not met, but the results did confirm the clinical benefit of sequential treatment, with median OS of approximately 30 mo. Further prospective randomised studies investigating the optimal sequencing of targeted agents are ongoing.

Author contributions: Christian Eichelberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Michel, Eichelberg, de Santis, Goebell.
Acquisition of data: Bos, de Santis, Eichelberg, Fischer von Weikersthal, Flörcken, Freier, Goebell, Lerchenmüller, Los, Michel, Pahernik, Schenck, Schirrmacher-Memmel, Staehler, van Arkel, Vervenne, Zimmermann.
Analysis and interpretation of data: Michel, Eichelberg, Gottstein, Hauswald, Indorf.
Drafting of the manuscript: Michel, Staehler, Eichelberg, de Santis, Goebell.
Critical revision of the manuscript for important intellectual content: Eichelberg, Vervenne, De Santis, Fischer von Weikersthal, Goebell, Lerchenmüller, Zimmermann, Bos, Freier, Schirrmacher-Memmel, Staehler, Pahernik, Los, Schenck, Flörcken, van Arkel, Hauswald, Indorf, Gottstein, Michel.
Statistical analysis: Gottstein.
Obtaining funding: Michel.
Administrative, technical, or material support: Indorf, Hauswald, Michel.
Supervision: Michel.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2015.04.017.

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