KURZPROTOKOLL
SUNNIFORECAST

Öffentlicher Titel	Phase II Studie zu first-line Nivolumab plus Ipilimumab bei fortgeschrittenem Nierenzellkarzinom
Wissenschaftl. Titel	A Phase 2, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Standard of Care in Subjects with Previously Untreated and Advanced (unresectable or metastatic) non-clear Cell Renal Cell Carcinoma
Kurztitel	SUNNIFORECAST
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, offen/unverblindet, zweiarmig, Investigator Initiated Trial (IIT)
Studienphase	Phase II
Erkrankung	Niere/Harnwege: Nierenzellkrebs: Erstlinie
Einschlusskriterien	- Signed Written Informed Consent a) Subjects must have signed and dated an approved written informed consent form according to the Institutional Review Board (IRB) and in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care. b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study. - Target Population a) Histological confirmation of non-clear cell renal cell carcinoma (nccRCC) with at least 50% non-clear cell component according to actual World Health Organization (WHO) classification. b) Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) nccRCC c) Performance status: Karnofsky (KPS) > 70% d) Measurable disease as per RECIST v 1.1 documented by an English radiology report e) Tumor tissue (FFPE archival or recent acquisition) must be available and sent to the central pathological reviewer (see Table 6) in order to confirm the diagnosis. (Note: Fine Needle Aspiration (FNA) and bone metastases samples are not acceptable for submission). f) Patients with all risk categories will be eligible for the study. Patients will be stratified for papillary or non-papillary non-clear cell histology and IMDC risk score Patients will be categorized according to favorable versus intermediate versus poor risk status at registration according to the International Metastatic RCC Database Consortium (IMDC) criteria: i. KPS equal to 70% ii. < 1 year from diagnosis to randomization iii. Hemoglobin < than the lower limit of normal (LLN) iv. Corrected calcium concentration greater than the upper limit of normal (ULN) v. Absolute neutrophil count greater than the ULN vi. Platelet count greater than the ULN If none of the above factors are present, subjects are only eligible for the favorable-risk cohort, if 1-2 factors are present subjects are categorized as intermediate risk and > 3 factors as poor risk. - Age and Reproductive Status: - a) Males and Females, > 18 years of age - b) WOCBP 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 study drug. - c) Women must not be breastfeeding - d) WOCBP must agree to follow instructions for method(s) of contraception for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo five half-lives. The terminal half-lives of Nivolumab and Ipilimumab are up to 25 days and 18 days, respectively. The terminal half-life of the active metabolite of Sunitinib is up to 110 hours. The terminal half-life of other Standard of Care agents has to be derived from the product information. i. WOCBP randomized to receive Nivolumab + Ipilimumab 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 investigational drug. ii. WOCBP randomized to receive the Standard of Care agent should use an adequate method to avoid pregnancy for 8 weeks (30 days plus the time required for the active metabolite of the Standard of Care agent to undergo five half-lives)

- e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for a period of 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo five half-lives. The terminal half lives of Nivolumab and Ipilimumab are up to 25 days and 18 days, respectively. The terminal half-life of the active metabolite of Sunitinib is up to 110 hours. i. Males randomized to receive Nivolumab combined with Ipilimumab who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for Nivolumab to undergo five half-lives) after the last dose of investigational drug. ii. Males randomized to receive Sunitinib who are sexually active and women of childbearing potential (WOCBP) must continue contraception for 16 weeks (90 days plus the time required for the active metabolite of Sunitinib to undergo five half-lives) after the last dose of investigational drug.
- f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section. Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or uncertain effective as listed below: HIGHLY EFFECTIVE METHODS OF CONTRACEPTION • Male condoms with spermicide • Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) by WOCBP subject or male subject's WOCBP partner • Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug • Nonhormonal IUDs Tubal ligation Vasectomy Complete Abstinence* Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. UNCERTAIN METHODS OF CONTRACEPTION • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal sponge • Male Condom without spermicide • Progestin only pills by WOCBP subject or male subject's WOCBP partner • Female Condom*. A male and female condom must not be used together

