Synopsis

Protocol No.	AIO-NZK-0116ass.
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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 (NIVOSWITCH)**
EudraCT No.	2016-002170-13
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Study design	Open label, randomized, phase II trial
Anticipated start date	Q3-4/2016
Duration of study	Approx. 72 month
Indication	Adult patients of at least 18 years of age and any gender and metastatic or advanced RCC will be included. Patients must have received first line therapy with a VEGFR-TKI prior to study inclusion for 10-12 weeks with documented disease control (PR/SD) according to RECIST 1.1 at time of study entry
Total number of sites	Approx. 35 in Germany and Austria
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.
Planned sample size	N=244
Inclusion criteria	1. Written informed consent and any locally-required authorization (EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations. 2. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. 3. Age ≥ 18 years at time of study entry 4. ECOG performance status 0-2. 5. Metastatic or locally advanced RCC with clear cell component, not amenable to surgery with curative intention. 6. First-line treatment with a TKI for 10-12 weeks (limited to sunitinib or pazopanib). 7. Patients with measurable disease (at least one uni-dimensionally 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. 8. Documented partial response or stable disease to first-line TKI exposure at 10-12 weeks. 9. Prior therapies other than indicated in the exclusion critiria 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.

10. 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)

11. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. *WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of nivolumab*.
12. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab
13. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for

	a period of 31 weeks after the last dose of investigational product. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic) men do not require contraception.
Exclusion criteria	1. Prior systemic therapy other than 10-12 weeks SOC TKI treatment for advanced or metastatic RCC. 2. Standard of care 1st-line TKI treatment for advanced or metastatic RCC for longer than 12 weeks. 3. Complete remission (CR) or progression during SOC TKI 1st-line treatment. 4. Termination of first-line treatment with TKI due to intolerance 5. Previous malignancy (other than renal cell cancer), requiring active treatment or diagnosed in metastatic state. Basal cell cancer of the skin, pre-invasive cancer of the cervix, T1a prostate carcinoma or superficial bladder tumor [Ta, Tis and T1] are exempted. 6. Brain metastases mandating active treatment. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for 4 weeks after treatment is completed and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. 7. Prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents. 8. Administration of a live, attenuated vaccine within 4 weeks of start of therapy 9. Any previous treatment with a an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways 10. Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

	11. Patients should be excluded if they have an active, known or suspected autoimmune disease. NOTE: Subjects are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger 12. Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. NOTE: Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. 13. Known chronic infection (i.e. hepatitis B or C, HIV) 14. Patients should be excluded if they have been positively tested for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. 15. Patients should be excluded if they have a known history of testing positive for human immunodeficiency virus (HIV) or a known acquired immunodeficiency syndrome (AIDS). 16. History of severe hypersensitivity reaction to any monoclonal antibody or any constituent of the product. 17. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have a psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent 18. Uncontrolled severe hypertension (failure of diastolic blood pressure to fall below 95 mmHg under adequate medication) 19. Current cardiac events such as arrhythmias, myocardial infarction, CHF, apoplexy, lung embolism

	20. Idiopathic pulmonary fibrosis or other risk for pneumonitis 21. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control (failure rate of less than 1% per year) 22. Any other serious or uncontrolled medical disorder, active infection, physical examfinding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results. 23. Previous enrollment or randomization in the present study. (Not applicable to screening failures) 24. Involvement in the planning and/or conduct of the study (applies to both BMS staff and/or staff of sponsor and study site) 25. Patient who might be dependent on the sponsor, site or the investigator. 26. Patients who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts [§ 40 Abs. 1 S. 3 Nr. 3a AMG]. 27. Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG.
Investigational agents	• Nivolumab **Active comparators** • Sunitinib • Pazopanib
Treatment schedule	Dosage/Time points Nivolumab arm: 240 mg fixed dose Q2W for 16 weeks, then 480 mg Q4W Continuous TKI arm: Previous TKI will be continued 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. Adaption of original dose and scheme of sunitinib or pazopanib due to toxicity is permitted at study entry. Cross-over between nivolumab and SOC TKI arms is not allowed. Treatment with nivolumab or TKI will be administered until disease progression, unacceptable toxicity or patient withdrawal up to a maximum of 3 years. **Study procedures (and routine procedures):** • 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 will be assessed after 4 weeks, 8 weeks, 12 weeks and every 12 weeks thereafter until end of treatment.
Primary endpoint	• OS
Secondary endpoints	Key Secondary Endpoint: • Best overall response (PR+CR) throughout the 1st-line treatment according to modified RECIST Additional secondary endpoints: • PFS and OS from time of randomization to death from any cause • OS rates at 24 and 36 months • PFS and OS from start of 1st line TKI therapy • Duration of response (DoR) • Health related-Quality of Life (Functional Assessment of Cancer Therapy-Kidney Symptom Index FKSI 15 score and changes in the FKSI 15 score)

