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Randomised study platform to optimize treatment in patients with metastatic renal cell carcinoma

Submission date 04/02/2025	**Recruitment status** Recruiting	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 28/03/2025	**Overall study status** Ongoing	
Last Edited 31/03/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Treating kidney cancer (renal cell carcinoma, RCC) uses two main types of drugs: 1. targeted therapies (anti-angiogenic drugs) that block signals that help tumors grow new blood vessels, like vascular endothelial growth factor tyrosine kinase inhibitors (VEGFR TKIs); and, 2. immunotherapies that boost the immune system by targeting proteins like Human programmed death-1/Human programmed death ligand-1 (PD1/PDL1) or Cytotoxic T-lymphocyte associated protein 4 (CTLA4). For clear cell RCC (a common type of RCC), combining these treatments is the standard approach. This study aims to determine if two immunotherapy drugs together (ICI-ICI) improve overall survival (OS) in PDL1-positive patients and if one immunotherapy drug with targeted therapy (ICI-VEGFR TKI) enhances both progression-free survival (PFS) and overall survival (OS) in PDL1-negative patients.

Who can participate?
Patients aged 18 years old and over with histologically confirmed metastatic RCC with a clear-cell component.

What does the study involve?
Doctors decide which combination to use, but there's no strong guidance from clinical tests or biomarkers yet. The only useful test so far is PDL1 staining, which helps predict which approach might work better:
- PDL1-positive patients often respond better to ICI-ICI.
- PDL1-negative patients tend to benefit more from ICI-VEGFR TKI.

What are the possible benefits and risks of participating?
No benefits provided at registration

Associated to procedures and clinical trial exams :
The participant may present events related to the trial's procedures: such as known risks linked to blood samples (risk of hematoma, pain or infection at the collection site), or to imaging examinations (anxiety, reaction to the injection product, etc.).

Associated with clinical trial treatment :
The effects of the medications in this trial are no different from the effects that are expected outside the trial and that have been explained to the participants by their doctor. Please note that there is no additional procedure compared to routine care. The risks of the procedures and the side effects of the treatments are therefore the same whether you take part in this trial or not.

New information on the clinical trial and the study treatment:
Not all of the risks associated with this clinical trial are necessarily known. The participant will be informed as soon as possible of any new information concerning their health or new data which could influence their desire to continue their participation in this clinical trial. If new information were to modify the information presented to the participant in this document, a new document would be given to them so that they are informed and so that they can confirm, or not, their wish to continue this clinical trial.

Where is the study run from?
Queen Mary University of London, UK

When is the study starting and how long is it expected to run for?
January 2025 to September 2029

Who is funding the study?
HORIZON EUROPE Programme

Who is the main contact?
bci-care1@qmul.ac.uk

Plain English summary under review with external organisation

Contact information

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Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1010455

ClinicalTrials.gov (NCT)
NCT06364631

Protocol serial number
CSET2023/3764

Study information

Scientific Title
CARE1: First-line randomised study platform to optimize treatment in patients with metastatic renal cell carcinoma

Acronym
CARE1

Study objectives
To compare the efficacy of immune checkpoint inhibitor combination (ICI-ICI) with nivolumab-ipilimumab (NIVO-IPI) versus ICI-VEGFR TKI combination in IMDC intermediate and poor risk patients with previously untreated mRCC based on PDL1 stratification. The efficacy will be compared in terms of overall survival for the PDL1(+) population and in terms of progression-free survival and overall survival (co-primary endpoints) for the PDL1(-) population.

- Progression-free survival based on Investigator assessments (using RECIST v1.1 criteria). NB: Progression-free survival is a co-primary endpoint in the PDL1- population
- Objective Response Rate (ORR) based on Investigator assessments (using RECIST v1.1 criteria) over the treatment period
- Quality of Life (assessed via EQ-5D-5L,NFKSI-19 and KSI questionnaires at baseline, M3, M6, M9 and M12)
- Time to treatment discontinuation
- Treatment-free survival
- Time to subsequent systemic anticancer therapy
- Safety

- Economic evaluation (France and the Netherlands only): To compare healthcare costs between arms; to determine the optimal combination strategy in each patient subgroup (PDL1 positive and PDL1 negative respectively).

