Tailored ImmunoTherapy Approach With Nivolumab in Subjects With Metastatic or Advanced Renal Cell Carcinoma (TITAN-RCC)

This study is currently recruiting participants.

See **Contacts and Locations**

Verified May 2017 by AIO-Studien-gGmbH

Sponsor:
AIO-Studien-gGmbH

Collaborator:
Bristol-Myers Squibb

Information provided by (Responsible Party):
AIO-Studien-gGmbH

ClinicalTrials.gov Identifier:
NCT02917772

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History of Changes

Full Text View | **Tabular View** | **No Study Results Posted** | Disclaimer

How to Read a Study Record

Purpose

TITAN RCC (0216-ASG) is a Phase 2, open-label study of nivolumab monotherapy with additional nivolumab/ipilimumab "boost" cycles in previously untreated and pretreated (2nd line), advanced or metastatic **renal cell carcinoma** (mRCC) subjects with intermediate and high risk disease according to IMDC.

Condition	Intervention	Phase
Carcinoma, Renal Cell Clear-cell Metastatic **Renal Cell Carcinoma**	Biological: Nivolumab/Ipilimumab	Phase 2

Study Type: Interventional
Study Design: Intervention Model: Single Group Assignment
Masking: None (Open Label)
Primary Purpose: Treatment

Official Title: A Phase II Single Arm Clinical Trial of a Tailored ImmunoTherapy Approach With Nivolumab in Subjects With Metastatic or Advanced **Renal Cell Carcinoma**

Resource links provided by NLM:

Drug Information available for: Ipilimumab Nivolumab

Genetic and Rare Diseases Information Center resources: Renal Cell Carcinoma

U.S. FDA Resources

Further study details as provided by AIO-Studien-gGmbH:

Primary Outcome Measures:

- Objective Response Rate (ORR) [Time Frame: until 30 weeks after last patient first treatment, LPFT]

  (RECIST 1.1) by CT or MRI measured at week 8 (+/- 1 week) and week 16 (+/- 1 week), 28 (+/- 1 week) and then every 12 weeks (+/- 1 week).

  The primary objective will be measured by the primary endpoint of ORR (based on investigator assessments) among all treated subjects, first line subjects and second line subjects. It is defined as the number of subjects with a best overall response of CR or PR divided by the number of all treated subjects, first line subjects or second line subjects. Best overall response is defined as the best response designation, as determined by investigator, recorded between the date of first dose and the date of objectively documented immunotherapy resistance per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented immunotherapy refractory disease or subsequent therapy, all available response designations will contribute to the ORR determination.

Secondary Outcome Measures:

- General considerations: RR, TTR, DoR, PFS, TIR (Time to Immunotherapy Resistance), OS [Time Frame: until 30 weeks after last patient first treatment, LPFT]

  All as assessed by investigators among all treated subjects, first line subjects, and second line subjects. Furthermore, patients with IMDC intermediate and high risk will be analysed separately.

- Remission Rates during **TITAN** treatment: RR1, RR2, RR2SD, RR3 [Time Frame: until 30 weeks after last patient first treatment, LPFT]

  1. RR1: Number of patients with CR/PR during nivolumab monotherapy (induction and maintenance, the latter only including protocol defined pseudoprogressors) divided by all treated patients.

2. RR2: Remission rate after progression during nivolumab monotherapy. It is defined as the number of patients with CR/PR after receiving nivolumab/ipilimumab "boost" cycles for initial progression during nivolumab monotherapy divided by all patients receiving "boosts" for this situation.
3. RR2SD: Remission rate after stable disease during nivolumab monotherapy. It is defined as the number of patients with CR/PR after receiving nivolumab/ipilimumab "boost" cycles for initial stable disease during nivolumab monotherapy divided by all patients receiving "boosts" for this situation.
4. RR3 is the subsequent remission event to RR2 for patients undergoing repeated nivolumab/ipiliumumab "boost" according to the algorithm described above.

