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 -

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1. Title page

Study Title	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 -
Study Title German	Phase III randomisierte sequentielle offene Studie zur Untersuchung der Wirksamkeit und Sicherheit von Sorafenib gefolgt von Pazopanib im Vergleich mit Pazopanib gefolgt von Sorafenib zur Behandlung von fortgeschrittenem /metastasierendem Nierenzellkarzinom
Short Title	SWITCH-2
Sponsor ID:	16037
EudraCT No	2011-004396-36
Name of test drug/product	Sorafenib + pazopanib
Comparator	Pazopanib + sorafenib
Dosage	Sorafenib 400 mg (per os twice daily, until progression or intolerable toxicity) followed by pazopanib 800 mg (per os, once daily, until progression or intolerable toxicity), Pazopanib 800 mg (per os, once daily, until progression or intolerable toxicity) followed by sorafenib 400 mg (per os twice daily, until progression or intolerable toxicity)
Indication	First-line followed by second-line therapy in advanced or metastatic renal cell cancer
Design	Sequential, randomized open-label (1:1), prospective, multicenter, two-arms
Development phase	Phase III
Sponsor	Technical University Munich, Germany
Coordinating investigator	Prof. Dr. Jürgen Gschwend, Munich, Germany
Author of report	Dr. Sigrun Niemitz, iOMEDICO
Study initiation date	14/June/2012
Study completion date	14/November/2016
Version and date of report	Final 1.0 dated 20-October-2017

This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

2. Synopsis

Name of Sponsor/Company: Technical University Munich, Germany	Volume:1 Page:	(For National Authority Use Only)
Name of Finished Product: Sorafenib (Nexavar®)		
Name of Active Ingredient: Sorafenib		

Title of study:

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 -

Coordinating investigator:

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Study center(s):

Eighty-five study centers in 3 countries (in Germany n=68, Netherlands n=11, and Austria n=6) participated in this study. Out of those 52 sites in Germany, 9 sites in the Netherlands and 6 sites in Austria randomized patients.

Publication (reference):

Studied period (years): 2012 to 2016	**Phase of development**: III

Objectives:

Primary objective:

- To evaluate if progression-free survival (PFS) from randomization to progression or death during second-line therapy (total PFS) of sorafenib followed by pazopanib is non-inferior compared to pazopanib followed by sorafenib.

Secondary objectives:

- Time from randomization to progression during second-line therapy (total TTP)
- Time to first-line treatment failure (progression, death, discontinuation due to toxicity) descriptively in each arm
- PFS in first-line and second-line treatment, descriptively
- Overall survival (OS), descriptively (data cut off same as for primary endpoint)
- Disease control rate (DCR); Response rates in first-line and in second-line (complete response [CR], partial response [PR], stable disease [SD] according to response evaluation criteria in solid tumors [RECIST] criteria)
- Health-related Quality of Life (QoL) (FACIT-F, FKSI-10)
- Safety and tolerability

Explorative:

- Biomarker programme
- C-reactive protein (CRP) as prognostic marker

Methodology:
This study was a sequential, randomized, open-label (1:1), multicenter phase III study starting in first-line of metastatic / advanced renal cell carcinoma (RCC) using in the experimental arm sorafenib until progression followed by pazopanib and in the control arm pazopanib until progression followed by sorafenib. Sorafenib-patients switched to pazopanib and vice versa, with a treatment-free period of at least seven and up to a maximum of 28 days after first-line treatment, in order to avoid additive toxicity.

Number of patients:	**planned**: 544 **screened**: 416	**randomized**: 377 318 in Germany 45 in the Netherlands 14 in Austria **completed**: 299	**analyzed efficacy**: 377 **analyzed safety**: 366

Diagnosis and main criteria for inclusion:

