European Journal of Cancer 107 (2019) 37–45

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

SWITCH II: Phase III randomized, sequential, open-label study to evaluate the efficacy and safety of sorafenib-pazopanib versus pazopanib-sorafenib in the treatment of advanced or metastatic renal cell carcinoma (AUO AN 33/11)

Margitta Retz [a,q,*], Jens Bedke [b], Martin Bögemann [c], Marc-Oliver Grimm [d], Uwe Zimmermann [e], Lothar Müller [f], Christian Leiber [g], Dogu Teber [h], Manfred Wirth [i], Christian Bolenz [j], Robbert van Alphen [k], Maria De Santis [l], Aart Beeker [m], Jan Lehmann [n,q], Martin Indorf [o], Melanie Frank [o], Carsten Bokemeyer [p], Jürgen E. Gschwend [a,q]

[a] *Dept. of Urology, Rechts der Isar Medical Center, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany*
[b] *Dept. of Urology, Eberhard Karls University Tübingen, Hoppe-Seyler-Str.3, 72076 Tübingen, Germany*
[c] *Dept. of Urology, Universitätsklinikum Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany*
[d] *Dept. of Urology, Universitätsklinikum Jena, Lessingstr. 1, 07743 Jena, Germany*
[e] *Dept. of Urology, Universitätsmedizin Greifswald, Ferdinand-Sauerbruch-Str., 17475 Greifswald, Germany*
[f] *Medical Oncology, Onkologie Leer–Emden–Papenburg, Annenestr. 11, 26789 Leer, Germany*
[g] *Dept. of Urology, Universitätsklinikum Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany*
[h] *Dept. of Urology, Universitätsklinikum Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany*
[i] *Dept. of Urology, Universitätsklinikum Dresden, Fetscherstr. 74, 01307 Dresden, Germany*
[j] *Dept. of Urology, Universitätsklinikum Ulm, Albert-Einstein-Allee 23, 89081 Ulm, Germany*
[k] *Dept. of Oncology, Elisabeth Tweesteden Ziekenhuis, Dr. Deelenlaan 5, 5042 AD Tilburg, Netherlands*
[l] *Dept. of Oncology, Kaiser-Franz-Josef-Spital and Department of Urology, Medical University of Vienna, Kundratstr. 3, 1100 Vienna, Austria*
[m] *Dept. of Oncology, Spaarne Ziekenhuis, Spaarnepoort 1, 2134 TM Hoofddorp, Netherlands*
[n] *Dept. of Urology, Städtisches Krankenhaus Kiel, Chemnitzstr. 33, 24116 Kiel, Germany*
[o] *IOMEDICO AG, Hanferstr. 28, 79108 Freiburg, Germany*

* *Corresponding author*: Dept. of Urology, Rechts der Isar Medical Center, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany.

E-mail addresses: margitta.retz@tum.de (M. Retz), jens.bedke@med.uni-tuebingen.de (J. Bedke), martin.boegemann@ukmuenster.de (M. Bögemann), marc-oliver.grimm@med.uni-jena.de (M.-O. Grimm), ziuro@uni-greifswald.de (U. Zimmermann), lothar.mueller@onkologie-leer.de (L. Müller), christian.leiber@uniklinik-freiburg.de (C. Leiber), dogu.teber@med.uni-heidelberg.de (D. Teber), manfred.wirth@uniklinikum-dresden.de (M. Wirth), christian.bolenz@uniklinik-ulm.de (C. Bolenz), r.vanalphen@etz.nl (R. van Alphen), maria@desantis.cc (M. De Santis), abeeker@spaarneziekenhuis.nl (A. Beeker), jan.lehmann@krankenhaus-kiel.de (J. Lehmann), martin.indorf@iomedico.com (M. Indorf), Melif@gmx.de (M. Frank), c.bokemeyer@uke.de (C. Bokemeyer), juergen.gschwend@tum.de (J.E. Gschwend).

https://doi.org/10.1016/j.ejca.2018.11.001

[p] Center for Oncology, II. Medical Clinic and Polyclinic, Universitätsklinikum Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany
[q] AUO Study Group, Germany

Received 17 June 2018; received in revised form 31 October 2018; accepted 5 November 2018
Available online 7 December 2018

KEYWORDS
Renal cell carcinoma (RCC);
Sequential therapy;
Sorafenib;
Pazopanib;
Tyrosine-kinase inhibitor

Abstract ***Purpose:*** This trial compared the sequential therapy with the multikinase inhibitor sorafenib (So) followed by pazopanib (Pa) or vice versa in advanced/metastatic renal cell carcinoma (mRCC) patients.
Methods: This multicenter, randomized phase 3 study assessed the sequential use of So-Pa versus Pa-So in patients with mRCC without prior systemic therapy. Pts were randomized to So 2 × 400 mg/day followed by Pa 1 × 800 mg/day in case of progression or intolerable toxicity or vice versa. Primary endpoint was total PFS (tPFS), defined as time from randomization to progression, or death during second-line therapy. Key secondary endpoints included overall survival (OS), first-line PFS, disease control rate (DCR) and safety.
Results: A total of 377 pts were randomized (So-Pa, n = 189; Pa-So, n = 188). Recruitment of a total 544 pts was calculated, but actual accrual rate turned out to be lower than expected. The primary endpoint median tPFS was 8.6 mo (95% CI 7.7–10.2) for So-Pa and 12.9 mo (95% CI 10.8–15.2) for Pa-So with a hazard ratio (HR) of 1.36 (upper limit of one-sided 95% CI 1.68), which exceeded a predefined HR <1.225 as a one-sided 95% confidence interval. Non-inferiority of So-Pa regarding tPFS was not met. Secondary endpoints displayed marked statistical differences in favor of Pa-So in first-line PFS and DCR but not for OS and 2nd-line PFS. Side effect profiles were consistent with known toxicities of the respective multikinase-inhibitor including diarrhea, fatigue, hand-foot skin reaction and hypertension.
Conclusions: Non-inferiority of the primary endpoint tPFS could not be demonstrated for So-Pa. The results for first-line PFS and DCR favored the Pa-So sequence.
Trial registration: NCT01613846, www.clinicaltrials.gov.