- Time to Immunotherapy Resistance: TIR [Time Frame: Time from first dosing date to the date of documented tumor progression based on investigator assessments (per RECIST 1.1) despite 4 "boost" cycles or within 3 months after the last "boost" cycle, or death due to any cause.]

  Subjects with disease progression despite 4 nivolumab/ipilimumab combination "boost" cycles or within 3 months after the last "boost" cycle will be considered immunotherapy resistant.

- Time-to-Response: TTR [Time Frame: Time from first dosing date or initiation of nivolumab/ipilimumab "boost" cycles to the date of the first confirmed response thereafter, as assessed by the IRC.]

  TTR may be recorded several times per patient.

- Duration of Response: DOR [Time Frame: Time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.]

  DOR may be recorded multiple times per patient.

- Overall survival:OS [Time Frame: Time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.]
- Safety: Adverse events assessment [Time Frame: Continuously: Treatment Visit day 1/week 1 until Survival Visits/Follow-up Visits]

  Treatment Emergent Adverse Events according to CTC 4

- Safety: Frequency of abnormal laboratory parameters [Time Frame: Screening Visit until Survival Visits/Follow-up Visits]

  Treatment Period: Within 72 hrs prior to re-dosing to include CBC w/ differential, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine. Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3).

  Follow-up Period: On site/local CBC w/differential, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine and TSH for X01, repeat at X02 if study drug related toxicity persists.

- Patient reported outcomes [Time Frame: Treatment Visit day 1/week 1 until Survival Visits/Follow-up Visits 1 and 2]

  NCCN-FACT FKSI-19 (Version 2)

- Exploratory objectives: Immune monitoring [Time Frame: Taken together with Laboratory Tests: Prior to induction (Baseline), Prior to Nivo dose 4, Prior to Nivo dose 8, Prior to 6th nivo maintenance dosing]
  - To monitor immunogenicity of nivolumab and nivolumab/ipilimumab "boosts" with regard to prediction of response as well as immune related adverse events, including:
    - frequency, differentiation and activation of blood-circulating CD4+ and CD8+ T cells (CD27, CD28, CD45RA, CD45RO, CD57, CD95, CD69, CD25, IFN-γ, TNF- α, IL-4, IL 17, IL-10, CD107a)
    - frequency of blood-circulating dendritic cells (HLA-DR, slan, CD1c, CD11c, CD123, CD141, CD303), myeloid-derived suppressor cells (HLA-DR, CD11b, CD14, CD15, CD33), and regulatory T cells (FoxP3, CD25, CD45RA, CD127)
    - expression of molecules involved in immune checkpoint modulation (ICOS, PD-1, PD-L1, CTLA-4) on blood-circulating dendritic cells and T cells
  - To determine the presence of autoantibodies in the serum of RCC patients
  - To explore the expression of PD-L1 and PD-L2 in tumor tissues of mRCC patients and correlation with efficacy parameters

Estimated Enrollment:	200
Study Start Date:	October 2016
Estimated Study Completion Date:	January 2021
Estimated Primary Completion Date:	April 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Nivolumab/Ipilimumab • Induction: Mono-Therapy with Nivolumab • If CR/PR: Nivolumab Maintenance Mono-Therapy • If SD/PD: Nivolumab/Ipilimumab "Boost 1+2"-Combination Therapy • If CR/PR: Nivolumab Maintenance Mono-Therapy • If SD/PD: Nivolumab/Ipilimumab "Boost 3+4"-Combination Therapy • If CR/PR/SD: Nivolumab Maintenance Mono-Therapy	Biological: Nivolumab/Ipilimumab • Induction: Mono-Therapy with Nivolumab (240 mg i.V. / Q2W x 8) • If CR/PR: Nivolumab Maintenance Mono-Therapy (240 mg i.V. / Q2W) • If SD/PD: Nivolumab/Ipilimumab "Boost 1+2"-Combination Therapy (Nivo 3 mg/kg i.V. and Ipi 1 mg/kg i.V. / Q3W x 2) • If CR/PR: Nivolumab Maintenance Mono-Therapy (240 mg i.V. / Q2W) • If SD/PD: Nivolumab/Ipilimumab "Boost 3+4"-Combination Therapy (Nivo 3 mg/kg i.V. and Ipi 1 mg/kg i.V. / Q3W x 2) • If CR/PR/SD: Nivolumab Maintenance Mono-Therapy (240 mg i.V. / Q2W) Other Name: Opdivo/Yervoy