1. Patients with metastatic / advanced RCC (all histologies), who were not suitable for cytokine therapy and for whom study medication constitutes first-line treatment. For cytokine-unsuitability at least one of the following criteria had to be fulfilled:
   - Age 66 to 88 years
   - Non-clear cell histology RCC
   - Intermediate risk according to MemorialSloan Kettering Cancer Center (MSKCC) score
   - Eastern Cooperative Oncology Group (ECOG) ≥1 **and** >1 organ metastasis **+** <24 months between diagnosis and establishing indication for interleukin-2 therapy
   - ECOG ≥1 **and** “unable to carry on normal activity or do active work” (Karnofsky Index 70%)
   - Creatinine ≥1x upper limit of normal (ULN) and <2x ULN
   - Total bilirubin ≥1x ULN and <2x ULN
   - Present autoimmune disease
   - Patients who required steroids
   - Hypersensitivity against cytokines
   - Severe organic disease, not interfering with other in-/exclusion criteria of the Switch-2 study
   - Non-symptomatic brain metastases
   - Severe lung disease (e.g. pulmonyra hypertension [PAH], chronic obstructive pulmonary disease [COPD]) with pulmonary artery (PA) O_2 <60 mmHg on rest
2. Age ≥18 and ≤85 years
3. Karnofsky Index ≥70%
4. MSKCC prognostic score (2004), low or intermediate
5. Life expectancy of at least 12 weeks
6. Subjects with at least one uni-dimensional (for RECIST 1.1) measurable lesion. Lesions were measured by computer tomography (CT) / magnet resonance imaging (MRI) scan
7. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to start of therapy
   - Hemoglobin >9 g/dL
   - Absolute neutrophil count (ANC) >1,500/µL
   - Platelet count ≥100,000/µL
   - Total bilirubin <1.5x ULN (Note: Subjects with Gilbert’s Syndrome were eligible if their total bilirubin was <3.0x ULN and direct bilirubin was ≤35%)
   - Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) <2.5x (ULN) (Note: concomitant elevations in bilirubin and ASAT / ALAT above 1x ULN were not permitted)

- Alkaline phosphatase <4x ULN
- Prothrombin (PT)-International Normalized Ratio (INR) / activated prothrombin time (aPTT) <1.2x ULN (Patients who were therapeutically anticoagulated with an agent such as Coumadin or heparin were allowed to participate provided that their INR was stable and within the recommended range for the desired level of anticoagulation and no prior evidence of underlying abnormality in these parameters existed)
- Serum creatinine <2x ULN

8. Written informed consent

Test product, dose and mode of administration:
Sorafenib 400 mg per os, twice daily, until progression or intolerable toxicity, followed by pazopanib 800 mg once daily orally until progression or intolerable toxicity.

Duration of treatment:
Approximately 17 months

Reference therapy, dose and mode of administration:
Pazopanib 800 mg per os, once daily until progression or intolerable toxicity followed by sorafenib 400 mg bid orally until progression or intolerable toxicity.

Criteria for evaluation:

Efficacy:

Primary endpoint:

Progression Free Survival

The primary endpoint of the study was measured by total PFS, defined as time from randomization until progression or death (whichever occurred first) during second-line therapy. If second-line was not reached, first-line progression or death served as event. Patients without tumor progression or death at the time of analysis were censored at their last date of tumor evaluation in the first-line or second-line period, respectively.

Secondary endpoints:

- Total time to progression defined as time from randomization to progression during second-line therapy (total TTP). Patients without tumor progression at the time of analysis will be censored at their last date of tumor evaluation.
- PFS in first-line and second-line treatment, defined as time from randomization or start of therapy (first or second-line respectively) to first progression or death after start of treatment line (whatever occurs first). Patients without tumor progression or death at the time of analysis will be censored at their last date of tumor evaluation in the first-line or second-line period, respectively.
- OS defined as time from randomization to death. Patients alive at the end of the study will be censored with the last observation
- Time to first-line treatment failure is defined as time from randomization to treatment failure in each arm. Reasons for end of therapy that count for an event (treatment failure) are adverse event, death, patient non-compliance, investigator's decision, progression of disease and use of illicit drugs. Patients with all other reasons will be censored at the end date of first-line treatment.
- Disease control rate (DCR); Response rates in first-line and second-line (Complete response [CR], partial response [PR], stable disease [SD] according to RECIST 1.1 criteria)

Safety and tolerability:

- Adverse events (AEs) characterized by type, frequency, severity (according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria v4.03) and any laboratory abnormalities
- Laboratory parameters and urinalysis
- Vital signs

- Electrocardiogram (ECG)
- Karnofsky Performance Score (KPS)
- Concomitant Medication

Quality of life assessment

- Health related quality of life was assessed by the two measurement systems Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-10)

Explorative:

- Biomarker program: Circulating tumor cells, single nucleotide polymorphisms, serum protein signatures
- C reactive protein (CRP) as prognostic marker

Statistical methods:

Summary statistics included:

- Nominal variables: frequencies and percentages
- Ordinal variables: frequencies, percentages, mean, median, minimum and maximum.
- Continuous variables: number (N) of observations, mean, standard deviation (SD), 25th percentile, median, 75th percentile, minimum and maximum.

