Prospective, randomized, neoadjuvant phase II study with combination immuno-oncology in primary clear cell renal cell cancer at risk for recurrence or distant metastases (NESCIO-trial; M21NSC; CA209-6DJ)

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This study has been transitioned to CTIS with ID 2024-515514-40-00 check the CTIS register for the current data. The primary objective is to investigate the rate of pathological responses following different neoadjuvant immunotherapy combinations in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52016

Source
ToetsingOnline

Brief title
NESCIO

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
clear cell renal cell carcinoma; kidney cancer

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: BMS,Bristol-Myers Squibb

Intervention

Keyword: clear cell renal cell cancer, immunotherapy, neoadjuvant, phase II

Outcome measures

Primary outcome

The rate of pathological responses following different neoadjuvant immunotherapy combinations in high-risk non-metastatic clear cell RCC in an adaptive trial design and the safety and feasibility of neoadjuvant IO approach in high-risk non-metastatic clear cell renal cell cancer patients

Secondary outcome

Secondary objectives:

1. To describe the safety and feasibility of neoadjuvant IO approach in high-risk non- metastatic clear cell renal cell cancer patients

2. To investigate the objective response rate according to RECIST 1.1

3. To assess EFS, RFS, rate of metastasis and local recurrence rate at 5 years after start of treatment

4. To investigate surgical morbidity according to Clavien Dindo classification

Exploratory objectives:

Collection of peripheral blood and tissue collection (both fresh frozen and paraffin embedded) on pretreatment biopsies and post-treatment partial/total

nephrectomies to correlate with pathological response rate and RFS for:

1. investigation of immune infiltrate and changes upon neoadjuvant

immunotherapy by (multiplex) IHC/IF/

2. investigation of predictive transcriptomics for response

3. investigation of TMB, frameshift mutations, INDELs, HERV-E

4. ctDNA (methylated DNA) to early predict response to treatment or progression

5. Collect fresh tumor materials for TIL isolation, TCR seq, sc RNA seq

Study description

Background summary

From neoadjuvant monotherapy and combination immunotherapy studies it has become clear that upfront immunotherapy can induce impressive pathological responses. The observation from OpACIN, that most of the stage III melanoma patients did not receive 4 courses ipilimumab 3mg/kg + nivolumab 1mg/kg due to treatment-related toxicities, but also the observation of a very high response rate after 2 courses in the neo-adjuvant arm, indicated, that stage 3 melanoma patients benefit already from only 2 infusions.
In addition, in several tumor types combination of ipilimumab plus nivolumab appear superior to monotherapy anti-PD-1, including melanoma and HNSSC. In NSCLC, single agent nivolumab led to a high major pathological response rate [42], while combination ipilimumab plus nivolumab was too toxic [43]. In mismatch repair (MMR) deficient colorectal cancer, 100% of patients treated so far in the NICHE trial [21] show a major pathological response and so far, none of these have progressed/relapsed post-surgery. In MMR proficient colorectal cancer and bladder cancer combination immunotherapy is also highly effective. These data have resulted in the initiation of several neoadjuvant phase I/II studies in primary RCC, which are currently ongoing. A phase I neoadjuvant trial in patients with RCC has investigated the lymphocytic infiltration, safety and early efficacy of pembrolizumab (NCT02212730). In addition, two safety and efficacy studies investigate neoadjuvant nivolumab, one in the non-metastatic setting and one as pre- and post-operative therapy in metastatic RCC (ADAPTeR) (NCT02575222; NCT02446860). Another neoadjuvant phase 1b study tests safety and efficacy of durvalumab plus tremelimumab in advanced RCC (NCT02762006).
Furthermore, data are emerging that help rationally design a neoadjuvant combination trial. Specifically, LAG-3 is upregulated in RCC TIL exposed to

anti-PD-1 (more than any other inhibitory receptors like TIM-3) [10]. Targeting LAG-3 in combination with anti-PD-1 (or ipi/nivo) may be another next logical step.
Another example for future combination is based on data from CD73, an ecto-5*-nucleotidase, which is highly expressed in clear cell renal cell cancer and maybe a marker for cancer stem cells or highly aggressive cells [11]. Recent data indicate that targeting the adenosine A2A receptor by ciforadenant could induce ORR in refractory RCC patients pointing towards the importance of targeting the CD39-CD73-A2AR axis [12].
We here propose to randomize patients to cohorts treated with nivolumab alone, ipilimumab + nivolumab, and relatlimab + nivolumab, using an adaptive trial design. In the future other promising combinations can be added, whereas treatments arms with no or little activity can be stopped

Study objective

This study has been transitioned to CTIS with ID 2024-515514-40-00 check the CTIS register for the current data.

The primary objective is to investigate the rate of pathological responses following different neoadjuvant immunotherapy combinations in high-risk non-metastatic clear cell RCC in an adaptive trial design. And to study the safety and feasibility of neoadjuvant IO approach in high-risk non-metastatic clear cell renal cell cancer patients. To investigate the objective response rate according to RECIST 1.1
To assess EFS, RFS, rate of metastasis and local recurrence rate at 5 years after start of treatment and to investigate surgical morbidity according to Clavien Dindo classification.