Detailed Description:
The primary object is to estimate the Objective response rate (ORR) based on investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 of the TITAN regimen in untreated (1st line) and pretreated (2nd line) subjects with International Metastatic RCC Database Consortium (IMDC) intermediate and high risk, advanced Renal cell carcinoma (RCC) with clear cell component

Eligibility

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Signed Written Informed Consent
  - Subjects 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 must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.
- Target Population
  - Histological confirmation of RCC with a clear-cell component.
  - Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC
  - One (anti-angiogenic or temsirolimus) [to be eligible for 2nd line tier] or no prior systemic therapy for RCC [to be eligible for 1st line tier] with the following exception:
    - One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors as well as CTLA-4- or PD-1/PD-L1 immune checkpoint inhibitors, respectively, and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy.
  - KPS of at least 70%
  - Measurable disease as per RECIST v1.1
  - Tumor tissue (FFPE archival or recent acquisition) must be received by the central vendor (block or unstained slides). (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission).
  - Patients with intermediate and poor risk categories will be eligible for the study.
- To be eligible as intermediate or poor-risk, at least one of the following prognostic factors as per the International Metastatic RCC Database Consortium (IMDC) criteria must be present:
  - KPS equal to 70%
  - Less than 1 year from initial diagnosis of RCC (eg, nephrectomy or first diagnostic biopsy) to registration (1st line) or to start of first-line targeted therapy (2nd line), respectively
  - Hemoglobin less than the lower limit of normal (LLN)

    - Corrected calcium concentration greater than the upper limit of normal (ULN)
    - Absolute neutrophil count greater than the ULN
    - Platelet count greater than the ULN
- If none of the above factors are present, subjects are not eligible (favorable-risk).
- 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.
    - 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.

Exclusion Criteria:

- 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.
- Medical History and Concurrent Diseases
    - Prior systemic treatment with more than one of the following drugs: mTOR, VEGF or VEGF receptor targeted therapy (including, but not limited to, temsirolimus, everolimus, sunitinib, pazopanib, axitinib, tivozanib, and bevacizumab).
    - 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 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.
- 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 alopecia, 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:
  - WBC < 2,000/mm3
  - Neutrophils < 1,500/mm3
  - Platelets < 100,000/mm3
  - AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present)
  - Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
  - Serum creatinine > 1.5 x upper limit of normal (ULN) or creatinine clearance < 40 mL/min (measured or calculated by Cockroft-Gault formula)
- Allergies and Adverse Drug Reaction
  - History of severe hypersensitivity reaction to any monoclonal antibody or any constituent of the product.
- Other Exclusion Criteria
  - 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.
  - Patient who has been incarcerated or involuntarily institutionalized by court order or by the authorities.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see

Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02917772

Contacts

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Sponsors and Collaborators

AIO-Studien-gGmbH

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Investigators

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More Information

Responsible Party:	AIO-Studien-gGmbH
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Individual Participant Data (IPD) Sharing Statement:
Plan to Share IPD: No

Keywords provided by AIO-Studien-gGmbH:
tailored immuno therapy
Nivolumab

Ipilimumab
boost

Additional relevant MeSH terms:

Carcinoma	Neoplasms by Site
Carcinoma, Renal Cell	Kidney Diseases
Neoplasms, Glandular and Epithelial	Urologic Diseases
Neoplasms by Histologic Type	Nivolumab
Neoplasms	Antibodies, Monoclonal
Adenocarcinoma	Antineoplastic Agents
Kidney Neoplasms	Immunologic Factors
Urologic Neoplasms	Physiological Effects of Drugs
Urogenital Neoplasms	

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