In general, summaries were presented by treatment arm and all data listings were sorted by treatment arm, center identification (ID) and patient ID.
P-values were presented as two-sided p-values and the level of significance was set to 5% (two-sided), if not otherwise stated. Additionally, corresponding 95% confidence intervals (CIs) were provided, where applicable.
All time-to-event analyses were calculated using the Kaplan-Meier method. All hazard ratios were adjusted for the two stratification variables MSKCC risk score and histology.
Efficacy analysis: The goal was to demonstrate that the PFS time in the experimental arm (Sorafenib first in sequence) was not inferior to the PFS time in the control arm. The experimental arm will be considered to be non-inferior as long as the upper limit of the one-sided 95% CI of the hazard ratio is not above 1.225 (corresponding to a decrease to 13.1 months compared to an assumed median total PFS in the control group of 16 months). 383 events needed to be observed to have 80% power to reject the null hypothesis of inferiority (Hazard Ratio [HR]≥1.225) when the true HR=0.95. The patients were stratified by MSKCC risk score low vs intermediate and clear cell vs non-clear cell histology.
Analysis populations:
Primary analysis population: Intent to Treat (ITT)
All subjects who were assigned a subject number at randomization were considered randomized subjects, and this population was relevant for all analyses but safety analyses.
Modified ITT population (mITT):
A modified ITT analysis included patients having received at least one full cycle of second-line therapy. This population was relevant for all efficacy analyses.
Per protocol population (PP):
The definition of this population was amended compared to the definition in the study protocol. Subjects had to

- be compliant with a wash-out time of 7 to 28 days, if second line had started
- meet all inclusion criteria and none of the exclusion criteria
- show a minimum of relative dose intensity (≥75% of planned medication)

This population was relevant for all efficacy analyses.
Safety Analysis Set (SAF):
The SAF included all patients who received at least one dose of study medication. This population was relevant for laboratory parameters, AEs and exposure data.

Summary - Conclusions:

Efficacy results:

Baseline characteristics:

The median age at date of informed consent was 67.5 years in the Sorafenib-Pazopanib (S-P) arm and 68.4 years in the Pazopanib-Sorafenib (P-S) arm. In both arms, more males (72.0% and 72.9%) than females (28.0% and 27.1%) participated in the study. The median number of disease sites differed in both arms (n=2.0 and 3.0, respectively), and the vast majority of patients had a clear cell cancer.

Main reason for end of first-line treatment was progression of disease (56.1% and 51.6%) followed by adverse events (14.8% and 13.3%).

Primary efficacy: It was the primary objective of this study to evaluate if PFS from randomization to progression or death during second-line therapy of sorafenib followed by pazopanib (S-P) is non-inferior compared to pazopanib followed by sorafenib (P-S). This objective was not met since total PFS in the S-P arm was shorter compared to P-S (median 8.6 [CI 7.7-10.2] vs 12.9 months [CI 10.8-15.2]; HR 1.36, 90% CI 1.11–1.68; ITT population). The upper limit of the 95% CI was 1.68 and therefore higher than the planned limit of 1.225. However, due to low recruitment rates only 377 patients instead of planned 544 patients were randomized. Total median PFS was longer in the P-S arm compared to S-P in all subgroups (MSKCC risk score, age, histology, KPS) except in the subgroup with a KPS of 70/80. The total median PFS by KPS 70/80 was in the S-P arm 7.9 months, 95% CI=4.4-9.2 months and 7.4 months (95% CI=4.5-10.7 months) in the P-S arm. Additionally in the subgroup with an intermediate MSKCC risk score there was almost no difference between the treatment arms. The total median PFS was in the S-P arm 8.2 months, 95% CI=5.4-10.0 months and 9.7 months (95% CI=6.0-11.9 months) in the P-S arm.

Secondary efficacy:

Median total time to progression was longer in the P-S arm compared to S-P treatment (median 12.9 vs 8.5 months in the ITT population; HR=1.37,). This was also true for the subpopulations studied (mITT population 8.8 months vs 12.9 months and PP population 7.4 months vs 12.8 months).

Median time to first-line treatment failure was 5.5 months in the S-P arm vs 7.8 months in the P-S arm, HR=1.42 (95% CI 1.12 -1.80).

Median first-line PFS was also longer in the P-S arm (median 9.3 [CI 7.4-10.6] vs 5.6 months [CI 4.7-6.3]; HR 1.56, 95% CI 1.22–1.98; ITT population). Median first-line PFS was also longer in all subgroups, stratified by MSKCC risk score, age, KPS or histology.