1. Introduction

Apart from the introduction of immune checkpoint inhibitors, a significant number of new targeted therapies vectored against the vascular endothelial growth factor receptor (VEGFR) have become available for the treatment of advanced or metastatic renal cell carcinoma (mRCC) over recent years [1–4]. A great deal of discussion regarding the optimal sequencing of available therapeutic options in individual patients led to several comparative studies [5–7]. The recent SWITCH study prospectively evaluated sequential use of the multikinase inhibitors sorafenib followed by sunitinib versus sunitinib followed by sorafenib in patients with mRCC [5].

Pazopanib is a selective multi-targeted receptor tyrosine-kinase inhibitor (TKI), approved for the first-line (1L) treatment of mRCC patients [8,9]. Efficacy and safety of pazopanib have been investigated versus the comparator sunitinib [10], describing both multikinase inhibitors as being comparable, but results from a patient preferences study favored pazopanib over sunitinib [11]. However, the optimal sequence of pazopanib (Pa) with other targeted agents such as sorafenib (So) has not been explored so far. Based on the design of the first SWITCH trial [5], the aim of this SWITCH II study is to investigate the hypothesis of non-inferiority regarding total progression free survival (tPFS) of the sequence So followed by Pa (So-Pa) versus Pa-So in mRCC patients. We hypothesized equivalent outcomes of both sequential treatment arms, defined as time from randomization to progression or death during second-line (2L) therapy [6,12].

2. Material and methods

2.1. Study design and patients

SWITCH II was designed in first-line palliative therapy of mRCC as a sequential, randomized (1:1), open-label, multicenter phase III study (NCT01613846, www.clinicaltrials.gov). Eligibility criteria included advanced/metastatic RCC (all histologies), age 18–85 years, unsuitable for cytokine therapy, Karnofsky Index ≥ 70%, Memorial Sloan Kettering Cancer

Center (MSKCC) risk score (based on 2004 definition) low or intermediate, at least one uni-dimensional measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as well as adequate bone marrow and organ function [13,14]. Exclusion criteria included unstable or severe cardiac dysfunction, clinically serious infectious disease, and uncontrolled brain metastases. All patients gave written informed consent. The study complied with legal, regulatory, ethical and Good Clinical Practice requirements including the Declaration of Helsinki.

Patients were randomized to sorafenib 400 mg twice daily until progression or intolerable toxicity followed by pazopanib 800 mg once daily (So-Pa) and vice versa pazopanib followed by sorafenib (Pa-So). After first-line therapy a treatment free period of 7–28 days was planned to avoid overlapping or additive toxicities. Before starting second-line therapy, re-staging imaging, including CT/MRT, defined the baseline status for evaluation of the second-line (2L) regimen. Treatment with study medication could be interrupted for up to four weeks for drug associated toxicity, or dose reductions with a maximum of two stepwise reductions were allowed as considered appropriate by the investigator. For patients in whom toxicity warranted the switch to the other medication, cross over should be held until improvement of side effects to a justifiable grade.

Randomization was stratified by low versus intermediate MSKCC risk score, as well as clear cell versus non-clear cell histology [13].

2.2. Study endpoints and study assessments

Primary objective of this study was the evaluation of tPFS (defined as the time from randomization to first-line treatment until progression or death during second-line treatment) with sorafenib followed by pazopanib and vice versa. Parameters of secondary interest were first-line PFS (time from randomization 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), overall survival (OS; time from randomization to time of death from any cause), objective response rate (ORR; complete and partial response), disease control rate (DCR; complete and partial response or stable disease), time to treatment failure (time between randomization and treatment stop due to disease progression, death or toxicity) and total-time-to-progression TTP (defined as time from randomization to progression during second-line therapy), safety and tolerability according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 [15] as well as quality of life by FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue measurement system) [16] and FKSI-10 (Functional Assessment of Cancer Therapy (FACT)- Kidney Symptom Index) [17]. All time-to-event analyses were based on the Kaplan–Meier method.

2.3. Statistical analysis

The SWITCH II study was planned to demonstrate a non-inferior hazard ratio for tPFS of sorafenib followed by pazopanib as compared to tPFS of the treatment sequence pazopanib followed by sorafenib. Efficacy analysis was to be performed on all randomized patients (intent-to-treat, ITT). A Cox's proportional hazard model stratified according to factors used for randomization was applied for tPFS analysis. The hazard ratio between the two treatment sequences was assessed with a one-sided upper 95% CI. According to prespecified calculations the upper limit of the CI needed to be ≤ 1.225 to demonstrate non-inferior efficacy in tPFS between the two treatment schemes. A sample size of 383 observed tPFS events would demonstrate an 80% power for non-inferiority and a one-sided type 1 error of 5%. Recruitment of a total 544 patients was calculated under prespecified assumptions. However, the actual accrual rate turned out to be lower than expected and the goal for the number of events required for the primary endpoint according to the protocol could not be reached in time. Therefore, the sponsor decided to stop the study prematurely by September 30th, 2016 after screening 416 and randomizing 377 patients. Statistical analyses for secondary endpoints are descriptive.