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 27/03/2025, South Central - Berkshire B Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048276; berkshireb.rec@hra.nhs.uk), ref: 25/SC/0057

Study design
Randomized active-control open parallel-group study

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Metastatic renal cell carcinoma

Interventions
ARM A:
ICI-ICI Arm (Nivolumab + Ipilimumab):
1. Nivolumab (3 mg/kg IV, every 3 weeks for 4 doses), followed by Ipilimumab (1 mg/kg IV, every 3 weeks for 4 doses).
2. After 4 doses of both, if no major side effects or disease progression, Nivolumab continues as maintenance (240 mg every 2 weeks or 480 mg every 4 weeks) for up to 2 years.
3. Nivolumab is administered first, followed by Ipilimumab with a 30-minute gap.
4. All 4 doses of Nivolumab and Ipilimumab must be completed before Nivolumab monotherapy begins (except in cases of Ipilimumab-induced toxicity).
5. Follow-Up Activity: Every 12 weeks ± 14 days, up to 5 years from randomisation. Long-term survival Follow-Up: Every 12 weeks ± 14 days, up to 8 years from randomisation.

ARM B:
VEGFR-TKI-ICI Arm (Axitinib + Pembrolizumab):
1. Axitinib (5 mg oral, twice daily) combined with Pembrolizumab (200 mg IV every 3 weeks or 400 mg IV every 6 weeks) for up to 2 years.
2. Pembrolizumab is infused for about 30 minutes. Axitinib should be started on Cycle 1 Day 1 and in subsequent cycles, ideally with Pembrolizumab.
3. Follow-Up Activity: Every 12 weeks ± 14 days, up to 5 years from randomisation. Long-term survival Follow-Up: Every 12 weeks ± 14 days, up to 8 years from randomisation

VEGFR-TKI-ICI Arm (Cabozantinib + Nivolumab):
1. Cabozantinib (40 mg oral, once daily, away from meals) with Nivolumab (480 mg IV every 4 weeks or 240 mg every 2 weeks) for up to 2 years.
2. Nivolumab is infused for about 30 minutes (240 mg) or 60 minutes (480 mg). Cabozantinib is started on Cycle 1 Day 1 and in subsequent cycles, alongside the first dose of Nivolumab.

3. Follow-Up Activity: Every 12 weeks ± 14 days, up to 5 years from randomisation. Long-term survival Follow-Up: Every 12 weeks ± 14 days, up to 8 years from randomisation.

VEGFR-TKI-ICI Arm (Lenvatinib + Pembrolizumab):
1. Lenvatinib (20 mg oral, once daily) with Pembrolizumab (200 mg IV every 3 weeks or 400 mg IV every 6 weeks) for up to 2 years.
2. Pembrolizumab is infused for 30 minutes. Lenvatinib is started on Cycle 1 Day 1 and in subsequent cycles, alongside the first dose of Pembrolizumab.
3. Follow-Up Activity: Every 12 weeks ± 14 days, up to 5 years from randomisation. Long-term survival Follow-Up: Every 12 weeks ± 14 days, up to 8 years from randomisation

Randomisation:
Randomization Method: The permuted block randomization method will be used, with randomization performed by Interactive Response Technology (IRT). The randomization schedule will be created by the Sponsor or their designee.