Ausschlusskriterien

- Target Disease Exceptions
- 1. Any active brain metastases requiring systemic corticosteroids. Baseline imaging of the brain by MRI is required in patients with clinical signs of potential central nerve system (CNS) involvement within 28 days prior to randomization.
- 2. Tumors with a clear-cell component of > 50% Medical History and Concurrent Diseases
- 3. Prior systemic treatment with vascular endothelial growth factor (VEGF) or VEGF receptor targeted therapy (including, but not limited to, Sunitinib, Pazopanib, Axitinib, Tivozanib, and Bevacizumab) or prior treatment with an mTOR inhibitor or cytokines.
- 4. Prior treatment with an immune checkpoint inhibitor as anti-programmed cell death (PD)PD-1, anti-PD-L1, anti-PD-L2, anti cytotoxic T-lymphocyte-associated Protein 4 (CTLA 4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

- 5. Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll.
- 6. Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- 7. Uncontrolled adrenal insufficiency.
- 8. Ongoing symptomatic cardiac dysrhythmias, uncontrolled atrial fibrillation, or prolongation of the Fridericia corrected QT (QTcF) interval defined as > 450 msec for males and > 470 msec for females, where QTcF = QT / 3RR
- 9. Poorly controlled hypertension (defined as systolic blood pressure (SBP) of > 150 mmHg or diastolic blood pressure (DBP) of > 90 mmHg), despite antihypertensive therapy.
- 10. History of any of the following cardiovascular conditions within 12 months of enrollment: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery by-pass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure, as defined by the New York Heart Association.
- 11. History of cerebrovascular accident including transient ischemic attack within the past 12 months.
- 12. History of deep vein thrombosis (DVT) unless adequately treated with low molecular weight heparin
- 13. History of pulmonary embolism within the past 6 months unless stable, asymptomatic, and treated with low molecular weight heparin for at least 6 weeks.
- 14. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the past 6 months.
- 15. Serious, non-healing wound or ulcer.
- 16. Evidence of active bleeding or bleeding susceptibility; or medically significant hemorrhage within prior 30 days.
- 17. Any requirement for anti-coagulation, except for low molecular weight heparin.
- 18. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
- 19. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- 20. Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection.
- 21. Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
- 22. Major surgery (eg, nephrectomy) < 28 days prior to the first dose of study drug.
- 23. Anti-cancer therapy < 28 days prior to the first dose of study drug or palliative, focal radiation therapy < 14 days prior to the first dose of study drug.
- 24. Receiving concomitant CYP3A4 inducers or strong CYP3A4 inhibitors (See Appendix 4, 14.4).

	- 25. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the Standard of Care agent (eg, malabsorptive disorder, ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or small bowel resection). - 26. Hypersensitivity to the Standard of Care or any of the excipients aa) Patients who were vaccinated with a live vaccine 2 weeks prior to the start of the CT - Physical and Laboratory Test Findings - a. Left ventricular ejection fraction (LVEF) less than the LLN as assessed by echocardiography or multigated acquisition (MUGA) scan. - b. Any of the following laboratory test findings: 2. WBC < 2,000/mm3 3. Neutrophils < 1,500/mm3 4. Platelets < 100,000/mm3 5. AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present) 6. Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL) 7. Serum creatinine > 2.5 x upper limit of normal (ULN) or creatinine clearance < 20 mL/min (measured or calculated by Cockroft- Gault formula): Female CrCl = (140 - age in years) x weight in kg x 0.85 72 x serum creatinine in mg/dL Male CrCl = (140 - age in years) x weight in kg x 1.00 - Allergies and Adverse Drug Reaction a) History of severe hypersensitivity reaction to any monoclonal antibody. - Other Exclusion Criteria a) Subjects who are incompetent to understand and sign the informed consent.
Alter	18 Jahre und älter
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Sponsor	Universität Frankfurt
Förderer	Bristol-Myers Squibb
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03075423 EudraCT 2016-000706-12
Links	Studiendokumente zum Download (roXtra) Weiterführende Informationen