3. Results

3.1. Patients

A total of 416 patients were screened, and 377 mRCC patients were randomized according to MSKCC prognostic group and histology at 67 study centers in Germany, Austria and the Netherlands (Fig. 1). Date of first patient randomization was June 14th, 2012 and end of the clinical part of study occurred on November 14th, 2016.

Baseline characteristics of the ITT population of SWITCH II study are displayed in Table 1, demonstrating similar and well-balanced demographical and disease specific characteristics.

3.2. Efficacy

The primary endpoint non-inferiority of tPFS for the sequence So-Pa versus Pa-So was not met. The median tPFS was 8.6 months (mo) [95% CI 7.7–10.2] for So-Pa and 12.9 mo for Pa-So [95% CI 10.8–15.2], HR 1.36 [95% CI 1.11–1.68], one-sided planned 95% CI upper limit was 1.225 (Fig. 2A).

The results for median tPFS from the primary ITT population in total and according to predefined

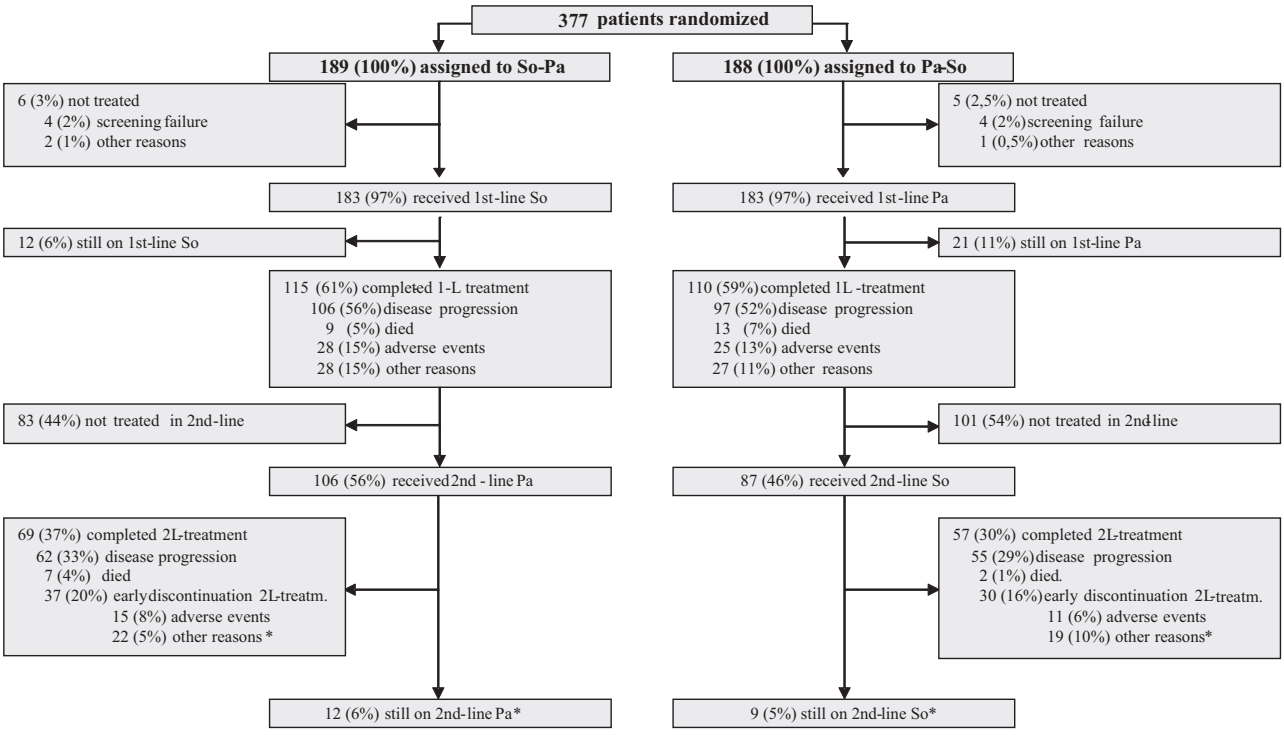

Fig. 1. Patient disposition. *patients still on 2L-treatment were counted as early discontinuation of 2L-treatment when study was closed on the request of the sponsor.

Table 1
Intent-to-treat population (ITT), baseline patient and disease characteristics at start of first-line treatment or initial diagnosis.[a]

Parameter	So-Pa n = 189	Pa-So n = 188
Age, years range		
median	68 (31–84)	68 (26–86)
Gender, n, (%)		
female	53 (28)	51 (27)
male	136 (72)	137 (73)
Histology, n, (%)		
clear-cell	168 (89)	160 (85)
Karnofsky Index, n, (%)		
100	96 (51)	85 (45)
90	32 (17)	46 (25)
80	52 (27)	44 (23)
70	9 (5)	12 (6)
missing	0	1 (1)
MSKCC risk score, n, (%)		
low	95 (50)	91 (48)
intermediate	90 (48)	89 (47)
high	4 (2)	5 (3)
missing/unknown	0	3 (2)
Metastatic sites n,[b] (%)		
lung	130 (69)	139 (74)
bone	38 (20)	37 (20)
liver	32 (17)	37 (20)
Nephrectomy n, (%)		
total	167 (88)	161 (86)
partial	19 (10)	24 (13)

So = sorafenib, Pa = pazopanib.
[a] At time of first diagnosis.
[b] Multiple sites possible.

stratification factors and further subgroup analyses are displayed in Table 2. Numerically, patients under 65 years of age, patients with a low MSKCC and a high Karnofsky index, as well as patients with non-clear cell histology showed a considerably longer mPFS, when sequential treatment started with pazopanib than vice versa.

