Clinical Study Report - Synopsis

A randomized phase II study with Nivolumab or continuation of therapy as an early SWITCH approach in patients with advanced or metastatic renal cell carcinoma (RCC) and disease control after 3 months of treatment with a tyrosine kinase inhibitor

Short Title: NIVOSWITCH
EudraCT No.: 2016-002170-13
Sponsor Protocol code: AIO-NZK-0116ass.

Sponsor	AIO-Studien-gGmbH Kuno-Fischer-Straße 8 14057 Berlin, Germany
Sponsor Signatory	Dr. Mischo Kursar
Investigational Product	Nivolumab
Study Title	A randomized phase II study with Nivolumab or continuation of therapy as an early SWITCH approach in patients with advanced or metastatic renal cell carcinoma (RCC) and disease control after 3 months of treatment with a tyrosine kinase inhibitor
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First patient enrolled **Last patient enrolled** **Last patient completed**	03-JAN-2017 30-OCT-2018 23-OCT-2020
Regulatory Authority **Vorlage-Nr.**	Paul-Ehrlich-Institut 2808/01
Ethics Committee **No.**	Ethikkommission der Medizinischen Hochschule Hannover 7210M
Objectives	***Primary objective*** To assess the survival benefit from an early switch approach from Sunitinib or Pazopanib to Nivolumab (anti-angiogenic to immunotherapy switch) ***Secondary objectives*** • to compare efficacy of early switch to Nivolumab vs. continuation of either Sunitinib or Pazopanib • to compare health-related quality of life (HR-QoL) during TKI and Nivolumab treatment after early switch • to assess the influence of response to previous TKI treatment on Nivolumab efficacy • to assess safety and toxicity ***Exploratory objectives*** • To explore predictive biomarkers in the tumor and serum • ORR, PFS, and OS in subgroups (MSKCC risk categories; previous response, type of TKI administered) • To assess efficacy, safety and HR-QoL in patients who treated beyond progression as assessed by RECIST 1.1.
Methodology	Adult patients with metastatic or locally advanced RCC with clear cell component, not amendable to surgery with curative intention were included in this study. Potential patients with a measurable disease (at least one measurable target lesion) received a first line treatment with TKI, limited to Sunitinib and Pazopanib, for 10-12 weeks. After this Pre-screening period the first staging was performed to assess the response of the therapy according to RECIST 1.1. In case of stable disease or partial response the randomization provided all other inclusion criteria and none of the exclusion criteria were met patients were randomized into the study stratified by response characteristics OR vs. SD, modified MKSCC score risk poor vs. other, and type of TKI Sunitinib vs. Pazopanib. Patients randomized in arm A received 240 mg Nivolumab fixed dose Q2W for 16 weeks followed by 480 mg Nivolumab fixed dose Q4W. Patients randomized in Arm B continued the same TKI they received in the Pre-screening period (Sunitinib or Pazopanib) according to SOC: • Sunitinib: recommended dose of Sunitinib is 50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2- week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks. • Pazopanib: The recommended dose of Pazopanib for the treatment of RCC is 800 mg once daily. Treatment in both arms was continued until disease progression, unacceptable toxicity, or patient withdrawal up to a maximum of two years. The following study and routine procedures were performed: • Tumor assessment time points: Screening (Day -21 to 1 from initiation of study treatment), Week 12, and then every 12 weeks until disease progression is documented

	• FKSI-15 was be assessed after 4 weeks, 8 weeks, 12 weeks, and every 12 weeks thereafter until end of treatment. Patients were assessed for adverse events by non-directive questioning at each visit. Adverse events also were detected when they were volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Adverse events were documented according to the CTCAE version 4.03. Additionally, relationship of an adverse event to the investigational agents was determined by the Investigator. Radiological tumor assessment (CT, MRI) was performed at baseline and then every 12 weeks according to standard of care. All patients were followed up for survival status and subsequent cancer therapies a maximum of 24 month after randomization every 12 weeks. Patients in arm A had an additional follow up visit to document SAEs 100 days post EoT.
Number of patients (planned and analyzed):	Planned: Initial planned sample size: N=244. Analyzed: Slow recruitment and change in standard first line therapy to be expected in the near future led to a stop of recruitment in 08/2018 followed by a protocol amendment. Analyzed: N=49 patients, thereof N=25 patients in Arm A and N=24 patients in Arm B

Diagnosis and main criteria for inclusion	• Patients with measurable disease (at least one unidimensionally measurable target lesion by CT-scan or MRI) according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). If prior palliative radiotherapy to metastatic lesions: ≥ 1 measurable lesion that has not been irradiated. Patients with bone lesions as the only measurable lesion are eligible, provided that lesions consist of soft tissue, which is assessed via CT or MRI.
	• ECOG performance status 0-2.
	• Metastatic or locally advanced RCC with clear cell component, not amenable to surgery with curative intention.
	• First-line treatment with a TKI for 10-12 weeks (limited to Sunitinib or Pazopanib).
	• Documented partial response or stable disease to first-line TKI exposure at 10-12 weeks.
	• Prior therapies other than indicated in the exclusion criteria and surgeries are allowed if completed 4 weeks (for minor surgery and palliative radiotherapy for bone pain: 2 weeks) prior to start of treatment and patient recovered from toxic effects.
	• Adequate blood count, liver-enzymes, and renal function (obtained no later than 14 days prior to start of study treatment):
	  • WBC ≥ 2000 /µL
	  • Neutrophils ≥ 1500 /µL
	  • Platelets ≥ 100 x10^3 /µL
	  • Hemoglobin > 9.0 g/dL
	  • Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below):
	