Stratification Factors: Patients will be stratified based on two factors during screening:
1. PDL1 status (tumor cell positivity ≥1%).
2. IMDC prognostic score (risk factor classification):
2.1. Intermediate risk: 1-2 risk factors.
2.2. Poor risk: 3-6 risk factors.
2.3. IMDC risk factors include:
2.3.1. Karnofsky performance status <80%
2.3.2. Less than 1 year from RCC diagnosis to treatment
2.3.3. Hemoglobin < LLN
2.3.4. Corrected calcium >10 mg/dL
2.3.5. Absolute neutrophil count (ANC) > ULN
2.3.6. Platelet count > ULN

Recruitment and Target Numbers: Recruitment will stop once the target number of patients is met in each population (PDL+ or PDL1-)

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Nivolumab, ipilimumab, cabozantinib, pembrolizumab, axitinib, lenvatinib

Primary outcome(s)
1. Overall Survival (estimand 1), defined as the time from the date of randomization to the date of death due to any cause, measured using data collected in patient medical records.
2. The primary estimand of the study is a treatment policy estimand, which estimates the effect of randomised treatments (ICI-ICI versus VEGFR-TKI ICI) including the effects of treatment discontinuation for any reason and at any time, the effects of received additional or prohibited treatment (after randomization), measured using data collected in patient medical records.

Key secondary outcome(s))

1. Progression-Free Survival (estimand 2) is defined as the time from randomization to the date of progression (based on Investigator assessment using RECIST v1.1) or death, whichever occurs first. In the absence of progression or death, the data will be censored at the date of the last RECIST assessment.
2. Objective Response Rate (estimand 3) is defined as the percentage of randomised participants (ITT set) who achieve the best response of complete response (CR) or partial response (PR) over the treatment observation period based on Investigators assessments (using RECIST v1.1 criteria, as described in Appendix 3 of protocol). The observation period for the ORR will start at the date of randomization and end at the date of initiation of the next line of treatment or the date of last news if no next line is initiated.
3. Time to treatment discontinuation (estimand 4) is defined as the time from the date of treatment initiation to the date of the last treatment dose. This outcome will be calculated for the combination therapy and each molecule of the combination therapy.
4. Time to subsequent systemic therapy (estimand 6) is defined as the time from the date of randomization to the date of the next subsequent systemic therapy. The initiation of another treatment from the same class (e.g. another VEGFR-TKI) is considered as a subsequent systemic therapy.
5. Treatment-Free Survival (estimand 6) is defined as the date from protocol therapy cessation (whatever the reason) to the date of subsequent systemic therapy initiation or death.

Completion date
01/09/2029

Eligibility

Key inclusion criteria
1. Histologically confirmed metastatic (AJCC Stage IV) renal cell carcinoma with a clear-cell component.
2. Intermediate- or poor-risk mRCC as defined by IMDC classification.
3. Adult male or female patients (≥ 18 years of age at inclusion).
4. Karnofsky Performance Status (KPS) ≥70%.
5. Adequate organ and marrow function, according to investigator assessment and
5.1. Absolute neutrophil count (ANC) ≥ 1000/µL (≥ 1.5 GI/L)
5.2. Platelets ≥ 100,000/µL (≥ 100 GI/L)
5.3. Hemoglobin ≥ 8 g/dL (≥ 80 g/L)
5.4. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 x ULN.
5.5. Calculated creatinine clearance ≥ 30 mL/min (≥ 0.67 mL/sec) using the CKD- EPI equation
6. The patient should understand, sign, and date the written informed consent form prior to any protocol-specific procedures performed.
7. The patient should be able and willing to comply with study visits and procedures as per protocol
8. Patients must be affiliated with a social security system or beneficiaries of the same
9. Female patients must either be of non-reproductive potential or must have a negative serum pregnancy test within 14 days prior to the administration of the study drug. Childbearing potential women must have agreed to use one barrier method of contraception, such as a condom, plus an additional highly effective method of contraception during treatment on this trial and for up to 5 months after the last dose of study treatment.
10. Fertile men with a female partner of childbearing potential must agree to use one barrier method of contraception, such as a condom, during treatment on this trial and for up to 4 months after the last dose of treatment. Their women of childbearing potential partner must