As a secondary endpoint the median overall survival of the ITT population lasted about half a year longer for patients receiving the sequence Pa-So with 28.0 mo, [95% CI 22.6–34.1] compared to 22.7 mo [95% CI 17.4–28.6] in the So-Pa arm (HR 1.22, 95%CI: 0.91–1.65) (Fig. 2B).

Median PFS of first-line therapy with sorafenib was 5.6 months [CI 4.7–6.3] versus 9.3 months [CI 7.4–10.6] under treatment with pazopanib. Both treatment arms showed a shorter second-line mPFS compared to first-line mPFS, respectively. In second-line treatment, patients receiving pazopanib reached a median PFS of 2.9 months [95% CI 2.0–3.7] compared to a median PFS with sorafenib of 2.1 months [95% CI 1.8–3.5] (Fig. 3A and B).

Time to first-line treatment failure in the ITT population was 5.5 mo [95% CI 3.9–5.8] for the So-Pa sequence and 7.8 mo [95% CI 5.8–9.6] for Pa-So. The median total-time-to-progression was also considerably longer with Pa-So (12.9 mo [95% CI 10.7–15.3]) compared to So-Pa (8.5 mo [95% CI 7.4–10.2]).

Results for overall response rate (ORR) and disease control rate (DCR) in first- and second-line treatments

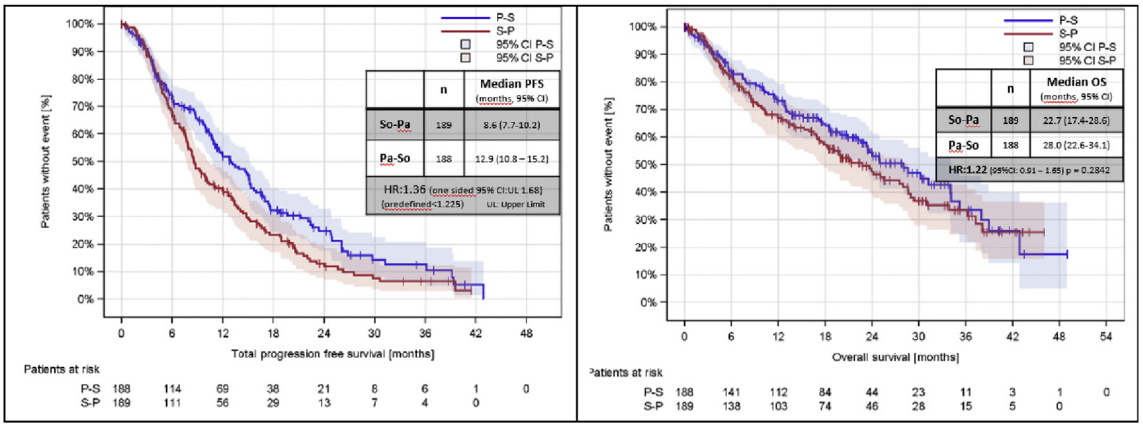

Fig. 2. a and b: Intent-to-treat population (ITT), total progression-free survival and overall survival according to treatment sequence.

Table 2
Median total mPFS of sequential therapy So-Pa vs. Pa-So for ITT and according to stratification factors and further subgroups.

Patient group	n	So-Pa tPFS median mo [95% CI]	n	Pa-So tPFS median mo [95% CI]
ITT	189	8.6 [7.7–10.2]	188	12.9 [10.8–15.2]
MKSCC score				
low	95	8.8 [7.6–12.6]	91	17.0 [15.1–24.9]
intermediate	90	8.2 [5.4–10.0]	89	9.7 [6.0–11.9]
Histology				
clear cell	164	8.7 [7.8–11.0]	158	12.8 [10.8–15.2]
non-clear cell	25	6.9 [3.5–12.0]	30	14.8 [6.2–31.2]
Age-group				
≤65 years	73	9.2 [6.8–13.4]	76	14.8 [10.8–15.9]
over 65 years	116	8.5 [7.7–10.2]	112	11.6 [9.9–16.7]
Karnofsky index				
90/100	128	9.5 [7.7–12.7]	131	15.3 [12.9–17.5]
70/80	61	7.9 [4.4–9.2]	56	7.4 [4.5–10.7]
mITT	92	9.5 [8.3–12.0]	72	13.4 [10.9–15.7]
PP	121	7.4 [6.0–8.5]	119	11.6 [9.9–14.9]

ITT = intent-to-treat population, MKSCC = Memorial Sloan-Kettering Cancer Center, mITT = modified ITT, PP = Per Protocol Population, So = sorafenib, Pa = pazopanib.

are displayed in Table 3. First-line and second-line outcomes favor the treatment with pazopanib.