Median second-line PFS was longer for S-P than for P-S (median 2.9 months [CI 2.0-3.7] vs 2.1 [CI 1.8-3.5]; HR 0.73, 95% CI 0.52–1.02; ITT population). Data were confirmed in the subpopulations mITT and PP with a HR of 0.79 and 0.94, respectively.

The median PFS in second line stratified by MSKCC risk score showed a longer PFS in the P-S arm when MSKCC was low (3.5 months [95% CI=1.8-3.9] vs 2.0 months [95% CI=1.8-3.7]) but PFS was longer in the S-P arm when MSKCC was intermediate 3.6 months [95% CI=1.9-5.2] vs 1.8 months [95% CI=1.5-3.1]). For PFS in second-line the S-P arm was also favored in groups stratified by age (e.g., median PFS of 3.2 months (95% CI=1.8-5.1) in the group ≤65 years vs median PFS of 2.0 months (95% CI=1.8-3.7), in patients with a clear cell histology, and in patients with a KPS 70/80. In contrast, the P-S arm was favored in groups stratified by Karnofsky score 90/100. Overall survival was longer in the P-S arm, ITT population (median 28.0 months for P-S and 22.7 months for S-P, HR 1.22, 95% CI 0.91-1.65, p=0.2842) and results were comparable in the mITT and PP populations. Stratified by MSKCC low risk score, age, KPS and histology OS was again longer in the P-S arm (ITT population). This was also true for the mITT and the PP population. However, in the group stratified by MSKCC intermediate risk score OS was comparable in the P-S arm and the S-P arm with median OS of 17.4 months vs 17.3 months.

In the S-P arm, first line therapy, 25.9% of patients presented a PR and 39.2% showed SD as best response, whereas in the P-S arm a PR was seen in 43.6% of patients and a SD in 31.4%. The percentage of patients with a CR was low in both arms.

In the S-P arm, during second-line therapy there were 18.9% of patients with a PR and 29.2% of patients who showed PD as best response, whereas only 8.0% of patients in the P-S arm had a PR and a PD was seen in 43.7%. The overall response rate first-line was 28.6% in the S-P arm

and 46.3% in the P-S arm, whereas the rate in second line was 19.8% vs 9.2%. The disease control rate first line was higher in the P-S arm (77.7% vs 67.7%) but was superior in the S-P arm second-line (56.6% vs 43.7%).

Efficacy findings were generally consistent in the mITT and PP populations with those in the ITT population except for some subgroup comparisons made, especially groups with a KPS 70/80 and an intermediate MSKCC risk score.

Safety results:

Exposure:

The median relative dose intensity was 97.8% and 93.6% in first-line in the S-P and P-S arms and 98.8% and 96.5% in second-line. In the S-P arm, there were 35.0% and 32.1% of dose modifications in first- and second-line therapy, and in the P-S arm, there were 43.7% and 37.9% of modifications. Investigator's decision was the main reason for dose modifications in both treatment arms.

Adverse events and NCI-CTCAE toxicities:

A total of 1,577 treatment-emergent adverse events (TEAEs) were reported in 179 patients (97.8%) in the S-P arm, first-line therapy, and 1,687 events were reported in 182 patients (99.5%) in the P-S arm, first-line therapy, in this study. Of all TEAEs 878 events in 165 patients and 936 events in 164 patients were related to the study medication and 38 events and 57 events were serious and related to the study medication. The three most commonly affected system organ classes (SOCs) in both arms (first-line therapy) during treatment were gastrointestinal disorders (total TEAEs were recorded in 80.3% of patients, and in 72.7% of patients assessed as possibly related in the S-P arm, and total TEAEs were recorded in 79.8% of patients, and in 72.1% assessed as possibly related in the P-S arm) skin and subcutaneous tissue disorders (total TEAEs were recorded in 73.8% of patients and in 68.9% of patients assessed as possibly related in the S-P arm and total TEAEs were recorded in 50.8% of patients, and in 44.3% of patients assessed as possibly related in the P-S arm), and general disorders and administration site conditions (total TEAEs were recorded in 57.5% of patients, and in 33.9% of patients assessed as being related in the S-P arm, and total TEAEs were recorded in 63.9% of patients and in 43.7% of patients assessed as possibly related in the P-S arm). The most prominent preferred terms (PTs) in both arms in the affected SOCs were diarrhea, palmar-plantar erythrodysaesthesia syndrome and fatigue.