	• proportion of subjects with increase from baseline in FKSI 15 (MID 3 points) • time to deterioration, measured as a composite endpoint consisting of decrease of QoL (defined by the minimal clinical relevant difference) or death (TUDD) • tumor shrinkage, i.e. relative change from baseline in sum of longest diameter • AEs / SAEs / Treatment Emergent Adverse Events according to CTCAE 4.03
Randomization procedure	1:1 (Arm A: Nivolumab; Arm B: SOC-TKI) randomization will be performed centrally. Stratification according to: • Response characteristics: OR vs. SD • Modified MSKCC score: risk poor vs. other • TKI: sunitinib vs. pazopanib
Rationale	Today, targeted therapies represent the standard of care (SOC) in metastatic RCC. Inhibition of the VEGF axis remains the cornerstone of first line therapy, with pazopanib and sunitinib being the predominant choices (Motzer et al., 2013). Objective response rates (ORR) are within the range of 25-31%. The depth of remission has been shown to be a prognostic factor in RCC (Seidel et al., 2013), which has been recently validated in 2749 RCC patients (Grünwald et al., 2015). Objective response was achieved in 30%, half of which occurred within a 3 months window. Summarized, deep remission predicts overall survival (OS) in mRCC patients and may serve as a surrogate marker. Combination therapies have explored cytokines and targeted agents as combinational partners in order to improve quality of response in RCC. However, such combinations were prohibitive due to excessive toxicity and resulting dose-compromises (Négrier et al., 2011; Ryan et al., 2007). Inhibitors of programmed death -1 (PD-1) have been recently

shown in early clinical trials in RCC to be active (Topalian et al., 2012). The initial phase I study detected clinical activity at any dose-level without reaching a formal maximum tolerated dose (MTD). Adverse events (AE) occurred in 41% of patients, with 6% of grade 3/4 AEs. The most common treatment-related events consisted of fatigue, rash, diarrhea, pruritus, anorexia, and nausea. About 50% of the responders derive sustained benefit (Topalian et al., 2013). A recent phase II study confirmed the favorable tolerability and clinical activity of nivolumab in RCC (Motzer et al., 2014). Based on this data, it is hypothesized that nivolumab is better tolerated and beneficial in terms of health-related Quality of Life (HR-QoL). A recent phase III study investigating nivolumab vs. everolimus in the second-line setting for mRCC demonstrated clear superiority of nivolumab in terms of overall survival (25.0 vs 19.6 mo; HR=0.73;p=0.002), response rate (25% vs. 5% p<0.001) and frequency of TEAEs (19% vs. 37%) [1]. The afore-mentioned results constituted the basis for the market approval of nivolumab in the U.S. and in the E.U.

The concomitant combination with targeted agents or Ipilimumab have set a new benchmark for response, but at the expense of toxicity (Amin et al., 2014; Hammers et al., 2014).

Today, it remains unknown whether a tyrosine-kinase inhibitor (TKI) may boost response of subsequent checkpoint inhibitors. It is known however, that resistance to antiangiogenic therapy is associated with an immunosuppressive tumor microenvironment in mRCC and the effect can be mechanistically explained by an increase of PD-L1 expression (Liu et al. CIR 2015). Pretreatment with cytotoxic agents has been reported to boost immune response in cancer (Honeychurch, Dive, & Illidge, 2013), but whether a rapid sequence or simultaneous treatment with TKI and nivolumab will yield improved immune response remains unknown.