All efficacy endpoints (i.e. tPFS, TTP, OS) assessing the whole treatment sequences were observed in favor of the Pa-So sequence, whereas all secondary efficacy endpoints were found in favor of pazopanib (i.e. 1L-PFS, 2L-PFS, TTF, ORR, DCR) when treatment lines were assessed separately.

3.3. Safety

Safety and tolerability of the two treatment sequences were assessed for all patients, having received at least one dose of study drug (n = 183 patients in each treatment arm). Adverse event summaries describe numbers or percentages of patients with a certain AE.

First-line median treatment duration for sorafenib was 3.9 months (range 0.0–42.2) and for pazopanib 3.6 months (range 0.1–37.1) in second-line, whereas first-line pazopanib was applied over a median of 5.7 months (range 0.3–43.3) and sorafenib over 2.1 months (range 0.3–21.4) in second-line treatment. There were slightly

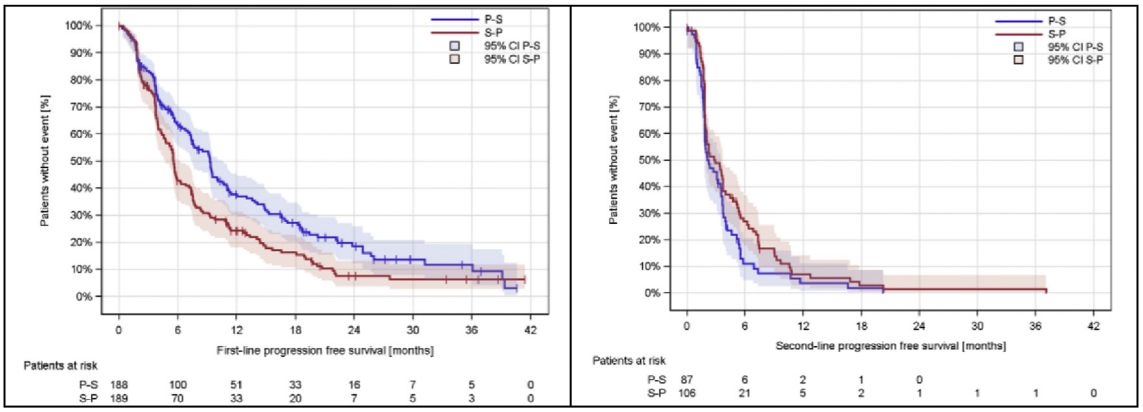

Fig. 3. a and b: Intent-to-treat population (ITT), Progression-free survival during first-line therapy and second-line therapy according to respective sequential administration.

fewer dose modifications on sorafenib than on pazopanib in both treatment lines.

Most frequently occurring TEAEs in patients irrespective of seriousness or severity clustered per system organ class terms were gastrointestinal disorders 80.3% (So) and 79.8% (Pa) during first-line treatment and 55.7% (Pa) and 57.5% (So) during second-line treatment. Gastrointestinal disorders were also the most frequent grade 3/4 TEAEs occurring under first- and second-line therapy with So-Pa 14.2% first-line and 9.4% second-line and the most frequent reported related TEAEs in both treatment sequences (So-Pa 72.7%, Pa-So 72.1%). The second most frequently related TEAEs were skin disorders with 69% (So) and 44% (Pa) during first-line and 20% (Pa) and 61% (So) during second-line treatment medications. A comparison of TEAEs of both first-line therapies is displayed in Table 4. With diarrhea and fatigue being widely comparable between the TKIs, hypertension and nausea were more frequent with pazopanib, and palmar-plantar erythrodysaesthesia syndrome (PPES) and alopecia with sorafenib, respectively. Percental incidences of respective TEAEs in second-line treatment were generally lower. Two patients each died due to related TEAE in first- and second-line in the So-Pa arm and 5 patients in the Pa-So arm under first-line treatment. These nine fatal TEAEs included hepatic-failure, diarrhea, gastrointestinal perforation, acute abdomen, multiorgan dysfunction, cerebral infarction, pulmonary embolism and cardiac failure.

Table 3
Overall response rate (ORR), complete and partial response (CR, PR), stable disease (SD), progressive disease (PD) and disease control rate (DCR) in first- and second-line treatment for ITT based on best response assessments, percentages of second-line treatment refer to number of patients who started second-line treatment.

Parameter n (%)	So-Pa 1L (n = 189) 2L (n = 106)	95% CI	Pa-So 1L (n = 188) 2L (n = 87)	95% CI
ORR 1L	54 (28.6)	22.1–35.0	87 (46.3)	39.1–53.4
CR	5 (2.6)	0.4–4.9	5 (2.7)	0.4–5.0
PR	49 (25.9)	19.7–32.2	82 (43.6)	36.5–50.7
SD	74 (39.2)	32.2–46.1	59 (31.4)	24.7–38.0
DCR 1L	128 (67.7)	61.1–74.4	146 (77.7)	71.7–83.6
PD	33 (17.5)	12.0–22.9	21 (11.2)	6.7–15.7
not reported/ evaluable	28 (14.8)	9.8–19.9	21 (11.2)	6.7–15.7
ORR 2L	21 (19.8)	12.2–27.4	8 (9.2)	3.1–15.3
CR	1 (0.9)	0.0–2.8	1 (1.1)	0.0–3.4
PR	20 (18.9)	11.4–26.3	7 (8.0)	2.3–13.8
SD	39 (36.8)	27.6–46.0	30 (34.5)	24.5–44.5
DCR 2L	60 (56.6)	47.2–66.0	38 (43.7)	33.3–54.1
PD	31 (29.2)	20.6–37.9	38 (43.7)	33.3–54.1
not reported/ evaluable	15 (14.1)	7.5–20.8	11 (12.6)	5.7–19.6

So = sorafenib, Pa = pazopanib, ORR = overall response rate, DCR = disease control rate.
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, 1L = first-line, 2L = second-line.
ORR: defined as complete plus partial response.
DCR: defined as complete plus partial response plus stable disease.

