Synopsis

Study Phase and 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 Objectives:	**Primary:** To evaluate if progression-free survival 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:** 1. Time from randomization to progression during second-line therapy (total TTP) 2. Time to first-line treatment failure (progression, death, discontinuation due to toxicity) descriptively in each arm 3. PFS in first-line and second-line treatment, descriptively 4. Overall survival, descriptively (data cut-off same as for primary endpoint) 5. Disease Control Rate (DCR); Response rates in first-line and in second-line (CR, PR, SD according to RECIST criteria) 6. Health-related Quality of Life (FACT-G, FKSI-10) 7. Biomarker programme 8. Safety and tolerability
Overall Study Design	Sorafenib and pazopanib are both effective and promising treatments for advanced RCC. Both drugs are registered for this indication. No prospective comparative data in advanced RCC (or other indications) have been published. A search in the clinicaltrials.gov database did not reveal any planned or ongoing studies. Only one comparative study in the adjuvant setting is ongoing. For optimal treatment of metastatic RCC patients it is essential to compare efficacy and safety of different sequential 1st and 2nd line treatments. This study should therefore explore the efficacy and safety of the sequential use of sorafenib followed by pazopanib or pazopanib followed by sorafenib in a randomized setting. This study is a sequential, randomized, open-label (1:1), multicenter phase III study starting in first-line of metastatic / advanced 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 will switch to pazopanib and vice versa, with a treatment-free period of at least seven and up to maximum 28 days after confirmed first-line treatment failure, in order to avoid additive toxicity. In general, the first-line treatment should be continued until progression (RECIST 1.1). However, if patients do not tolerate the first-line medication (sorafenib or pazopanib) because of toxicity, they may cross-over to the second-line therapy (pazopanib or sorafenib) despite the lack of progression, if an appropriate attempt according to a specific dose reduction / interruption scheme has been made to cope with the toxicity and try to resume first line therapy, if deemed appropriate with a reduced dose. In case of discontinuation of first-line treatment because of toxicity, patients will be enrolled for the second-line treatment, only after non-hematological toxicity has resolved to grade ≤1 and hematological toxicity to grade ≤2. As an exception, patients who

	refuse to be treated further with the first-line regimen due to intolerability despite having no progression may be crossed over to the second-line treatment, if they consent and are in general compliance. Any cross-over, also without progression, requires a CT scan, which is in this case also considered the baseline scan for the second-line treatment. One cycle is of four weeks duration. Patients will undergo a CT/MRI scan after every second cycle (i.e. after 8 weeks each), which will be evaluated according to RECIST 1.1 criteria. There will be no continuation of the same study medication beyond progression in both first- or second-line therapy. After the study reached its primary endpoint cut off, i.e. after 383 disease progressions under second-line therapy have occurred, clean data for these patients exist and a statistical analysis has been performed data collection will be stopped. After that the trial is terminated and a close out visit will be performed. Remaining patients will be treated outside the study and will be censored in the analysis.
Main Inclusion/ Exclusion Criteria	
Inclusion Criteria	1. Patients with metastatic / advanced RCC (all histologies), who are not suitable for cytokine therapy and for whom study medication constitutes first-line treatment 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 must be measured by CT/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 > 9.0 g/dl • Absolute neutrophil count (ANC) > 1,500/µl • Platelet count ≥ 100,000/µl • Total bilirubin < 1.5x the upper limit of normal • ALAT and ASAT < 2.5x upper limit of normal (< 5x upper limit of normal for patients with liver involvement of their cancer) • Alkaline phosphatase < 4x upper limit of normal • PT-INR/PT < 1.5x upper limit of normal [Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in these parameters exists.] • Serum creatinine < 2 x upper limit of normal 8. Written Informed Consent