In second-line therapy, most commonly affected SOCs in both arms were the same as in first-line therapy, but rates were distinctly lower compared to first-line treatment (e.g., total TEAEs recorded in 55.7% of patients and in 44.3% of patients assessed as possibly related, and total TEAEs recorded in 57.5% of patients and in 47.1% of patients assessed as possibly related in the SOC gastrointestinal disorders), except skin and subcutaneous tissue disorders. In this SOC, there were 67.8% of patients with a TEAE out of which in 60.9% of patients in the P-S arm TEAEs were assessed as possibly related. Prominent PTs were again diarrhea, fatigue and palmar-plantar erythrodysaesthesia syndrome, but besides this condition also rash occurred frequently in second-line therapy.

All TEAEs that occurred frequently in this trial are already listed as "common" or "most common" in the Summary of Product Characteristics (SPCs) for Nexavar® and Votrient®. According to the SPC for Nexavar® diarrhea, fatigue, alopecia, infection, hand-foot skin reactions and rash represent the most common AEs with sorafenib and those occurred frequently in this study. According to the SPC for Votrient® diarrhea, fatigue, hypertension, nausea, headache, vomiting, dysgeusia, elevated ALAT and ASAT levels, hand-foot skin reactions, hair color changes and rash represent the most common AEs with pazopanib and were also frequently seen in this study. Most of the Serious Adverse Events (SAEs) or fatal events were already mentioned in both SPCs but the following suspected unexpected serious adverse reactions (SUSARs) were reported during the study and need to be added to the respective SPC: During treatment with sorafenib (Nexavar®) one case each of stroke, pleural effusion and sigma diverticulitis was described. During treatment with pazopanib (Votrient ®) one case each of retinal haemorrhage, delirium and tachycardia was described.

There were 19 patients each (first- and second-line treatment) in the S-P arm that died due to an SAE in this study and 23 patients during first-line treatment and 9 patients during second-line treatment in the P-S arm . Two patients each died due to related TEAE in first- and second-line in the S-P arm and 5 patients died due to a related TEAE in the P-S arm, first-line. TEAE leading

to discontinuation of study treatment were reported in 33.3% and 24.0% of patients in both arms during first-line treatment. TEAE leading to discontinuation of study treatment were reported in 20.8% and 20.7% of patients in both arms during second-line treatment.

Non-fatal serious TEAEs related to the study medication were observed in 18.0% and in 22.4% of patients in both treatment arms, first-line. In second-line therapy 13.2% and 10.3% of patients experienced serious and related non-fatal TEAEs. Gastrointestinal disorders were reported in >4.0% of patients in all treatments, except second line pazopanib. In this group a rate of 4.7% of serious non-fatal investigations (Medical Dictionary for Regulatory Activities [MedDRA] SOC, e.g. ALAT increased), related to study drug were seen. In first-line pazopanib the highest rate of serious non-fatal events was seen in the SOC hepatobiliary disorders (6.0%) and non-fatal investigations (6.6%).

In the SPC for Votrient® cardiac disorders, abnormal hepatic function and gastrointestinal hemorrhage are identified as most important serious AEs and those were also observed in this study.

The most important serious AEs listed in the SPC for Nexavar® are myocardial infarction, gastrointestinal perforation, hemorrhage and hypertension and were also seen in this study. Most of the SAEs or fatal events were already mentioned in both SPCs but some SUSARs were reported during the study and need to be added to the respective SPC.

Other observations related to safety:

There were some changes in laboratory parameters observed in the study, almost all were increases in liver enzymes and all serious changes occurred in first-line or second-line pazopanib treatment. Changes in vital signs were generally not meaningful but more changes in ECG parameters that were marked as clinically significant were seen in the P-S arm compared to the S-P arm (15 patients versus 6 patients). Changes in KPS were not meaningful in both treatment arms.

Conclusion:

SWITCH-2 was a prospective, randomized phase III study of sequential TKI therapy (S-P vs P-S) for advanced and/or metastatic RCC. The study was stopped prematurely after recruiting of 377 patients since the recruitment rate was substantially lower than expected and primary endpoint cut off could not be reached in time. The primary endpoint of non-inferiority of the sequence S-P was not met. Overall, marked differences in favor of P-S for total PFS, total TTP, 1st-line PFS and DCR could be observed in this study but some subgroups (patients with a with a KPS 70/80 and patients with a MSKCC intermediate risk score) could benefit from the treatment sequence S-P.

When investigating CRP as prognostic marker for OS and total PFS in our models baseline CRP was a valid prognostic marker for OS/PFS. However, this statement is limited by the fact that values were only available for a subset of patients.

Date of report: 20-October-2017