agree to use a highly effective method of contraception during the same period.
11. Female subjects of childbearing potential must not be pregnant at screening.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Prior systemic anticancer therapy for mRCC including investigational agents.
Note: One prior systemic adjuvant therapy is allowed for completely resected RCC and if recurrence occurred at least 6 months after the last dose of adjuvant therapy.
2. Uncontrolled brain metastases (adequately treated with radiotherapy and/or radiosurgery prior to randomization are eligible). Subjects who are neurologically symptomatic as a result of their CNS metastasis or are receiving systemic corticosteroid treatment (prednisone equivalent > 10 mg/day) at the planned time of randomization are not eligible.
3. Concomitant oral anti-vitamin K anticoagulation. An exception is the use of LMWH or direct oral anticoagulants (DOAC), if considered safe by investigator assessment.
4. The subject has an uncontrolled, significant intercurrent or recent illness such as the following conditions:
4.1. Cardiovascular disorders:
4.1.1. Congestive heart failure (CHF) class III or IV as defined by the New York Heart Association, unstable angina pectoris, myocardial infarction, serious cardiac arrhythmias (e.g., ventricular flutter, ventricular fibrillation, Torsades de pointes).
4.1.2. Uncontrolled hypertension despite optimal antihypertensive treatment.
4.1.3. Stroke, or other symptomatic ischemic event or severe thromboembolic event (e.g., symptomatic pulmonary embolism [PE], incidental PE is acceptable if deemed safe by the investigator) within 3 months before randomization.
4.2. Active GI bleeding or symptomatic Gastrointestinal (GI) tract obstruction
4.3. Clinically significant bleeding including uncontrolled hematuria, hematemesis, or hemoptysis
4.4. Autoimmune disease that has been symptomatic or required immunosuppressive systemic treatment within the past two years from the date of randomization.
Note: Patients with a history of Crohn’s disease or ulcerative colitis are always excluded
4.5. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization.
Note: Inhaled, intranasal, intra-articular, or topical steroids are permitted. Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted. Transient short-term use of systemic corticosteroids for allergic conditions (e.g., contrast allergy) is also allowed.
4.6. Active infection requiring systemic treatment.
4.7. Major surgery (e.g., nephrectomy, GI surgery, removal of brain metastasis) within 4 weeks

prior to randomization or serious non-healing wound/ulcer/bone fracture.
5. Pregnant or breastfeeding females.
6. Any other active malignancy at the time of randomization or diagnosis of another malignancy within 3 years prior to randomization that requires active treatment, except for locally curable cancers that have been apparently cured.
7. Hypersensitivity to any of the active substances or to any of the excipients administered during the study
8. Use of live vaccines within 28 days before randomization
9. Persons deprived of their freedom or under guardianship, or for whom it would be impossible to undergo the medical follow-up required by the trial, for geographic, social or psychological reasons.

Date of first enrolment
11/04/2024

Date of final enrolment
31/03/2027

Locations

Countries of recruitment
United Kingdom

England

Austria

France

Germany

Italy

Netherlands

Spain

Study participating centre
Queen Mary University of London
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E1 4NS

Study participating centre

Churchill Hospital
The Oxford Cancer & Haematology Centre, Roosevelt Dr
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Mount Vernon Cancer Centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Institut Gustave Roussy

ROR
https://ror.org/0321g0743

Funder(s)

Funder type
Government

Funder Name
HORIZON EUROPE Framework Programme

Alternative Name(s)
Horizon Europe, Horizon Europe Programme, Framework Programme, Horizon Europe, EU Framework Programme, Horizon

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The decision to share individual participant data (IDP) has not yet been made. Data sharing feasibility will be evaluated after study completion, considering ethical, regulatory, and logistical factors

Investigator hereby expressly consents to the processing of pseudo-anonymised data collected by the Sponsor. Such consent shall authorize the transfer of pseudo-anonymised data to countries other than the Institution's own country, for the following purposes:
1. The conduct and interpretation of the Clinical Trial
2. Review by governmental or regulatory agencies, Sponsor, and its agents, affiliates and collaborators
3. Satisfying legal or regulatory requirements
4. Publication on national and international public websites and other websites and databases that serve a comparable purpose
5. Upon request of individual patients and doctors provision to individual patients and doctors who may be interested in participating in a clinical trial at the Institution
6. Storage in Sponsor’s databases to select sites in future clinical trials

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes