KURZPROTOKOLL
NIVOSWITCH

Öffentlicher Titel	Phase II Studie zur Therapieumstellung von Tyrosinkinase-Inhibitoren auf Nivolumab bei fortgeschrittenem oder metastasiertem Nierenzellkarzinom
Wissenschaftl. Titel	A randomized Phase II study with Nivolumab or continuation of therapy as an early SWITSCH Approach in patients with advanced or metastatic renal cell carcinoma(RCC) and disease cotrol after 3 months of Treatment with tyrosine kinase inhibitor
Kurztitel	NIVOSWITCH
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, zweiarmig, Investigator Initiated Trial (IIT)
Studienphase	Phase II
Erkrankung	Niere/Harnwege: Nierenzellkrebs: Zweitlinie oder höher

Einschlusskriterien

- 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.
- 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.
- Age >= 18 years at time of study entry
- Eastern Co-operative Oncology Group (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).
- 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.
- 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): (a) White Blood Cells (WBC) >= 2000/L; (b) Neutrophils >= 1500/L; (c) Platelets >= 100 x10^3/L; (d) Hemoglobin > 9.0 g/dL; (e) Serum creatinine 1.5 x Upper limit of normal (ULN) or creatinine clearance (CrCl) >= 40 mL/min (if using the Cockcroft-Gault formula below): (1) Female CrCl = ((140-age in years) x weight in kg x 0.85)/(72 x serum creatinine in mg/dL); (2) Male CrCl=((140 -age in years) x weight in kg x 1.00)/(72 x serum creatinine in mg/dL); (f) Aspartate Aminotransferase (AST)/Alanine Aminotransferase (ALT) <= 3 x ULN; (g) Total Bilirubin <= 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
- 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.
- 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

- 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.

Ausschlusskriterien

- Prior systemic therapy other than 10-12 weeks SOC TKI treatment for advanced or metastatic RCC.
- Standard of care 1st-line TKI treatment for advanced or metastatic RCC for longer than 12 weeks.
- Complete remission (CR) or progression during SOC TKI 1st-line treatment.
- Termination of first-line treatment with TKI due to intolerance
- 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.
- 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.
- Prior therapy with anti-tumor vaccines or other immuno-stimulatory antitumor agents.
- Administration of a live, attenuated vaccine within 4 weeks of start of therapy
- Any previous treatment with a an anti-Programmed Cell Death 1 protein (anti-PD-1), anti-PD-L1, anti-PD-L2, anti-Cytotoxic T-Lymphocyte-Associated protein (anti-CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways
- 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.
- 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
- 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.
- Known chronic infection (i.e. hepatitis B or C, HIV)
- 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.
- 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).
- History of severe hypersensitivity reaction to any monoclonal antibody or any constituent of the product.

	- 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 - Uncontrolled severe hypertension (failure of diastolic blood pressure to fall below 95 mmHg under adequate medication) - Current cardiac events such as arrhythmias, myocardial infarction, Congestive heart failure (CHF), apoplexy, lung embolism - Idiopathic pulmonary fibrosis or other risk for pneumonitis - 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) - Any other serious or uncontrolled medical disorder, active infection, physical exam finding, 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. - Previous enrollment or randomization in the present study. (Not applicable to screening failures) - Involvement in the planning and/or conduct of the study (applies to both Bristol-Myers Squibb (BMS) staff and/or staff of sponsor and study site) - Patient who might be dependent on the sponsor, site or the investigator. - 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 Arzneimittelgesetz (AMG)]. - Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities § 40 Abs. 1 S. 3 Nr. 4 AMG. - History of allogeneic solid organ or tissue transplant including allogeneic hematopoetic stem cell transplantation
Alter	18 Jahre und älter
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Sponsor	AIO-Studien GmbH
Förderer	Bristol-Myers Squibb
Registrierung in anderen Studienregistern	EudraCT 2016-002170-13 ClinicalTrials.gov NCT02959554