	Female CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$
	
	Male CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$
	
	• AST/ALT≤ 3 x ULN

	• Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
Test product, dose and mode of administration, batch number	Nivolumab: • Batch No.: AAK4481, AAV7017, AAN8159, AAZ0636 • Formulation: Nivolumab Injection, 100 mg/10 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentaacetic acid (pentetic acid), and polysorbate 80 (Tween 80), pH 6.0 and includes a 0.7-mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers, and sealed with aluminum seals. • After switch to Nivolumab study drug will be given every two weeks at a dose of 240 mg to be administered as a 60 minute IV infusion for the first 16 weeks. From there on a fixed dose of 480 mg Q4W will be administered. • Package size: 100 mg/10 mL (10 mg/mL) glass vials • Route of administration: intravenous infusion • Source: BMS TKI: • Batch numbers: Not applicable (medication not provided as IMP but standard use of products with marketing authorization). • The recommended standard approach is a dosage of 50 mg Sunitinib once daily for 4 weeks followed by 2 weeks off treatment [4/2 schedule; total cycle length = 6 weeks], which is given until progression or intolerance. The recommended dose of Pazopanib for the treatment of RCC is 800 mg once daily.
Duration of treatment:	Treatment with Nivolumab or TKI was planned to be administered until disease progression (according to RECIST v1.1), unacceptable toxicity or patient withdrawal of consent to a maximum of 24 months.
Criteria for evaluation: **Efficacy:** **Safety:**	All patients randomized, with study drug assignment designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized are considered the primary efficacy population and were analyzed accordingly. A patient receiving at least one dose of study medication was considered evaluable for safety.
Statistical methods:	This phase II study was intended to assess an improve of OS due to the early switch of TKI therapy to Nivolumab treatment compared to a continued TKI therapy. The present trial was designed as a randomized phase II study which aims at estimating the therapeutic efficacy of the experimental early switch to Nivolumab (arm A) in relation to the continued standard of care combination (arm B). Overall survival (OS) is chosen as primary efficacy endpoint. The period for endpoint calculation began with the date of randomization and ended with the reported date of death (for whatever reason) or the final date of the patient being recorded as alive during the treatment or follow-up period (censored cases). In addition, major protocol violations, e.g., unauthorized tumor treatment before progression, lead to censoring at the time point of this event. OS (and likewise PFS, duration of response, and other time-to-event endpoints) were estimated by the product limit method of Kaplan and Meier, with survival curves compared using the log rank test (two-sided) as well as the correspondingly calculated hazard ratio with 95% confidence interval (from a univariate Cox model).

	However, due to the premature termination of study recruitment with only about 20% of the planned patient number enrolled, the primary analysis (as well as all secondary ones) suffers from low power. This has to be considered when interpreting the results.
SUMMARY CONCLUSIONS EFFICACY RESULTS:	The early trial termination decreased the sample size significantly and allowed only descriptive analyses. Despite such limitations the data did not indicate that an early switch from TKI treatment to Nivolumab improved efficacy or overall survival. The objective response rate (ORR) from time of randomization showed in ITT and PP populations superiority for TKI continuation vs. switch to Nivolumab (ORR: 52% vs. 20% and 58% vs. 24%, respectively). This translated into a similar PFS pattern in the ITT population, favoring TKI continuation vs. switch to Nivolumab (median PFS: 3 vs. 11.9 months; P=0.0030). These differences did not confer into OS detriments. Although there was some advantage for the OS probability during the first 2 years in favor for TKI continuation, this was followed by a survival plateau in both arms after the 2 years' time point in the ITT population. OS rates at 2 years (OS2Y) were similar between arms. The switch to Nivolumab revealed an OS2Y of 64% (CI 95% 48-86), which was similar to the 66% (CI 95% 48-90) for TKI continuation. The median OS was not reached for the switch to Nivolumab and was 43.8 months for patients who continued TKI treatment. FKSI-15 was utilized to assess patient reported outcomes (PRO). Although some differences for FKSI-15 favored the switch to Nivolumab rather than TKI continuation during the study treatment, those differences did not reach clinical relevance. The time to deterioration tended to favor the switch to Nivolumab when compared to TKI continuation, but differences were not significant.
SAFETY RESULTS:	Dose adjustment or discontinuation occurred in 4 (16%) patients. in arm A, while it was more frequent (n=12, 50%) in arm B. This corresponds to treatment discontinuation due to toxicity in 4% during Nivolumab treatment, while it was 17% for patients who continued TKI therapy. This data is supported by the incidence of CTCAE grade ≥3, which favored Nivolumab treatment (56%) when compared to TKI continuation (71%). However, the incidence of SAEs remained similar between Nivolumab and TKI treatment (48% and 50%, respectively). Overall, the Nivolumab treatment had some advantages regarding its toxicity profile.
CONCLUSION:	Overall, the data indicated that an early switch to Nivolumab maintenance is not warranted. Although the Nivolumab switch approach is associated with inferior efficacy, it does not confer to an OS detriment. While some advantages in regard to the toxicity profile exist, no clinically relevant benefit was detected by the PRO instrument. The small sample size was a major limitation for these analyses. However, the trial did not indicate relevant benefits for Nivolumab maintenance therapy that would outweigh the detriment of efficacy.
Date of the report:	15 September 2021