The goal of our study is to investigate whether an early switch

	from TKI to nivolumab may improve clinical outcome, in particular survival and tumor response, compared to the continuation of VEGFR inhibition in RCC. In subgroup analyses, efficacy of nivolumab for different patient populations is explored. Hypothesis: A brief exposure (10-12 wks.) with a TKI will boost immune responsiveness to nivolumab in mRCC patients and, hence, improve OS in mRCC patients to an early switch of therapy. As a key secondary endpoint, overall response rate will be assessed and analyzed. We hypothesize that nivolumab treatment is associated with improved overall survival and ORR as compared to TKI treatment.
Interim analysis	A first interim analysis will be conducted after 183 patients have been enrolled and followed-up for progression for 6 month (approx. 33 month after FPI). The read-out of the interim analysis will consist of: • ORR • PFS • AEs/SAEs The interim analysis does not include provisions for early termination and the study will continue recruitment until the required sample size for OS analysis has been reached.
Safety data	• AEs / SAEs / Treatment Emergent Adverse Events according to CTC 4.03 • Frequency of abnormal laboratory parameters
Sample size estimation	In order to detect a difference between groups in the primary endpoint overall survival using a log-rank test with a two-sided significance level of 5% and assuming a 2-year survival of 75% vs. 60% (corresponding to a hazard ratio of 1.78), a total of 128 events is necessary to achieve 90% power. Under the assumption of a total study duration of 72 month (36 month accrual + 36 month treatment and FU) and a 5% drop-out rate per year the required number of observable events translates into 122 patients per treatment arm. To reach this recruitment goal in

	36 month 35 sites with an average total enrollment of 6-7 patients per month are required. Key secondary endpoint and interim analysis: Because patients without response to pazopanib or sunitinib are excluded from study participation, a 35% ORR is estimated in eligible mRCC patients (i.e. those who have CR/PR/SD after 10-12 weeks of TKI treatment). It is expected that with the early switch to nivolumab, the ORR can be increased by 20%. A total sample size of N=244 achieves 89% power to detect a difference of 0.2 between the group proportions of 0.35 and 0.55 at a global significance level (alpha) of 0.05 using a one-sided z-test with continuity correction. These results assume that 2 sequential tests (one interim analysis + final analysis) are made using the Pocock spending function to determine the test boundaries. The interim analysis will achieve 81.1% power at a nominal alpha=0.041 after the accrual and follow-up for tumor response for at least 6 month of n=183 patients (75%).
Biomarker measurements	Biomarkers will consist of tumor tissue and soluble markers. Tumor tissue is mandatory and must be taken from metastatic disease prior to start of TKI (≤6 mo.). In the case of synchronous metastases, tissue from the primary is an acceptable alternative. If no tissue was obtained prior to start of TKI, a biopsy is mandatory prior to randomization. Markers will be tested for its predictive and prognostic value. **Work package 1 - tumor tissue analysis:** • Tumor blocks of the primary tumor and optional re-biopsies before and during treatment will be collected centrally • Standardized histopathological examination will be performed including immunohistochemistry and molecular pathology if necessary (Tumor type according to WHO 2016, WHO grade) • DNA and RNA will be isolated using automatized and standardized methods

	• Tumors will be tested for PD-L1, PD-L2 and PD-1 expression using immunohistochemistry (antibody PD-L1 28-8, DAKO, approved for Nivolumab, 3 other antibodies for comparison) and qPCR (Checkpointtyper) • Immune cell infiltrate (T-cells, cytotoxic T-cells, NK cells) will be characterized on protein and RNA level (CD3, CD8, CD57) and customized Nanostring Immunotyper test (48 genes). • VEGFR polymorphisms will be characterized using pyrosequencing **Work package 2 – blood and serum analysis:** • Quantification of serum markers including angiogenesis and cytokine/chemokine related proteomics, prior to and during treatment. • monitor CD4/CD8 T-cell populations and their functional subgroups as well as the T_{reg} and their different functional subgroups • quantification of PD-1 expression on these T-cell populations • Isolation and quantification of circulating exosomes from serum prior and during therapy
QoL measurements	FKSI15
Study plan / time lines	First Patient In (FPI): Q3-4/2016 Interim analysis for ORR after approx. 33 month Last Patient In (LPI): after approx. 36 month End of treatment and follow-up for LPI: after approx. 72 month Study report: after approx. 81 month Publication (OS data): after approx. 84 month