3.4. Quality of life

Quality of life measures as secondary endpoint were evaluated at baseline and at the start of every treatment cycle with higher scores revealing a better patient's QoL-perception. A change of 4 points in either direction for FKSI and 3 points for FACIT-F, respectively, indicated a clinically relevant change. In principle, no significant difference was reported between the two TKIs, however QoL-perception in general was better for second line treatments. Results are displayed in (appendix Table A1).

4. Discussion

SWITCH II was initiated following the first SWITCH study published by Eichelberg *et al.* [5] which compared the sequential use of sorafenib followed by sunitinib versus sunitinib followed by sorafenib. The first endpoint in that study was non-inferiority for total PFS. At one point this first SWITCH study was amended for a superiority endpoint following retrospective data by *Porta et al.* [18]. However, the superiority design failed to reach statistical significance. As a result, total progression free survival (tPFS) and overall survival (OS) were similar for both treatment sequences, and adverse event profiles of both treatment schedules were also comparable, suggesting an equal benefit from both schemes.

Therefore, the statistical hypothesis of SWITCH II was aimed at demonstrating non-inferiority for the two sequences So-Pa and Pa-So as well [6,12]. Although addressing a clinically relevant aspect in mRCC treatment, patient recruitment into this actual study was challenging and did not reach the intended patient number in a timely manner. This can in part be explained by the introduction of immunotherapy in mRCC clinical research and thus many ongoing competing trials using PD1-/PD-L1-checkpoint inhibitors e.g. nivolumab [19], pembrolizumab [20] or atezolizumab [21] for second- and lately also first-line treatment [22,23]. In this study 56% (So-Pa) and 46% (Pa-So) received second-line treatment which is comparable to the former SWITCH trial of 57% in the So-Su arm and 42% in the Su-So arm. The most common reasons in both trials for not continuing to second-line treatment were death, AEs, and withdrawn consent.

The rate of patients not receiving sequential second-line therapy within the trial were 44% (n = 83) in the So-Pa arm and 54% (n = 101) in the Pa-So arm. In the So-Pa arm 15/189 pts (8%) received second-line therapy outside the trial as well as 23/188 pts (12%) in the Pa-So arm (appendix Table A3&A4).

Table 4
Safety overview, therapy duration, therapy modifications and treatment-emergent-adverse-events (including most frequently reported) for the two different treatment sequences, for all patients who received allocated study intervention.

	So-Pa				Pa-So			
	sorafenib 1L n = 183		pazopanib 2L n = 106		pazopanib 1L n = 183		sorafenib 2L n = 87	
Median treatment duration, months, range	3.9 (0.0–42.2)		3.6 (0.1–37.1)		5.7 (0.3–43.3)		2.1 (0.3–21.4)	
dose reduction, n (%)	64 (35)		34 (32)		80 (44)		33 (38)	
dose interruptions, n (%)	35 (19)		25 (23)		28 (15)		16 (18)	
any TEAE, n (%)	179 (98)		96 (91)		182 (99.5)		81 (93)	
grade 3 or 4 TEAE, n (%)	108 (59)		47 (44)		117 (64)		47 (54)	
any serious TEAE, n (%)	96 (52.5)		51 (48)		97 (53)		32 (37)	
any TEAE leading to treatment stop, n (%)	61 (33)		22 (21)		44 (24)		18 (21)	
related fatal TEAE, n (%)	2 (1)		2 (2)		5 (3)			
most frequent TEAE (patients)	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
diarrhea, n (%)	102 (56)	11 (6)	29 (27)	4 (4)	109 (60)	6 (3)	26 (30)	3 (3)
fatigue, n (%)	68 (37)	3 (2)	16 (15)	2 (2)	82 (45)	3 (2)	9 (10)	1 (1)
palmar-plantar erythro-dysesthesia syndrome, n (%)	64 (35)	10 (6)	4 (4)	1 (1)	30 (16)	1 (1)	20 (23)	5 (6)
hypertension, n (%)	49 (27)	17 (9)	15 (14)	5 (5)	82 (45)	40 (22)	10 (12)	4 (5)
alopecia, n (%)	46 (25)	1 (1)[a]	5 (5)	–	11 (6)	–	9 (10)	–
nausea, n (%)	45 (25)	5 (3)	27 (26)	1 (1)	66 (36)	1 (1)	4 (5)	–
decreased appetite, n (%)	36 (20)	3 (2)	7 (7)	–	44 (24)	1 (1)	6 (7)	2 (2)
stomatitis, n (%)	32 (18)	1 (1)	2 (2)	–	20 (11)	1 (1)	6 (7)	–
weight decreased, n (%)	31 (17)	3 (2)	4 (4)	1 (1)	15 (8)	1 (1)	5 (6)	4 (5)
pruritus, n (%)	30 (16)	2 (1)	–	–	9 (5)	–	11 (13)	–
rash, n (%)	30 (16)	2 (1)	6 (6)	1 (1)	14 (8)	1 (1)	19 (22)	3 (3)

TEAE = treatment-emergent-adverse-events, 1L = first-line treatment, 2L = second-line treatment, n = number of patients, So = sorafenib, Pa = pazopanib.
[a] Symptom was reported under preferred term "skin-other" – therefore documentation > grade 2 was possible.

