KURZPROTOKOLL
TITAN TCC

Öffentlicher Titel	Phase II Studie zu Nivolumab bei metastasiertem Urothelkarzinom
Wissenschaftl. Titel	A phase II single arm clinical trial of a Tailored ImmunoTherapy Approach with Nivolumab in subjects with metastatic or advanced Transitional Cell Carcinoma
Kurztitel	TITAN TCC
Studienart	multizentrisch, prospektiv, Therapiestudie, offen/unverblindet, einarmig, Investigator Initiated Trial (IIT)
Studienphase	Phase II
Erkrankung	Niere/Harnwege: Harnblasenkrebs: Erstlinie
Einschlusskriterien	- Signed Written Informed Consent: Subjects or legally acceptable representatives must have signed and dated an IRB/IEC approved written informed consent form 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. Subjects or legally acceptable representatives must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study - Target Population: Histological evidence of metastatic or surgically unresectable transitional cell carcinoma of the bladder, urethra, ureter, or renal pelvis. Minor histologic variants of transitional cell carcinoma (e.g. squamous cell, comprising <50 % of the tumor overall) are acceptable. Subjects must have advanced or surgically unresectable TCC (cT4b, any N or any T, N2-N3 or any M1) or having progressed during or after platinum-based first line therapy and up to 1 further treatment line (2nd and 3rd line cohort). Subjects, who have received neoadjuvant or adjuvant cisplatin based chemotherapy are eligible and considered first line provided that progression has occurred >12 months from last therapy [for chemoradiation and adjuvant treatment] or >12 months from last surgery [for neoadjuvant treatment]; in all other patients who received cisplatin based neoadjuvant and/or adjuvant chemotherapy and progression within 12 months this will be considered one line of therapy. [*Update January 2020:First-line cohort has been stopped since 31-Jan-2019 and wont be restarted], KPS of at least 70% (See Appendix 1), Measurable disease as per RECIST v1.1 (See Appendix 2), Formalin-fixed paraffin embedded tumor tissue obtained within 2 years prior to screening must be available and received by the central pathology (tumor block is preferred, alternatively 15 unstained slides). Note that: 1. Fine Needle Aspiration [FNA] and bone metastases samples (without soft tissue component) are not acceptable for submission). 2. Tumor lesions used for newly acquired biopsies should not be target lesions, unless there are no other lesions

	- Age and Reproductive Status: Males and Females, >= 18 years of age; Women of childbearing potential (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; Women must not be breastfeeding; Women of childbearing potential (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. 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 investigational drug; 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. Males who 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;Comment: Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing as described in this section. nvestigators 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 less 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) such as Mirena® 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, such as ParaGard®, 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.LESS EFFECTIVE 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: Any history of or current CNS metastases. Baseline imaging of the brain by MRI (preferred) or CT scan is required within 28 days prior to registration in 2nd/3rd line patients only

- Medical History and Concurrent Diseases: Prior systemic treatment with more than two different chemotherapy regimen (Sequential chemotherapy as a planned sequence to optimize response will count as 1 regimen); Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA 4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways; 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; 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; Prior malignancy active within the previous 3 years except for 1. 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. 2. Patients in active surveillance for prostate cancer; Human immunodeficiency virus (HIV) infection or known acquired immunodeficiency syndrome (AIDS); Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection; 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; Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug; Anti-cancer therapy less than 28 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug; Presence of any toxicities attributed to prior anti-cancer therapy other than neuropathy, alopecia and fatigue, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study drug
- Physical and Laboratory Test Findings: Any of the following laboratory test findings: 1. WBC < 2,000/mm^3; 2. Neutrophils < 1,500/mm^3; 3. Platelets < 100,000/mm^3; 4. AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present); 5. Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL); 6. Serum creatinine > 1.5 x upper limit of normal (ULN) or creatinine clearance < 40 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] / [72 x serum creatinine in mg/dL]
- Allergies and Adverse Drug Reaction: History of severe hypersensitivity reaction to any monoclonal antibody or any constituent of the products
- Other Exclusion Criteria: Prisoners or subjects who are involuntarily incarcerated; Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness; Participation in another clinical intervention trial 30 days prior to registration

Alter 18 Jahre und älter

Prüfzentren **Universitätsklinikum Gießen und Marburg, Standort Marburg** (Geschlossen)
Baldingerstraße
35043 Marburg
Bettina-Petra Seifert-Heinze
Tel: 06421 58 63695
Seifertk@med.uni-marburg.de

Sponsor AIO-Studien GmbH

Förderer Bristol-Myers Squibb

Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03219775 EudraCT 2016-004857-33