Study design

This is an adaptive design, randomized controlled, open-label three-arm phase 2 trial (including a Simon stage 2 design) consisting of 60 intermediate to high-risk clear cell RCC patients randomized 1:1:1 to receive 2 courses nivolumab 360 mg q3wk (arm A), 2 courses ipilimumab 1 mg/kg + nivolumab 3 mg/kg q3wk (arm B), or 2 courses of nivolumab 360 mg + relatlimab 360 mg q3wks (arm C), prior to surgery at week 7 (23 patients per arm). After 42 patients (14 per arm) an interim analysis will be performed. Patients will be stratified according to treatment center.
After 27 patients (9 per arm) an interim analysis will be performed about the observed efficacy and toxicity within each arm, and based on this information, the study will be continued.

Intervention

Tumor nephrectomy at 7 weeks

Study burden and risks

Currently, there is no standard systemic adjuvant immunotherapy for RCC approved. In that way this trial offers an opportunity for the high relapse risk patient population. However, participation in this trial also sets the patients at high risk of developing immune related adverse events. Algorithms have been developed to treat patients developing irAEs. Recovery is commonly observed (except for endocrine irAE) and depends on the fast onset of the advised immunosuppression.
Systemic recurrences and overall survival could be improved by treatment with ipilimumab + nivolumab based on strong data in advanced clear cell RCC patients.

To ensure the safety of these patients, a data safety monitoring board will be installed

An interim analysis will be planned using a Simon two-stage approach within arms A, B and arm C separately with the focus on response rate and will be presented and discussed with the DSMB. In the first stage, 14 patients per arm, thus in total 42 patients, will be accrued. If there are 0-1 responses within the 14 patients per arm, then this arm will be closed. Otherwise, 9 additional patients will be accrued for a total of 23 patients.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Adults at least 18 years of age
• World Health Organization (WHO) Performance Status 0 or 1
• Histologically confirmed resectable clear cell RCC (measurable according to RECIST 1.1), that can be biopsied, and no history of distant metastases
• Intermediate to high risk will be based on clinical TNM and biopsy nuclear grade. These are:
1. cT1b-cT2a grade 4 cN0 cM0
2. cT2b grade 3-4 cN0 cM0
3. cT3 any grade cN0 cM0
4. cT4 any grade cN0 cM0
5. cT any cN1 (fully resectable) cM0

• No other malignancies, except adequately treated and a cancer-related life-expectancy of more than 5 years
• Patient willing to undergo triple tumor biopsies and extra blood withdrawal during screening and in case of relapse
• No prior immunotherapy targeting CTLA-4, PD-1 or PD-L1, or LAG-3
• No immunosuppressive medications within 2 weeks prior start immunotherapy
• Screening laboratory values must meet the following criteria: WBC >= 2.0x109/L, Neutrophils >=1.5x109/L, Platelets >=100 x109/L, Hemoglobin >=5.5 mmol/L, Creatinine <=1.5x ULN, AST <= 1.5 x ULN, ALT <= 1.5 x ULN, Bilirubin <=1.5 X ULN, normal CK and Troponin T, normal LDH
• Women of childbearing potential must use appropriate method(s) of contraception. They 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
• 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 study treatment
• Women who are not of childbearing potential (i.e., who are postmenopausal), or surgically sterile as well as azoospermic men do not require contraception
• Patient is capable of understanding and complying with the protocol requirements and has signed the Informed Consent document.

Exclusion criteria

• Distantly metastasized RCC • Brain metastases (based on symptoms) • Non-clear cell RCC • No measurable lesion according to RECIST 1.1 • Subjects with any active autoimmune disease or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy • Prior CTLA-4 or PD-1/PD-L1 or LAG-3 targeting immunotherapy • Radiotherapy prior or post-surgery • Patients will be excluded if they test positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody), indicating acute or chronic infection; if treated and being at least one year free from HCV patients are allowed to participate • Patients will be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) • Allergies and Adverse Drug Reactions (like mastocytosis) • History of severe hypersensitivity reaction to any monoclonal antibody • Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug(s) hazardous or obscure the interpretation of toxicity or adverse events; • Pregnant or nursing • Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids; • Use of other investigational drugs before study drug administration 30 days and 5 half-times before study inclusion Relatlimab-specific exclusion criteria • Participants with history of myocarditis, regardless of etiology. • Troponin T (TnT) > 2 × institutional ULN. Participants with TnT levels between > 1 to 2 × ULN will be permitted if a repeat levels within 24 hours are <= 1 ULN. If TnT levels are between >1 to 2 × ULN within 24 hours, the participant may undergo a cardiac consultation and be considered for treatment, following cardiologist recommendation. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT repeat levels beyond 24 hours are < 2 × ULN, the participant may undergo a cardiac consultation and be considered for treatment, following cardiologist recommendation. Notification of the decision to enroll the participant following cardiologist recommendation has to be made to the BMS Medical Monitor or designee. • Left ventricular ejection fraction (LVEF) assessment with documented LVEF < 50% by either transthoracic echocardiogram (TTE) or multigated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to start of study treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-04-2022
Enrollment:	46
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	relatlimab
Product type:	Medicine
Brand name:	Opdivo
Generic name:	nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	16-11-2021
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	25-11-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-07-2024
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-515514-40-00
EudraCT	EUCTR2021-002360-51-NL
ClinicalTrials.gov	NCT05148546
CCMO	NL77681.031.21