Non-inferiority of the primary endpoint tPFS could not be demonstrated for So-Pa compared to Pa-So. Pazopanib in first-line treatment followed by sorafenib in second-line resulted in longer median tPFS, first-line PFS, median total-time-to-progression and overall survival for the ITT and all pre-specified subgroups. Only patients with a Karnofsky index of 70/80 at entry had a slightly shorter median tPFS when receiving Pa-So (Table 2). Overall, Pa in second-line treatment showed a longer second-line mPFS, however there were some subgroups that differed. The analysis of best response in first-line treatment favored the Pa-So sequence. The second-line treatment results were better for the sequence starting with sorafenib followed by pazopanib.

Comparing safety results of the two treatment sequences no critical differences were reported. Safety profiles were as expected and previously published [5,8]. Acknowledging the fact that simple cross trial comparisons are not valid, as each trial has slightly different trial designs and the two drugs pazopanib and sunitinib show slightly different toxicity profiles, our SWITCH II compared with the first SWITCH study (5) showed no relevant differences concerning safety, in terms of frequency of TEAEs, including serious or fatal TEAEs. Results from quality of life assessments from this study could not identify an explicit patient reported difference between the two treatment sequences in SWITCH II.

The current study was based on the hypothesis of a comparability of both treatment arms and for this reason the study was designed with a non-inferiority approach. The SWITCH II study - even though it did not reach statistical significance - suggests pazopanib to be more effective in first-line treatment as compared to sorafenib. Assumptions of a different outcome of results in case of complete patient recruitment do not seem to be justified as presented outcomes appear statistically robust and would not change fundamentally with additional data. Overall, from a statistical perspective with a prespecified hypothesis and boundaries, the present study does not answer the question of an optimal TKI sequence, nor did the first SWITCH study.

When comparing results from the current trial to the former SWITCH study total median PFS seems lower in the So-Pa arm compared to the So-Su arm (8.6 vs 12.5 months). Although the first-line median PFS of So in both trials was comparable (5.6 months in SWITCH2 vs 5.9 months in SWITCH), the second-line median PFS of Pa in the presented trial seemed markedly lower than for Su in the former SWITCH trial (2.9 vs 5.4 months). Whether Sunitinib is a more potent second-line drug than pazopanib when given after sorafenib remains hypothetical.

Meanwhile, immune checkpoint inhibitors have altered the treatment paradigms for mRCC patients. Based on the outcomes of Checkmate025 [4,19], nivolumab has become a new standard of care for 2L mRCC, furthermore first evidence of significant benefit of immunotherapy with nivolumab and ipilimumab in

the first line setting was recently presented [22]. Therefore, actual considerations and studies regarding treatment optimization focus on promising combinations like bevacizumab plus atezolizumab [7,23,24] or pembrolizumab and lenvatinib [25]. Rapidness of newly evolving therapeutic options and standards hardly allow for studies on treatment sequencing, as design and concept easily become obsolete during the conduct of a study. However, diligent studies incorporating effective sequencing of available therapeutic alternatives like switching from a targeted therapy to an immune checkpoint inhibitor (ICI) or vice versa (NivoSwitch) are crucial as they will offer new general and personalized options for the treatment of mRCC [26].

5. Conclusions

SWITCH II is the second prospective, randomized, phase III study of sequential TKI therapy (So-Pa vs Pa-So) for advanced/metastatic RCC. The primary endpoint of non-inferiority of tPFS for the treatment sequence So-Pa was not met. Treatment sequence starting with pazopanib in first-line resulted in longer median PFS of first-line therapy and a longer median tPFS. Median OS was 28.0 months for Pa-So and 22.7 months for So-Pa. Meanwhile, multiple prospective randomized studies investigating the optimal combination and sequence of ICI and TKI compounds are underway to expand and improve the treatment options for mRCC.

Acknowledgments

We thank all the patients, caregivers, and investigators who participated in this study; the principal investigators are listed in Supplementary Appendix A. We also thank Dorothee Schneider, S&P GmbH, who provided medical writing support. We acknowledge Heidrun Rexer from MeckEvidence, Schwarz as well as Dunja Klein from iOMEDICO AG, Freiburg as trial coordinator and medical manager.

The results were presented in part at scientific congresses as follows: oral presentation at the 43rd European Society for Medical Oncology meeting, Madrid, Spain, September 9, 2017 (abstract 8450).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.11.001.

Funding/support and role of sponsor

The SWITCH II trial was sponsored by the Technical University of Munich, Germany with financial grants from Bayer HealthCare GmbH and Novartis GmbH. Bayer HealthCare GmbH and Novartis GmbH were not involved in the trial concept and design. The Association for Urologic Oncology (AUO) of the German Cancer Society supported this study (AN 33/11) as well as the main Association of Austrian Social Security Institutions. The specific role of the sponsors was in the design and conduct of the study.