Exclusion Criteria	
Excluded medical conditions:	1. History of cardiac disease: congestive heart failure >NYHA class 2 or with LVEF at baseline echocardiography < 50%, (echocardiography is optional); active CAD (MI more than 6 months prior to study entry is allowed); cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted) or uncontrolled hypertension (defined as blood pressure ≥ 160 mmHg systolic and/or ≥ 90 mmHg diastolic on medication). 2. History of HIV infection or chronic hepatitis B or C 3. Active clinically serious infections (> grade 2 NCI-CTC version 4.03) 4. Symptomatic metastatic brain or meningeal tumors (unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry and is clinically stable with respect to the tumor at the time of study entry) 5. Patients with seizure disorder requiring medication (such as steroids or anti-epileptics) 6. History of organ allograft 7. Patients with evidence or history of bleeding diathesis 8. untreated hypothyroidism 9. Patients undergoing renal dialysis 10. Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors [Ta, Tis & T1] or any cancer curatively treated > 3 years prior to study entry 11. Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must use adequate barrier birth control measures during the course of the trial and 3 months after the completion of trial 12. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results 13. Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study 14. Patients unable to swallow oral medications 15. Known allergy to Votrient® or Nexavar® (i.e. to active substance or one of the constituents)

Excluded therapies and medications, previous and concomitant:	1. Anticancer chemo-, cytokine- or targeted therapy for RCC 2. Radiotherapy during study or within 3 weeks of start of study drug. (Palliative radiotherapy will be allowed). Major surgery within 4 weeks of start of study (if wound healing is considered to be completed investigator can decide to start with study earlier). 3. Autologous bone marrow transplant or stem cell rescue within 4 months of study 4. Use of biologic response modifiers, such as G-CSF, within 3 weeks of study entry. [G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator; however they may not be substituted for a required dose reduction.] [Patients taking chronic erythropoietin are permitted provided no dose adjustment is undertaken within 2 months prior to the study or during the study] 5. Investigational drug therapy outside of this trial during or within 4 weeks of study entry 6. Prior exposure to the study drugs 7. Any St. John's wort containing remedy 8. Grapefruit juice during pazopanib therapy		
Number of subjects:	544	**Number of centres:**	ca 80
Participating Countries	Austria, Germany, The Netherlands The recruitment will be competitive.		
Drug Dose: (doses, regimen, treatment duration):	<u>Arm 1</u>: Sorafenib 400 mg bid orally until progression or intolerable toxicity, followed by pazopanib 800 mg once daily orally until progression of intolerable toxicity <u>Arm 2</u>: Pazopanib 800 mg once daily orally until progression or intolerable toxicity, followed by Sorafenib 400mg bid orally until progression or intolerable toxicity During first- and second-line, treatment visits are scheduled in weeks 0, 2, 4, 8, 12, and every 4 weeks thereafter, with tumor assessments after every other cycle.		

Planned Study Timelines:	• Final protocol: 30 September 2011 • Submission to EC and CA: 31 October 2011 • EC and CA approval: 31 December 2011 • FPFV: 31 January 2012 • Last center initiated: 31 May 2012 • Duration of enrolment: 37 months • LPFV: 28 February 2015 • Estimated Duration of treatment 15 months • LPLV: 30 April 2016
Evaluation of efficacy: (Sample Size, Study variables, Safety Assessments, Endpoints, Statistical Analysis Plan)	The goal is to demonstrate that the PFS time in the experimental arm (Sorafenib first in sequence) is not inferior to the PFS time in the control arm (Sorafenib second in sequence). The experimental arm will be considered to be non inferior as long as the lower limit of the 95% confidence interval (one-sided) of the median total PFS is not lower than 13.1 months (=non inferiority margin). We need to observe 383 events to have 80% power to reject the null hypothesis of inferiority (HR >=1.225) when the true HR=0.95 (we assume that the experimental arm -Sorafenib first in sequence- may be a little bit better than the control arm: median PFS 16 months in the control group and 16.8 months in the experimental group). Assuming exponential distributions, a 5% drop-out rate at 12 months, an accrual time of 37 months and total study duration of 52 months, 544 patients should be randomized. The patients will be stratified by Memorial Sloan Kettering Cancer Center (MSKCC, 2004) risk score low versus intermediate, and clear cell versus non-clear cell histology.
Publication/ Presentation Plan:	2016