Conflict of interest statement

It is certified that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following:

Margitta Retz: Consultancies & honoraria: Astellas, Bayer Health Care, Bristol-Myers Squibb, AstraZeneca, Ipsen, Janssen Cilag, MSD, Novartis, Pfizer, Roche, Sanofi Aventis

Janssen-Cilag, MSD, Pfizer and Roche; Jens Bedke: Consultancies and honoraria: Bayer, BMS, Eisai, Ipsen, MSD, Novartis, Pfizer, Roche; Grants: Novartis.

Martin Bögemann: Advisory role for Bayer, Novartis, Bristol-Myers Squibb, Roche; Honoraria from Beyer, Novartis, Bristol-Myers Squibb, Roche.

Marc-Oliver Grimm: Honoraria from Bayer Health Care, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Pfizer, Roche; grants from BMS and Novartis.

Uwe Zimmermann: No conflicts of interest.

Lothar Müller: No conflicts of interest.

Christian Leiber: No conflicts of interest.

Dogu Teber: No conflicts of interest.

Manfred Wirth: No conflicts of interest.

Christian Bolenz: Consultant, membership in an advisory board or travel grants for Janssen-Cilag, Bayer, Astellas and Roche.

Robbert van Alphen: No conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Maria De Santis: Study Grants: Pierre Fabre Oncologie; Consultation Fees: Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., ESSA, Ferring, GSK, Ipsen, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthon, Takeda, Teva/OncoGenex.

Aart Beeker: No conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Jan Lehmann: No conflicts of interest, including specific financial interests and relationships and

affiliations relevant to the subject matter or materials discussed in the manuscript.

Martin Indorf: No conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Melanie Frank: No conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Carsten Bokemeyer: Consultancies & Honoraria by Bayer, Novartis, Roche, Merck Serono, Lilly, Sanofi, Bristol-Myers Squibb, Astra-Zeneca, Hexal.

Jürgen E. Gschwend: Consultancies & Honoraria by Astellas, Amgen, Bayer, Janssen, Novartis, Roche.

References

[1] Bedke J, Stühler V, Stenzl A, et al. Immunotherapy for kidney cancer: status quo and the future. Curr Opin Urol 2018;28:8–14.

[2] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms, Langversion 1.2. 2017. AWMF Registernummer: 043/017OL, http://leitlinienprogramm-onkologie.de/Nierenzellkarzinom.85.0.html.

[3] Ljungberg B, Albiges L, Bensalah K, et al. Guidelines on renal cell carcinoma. Arnhem, The Netherlands: European Association of Urology (EAU); 2016.

[4] Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2016;27(Suppl 5):v58–68.

[5] Eichelberg C, Vervenne WL, de Santis M, et al. 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. Eur Urol 2015;68:837–47.

[6] Gschwend JE, Beeker A, De Santis M, et al. Phase III randomized sequential open-label study to evaluate the efficacy and safety of sorafenib followed by pazopanib versus pazopanib followed by sorafenib in the treatment of advanced/metastatic renal cell carcinoma (SWITCH-2 study). J Clin Oncol 2013;31(Suppl 15):TPS4591.

[7] Powles T, McDermott DF, Rini B, et al. IMmotion150: novel radiological endpoints and updated data from a randomized phase II trial investigating atezolizumab with or without bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC). Ann Oncol 2017;28(Suppl 5):v605–49.

[8] Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061–8.

[9] Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013;49:1287–96.

[10] Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722–31.

[11] Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol 2014;32:1412–8.

[12] Retz M, Bedke J, Herrmann E, et al. Phase III randomized sequential, open-label study to evaluate the efficacy and safety of sorafenib followed by pazopanib versus pazopanib followed by sorafenib in the treatment of advanced/metastatic renal cell carcinoma. Ann Oncol 2017;28(Suppl 5):v295–329.

[13] Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004;22:454–63.

[14] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

[15] Common terminology criteria for adverse events (CTCAE) version 4.0 published: May 28, 2009 (v4.03: June 14, 2010) U.S. Department of health and human services, National Institutes of Health, National Cancer Institute Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

[16] Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation Health. Qual Life Outcomes 2003;1:79.

[17] Cella D, Yount S, Du H, et al. Development and validation of the functional assessment of cancer therapy kidney symptom index (FKSI). J Support Oncol 2006;4:191–9.

[18] Porta C, Procopio P, Cartenì G, et al. Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma: an Italian multicenter retrospective analysis of 189 patient cases. BJU Int 2011;108:E250–7.

[19] Motzer RJ, Escudier B, McDermitt DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.

[20] Lee CH, Makker V, Rasco D, et al. A Phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with renal cell carcinoma. NCT02501096. ESMO 2017. Ann Oncol 2017;28(Suppl 5):v295–329.

[21] McDermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: long-term safety, clinical activity, and immune correlates from a phase Ia study. J Clin Oncol 2016;34:833–42.

[22] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.

[23] Motzer RJ, Powles T, Atkins MB, et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC). J Clin Oncol 2018;36(Suppl 6S). abstr 578.

[24] Atkins MB, McDermott DF, Powles T, et al. IMmotion150: a phase II trial in untreated metastatic renal cell carcinoma patients of atezolizumab and bevacizumab vs and following atezolizumab or sunitinib. J Clin Oncol 2017;35(Suppl 15). abstr 4505.

[25] NCT0 2811861: a multicenter, open-label, randomized, phase 3 trial to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma.

[26] NCT02959554 study in which therapy is either switched to nivolumab after 3 months of treatment or therapy is continued with a tyrosine kinase inhibitor in patients with metastatic renal cell carcinoma (RCC) and disease control, Grünwald, Hannover.