UroCCR
RÉSEAU FRANÇAIS DE RECHERCHE SUR LE CANCER DU REIN

Fiche de soumission de projet au Comité Scientifique et Ethique

TITRE DU PROJET : Retrospective study assessing the efficacy of systemic therapies in metastatic non-clear cell renal carcinoma
Titre abrégé : Efficacy of First-Line systemic therapies in NCCRC
Acronyme : Study m**E**tastatic **NO**n-clea**R** carcinoma (**SENOR)**
UroCCR n°240

PROMOTEUR / RESPONSABLE DE TRAITEMENT :

☑ ACADEMIQUE ❒ INDUSTRIEL

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PROJET

❒ PROSPECTIF ☑ RETROSPECTIF

Date de début des inclusions : depuis le début de la base UroCCR
Date de fin des inclusions : 03/02/2025
Période d'étude : Depuis le début de la base UroCCR

Partenaires (équipes) associés au projet : oui
National : Centres UroCCR
International :

DESCRIPTION / JUSTIFICATION SCIENTIFIQUE DU PROJET

Contexte : Non-clear cell RCC (NCCRC), which represents around 25% of all renal cell cancers (RCC), encompasses a variety of subtypes, including papillary, chromophobe, and collecting duct carcinomas (1). These subtypes exhibit diverse clinical presentations (e.g., age at diagnosis) and molecular characteristics, leading to varying levels of disease aggressiveness (2). Despite advancements in treatment options, optimal therapeutic strategies for these patients remain poorly defined, particularly in the context of metastatic disease.
The publication of the PAPMET trial has highlighted the role of cabozantinib as a first-line treatment for metastatic papillary RCC, with subsequent ESMO guidelines recommending its use in this context (3). Similarly, axitinib has shown promising activity in papillary RCC (AXIPAP) with an objective response rate (ORR) of 28.6% (4).
For collecting duct carcinomas, cabozantinib demonstrated a 35% ORR and a median progression-free survival (PFS) of 6 months in the BONZAI trial (5). In chromophobe RCC, sunitinib has shown efficacy with an ORR of 13% and a median overall survival (OS) of 17.8 months in the SUPAP trial (6). The phase 2 COMBOS trial demonstrated the efficacy of lenvatinib in combination with everolimus, achieving an ORR of 44% (7).
Immunotherapy has also been explored in NCCRC through various clinical trials (Keynote-427, Checkmate-374, Checkmate-920), with response rates ranging from 13.6% to 26.7% (8-10). The SUNIFORECAST phase II trial evaluated the combination of ipilimumab and nivolumab as a first-line treatment for NCCRC, showing a 12-month OS rate of 86.9% in the immunotherapy arm compared to 76.8% in the standard of care arm, with an ORR of 32.8% versus 19.8% (11).
Additionally, combinations of immunotherapy and tyrosine kinase inhibitors (TKIs) have shown promising results in NCCRC (COMBOS studies), with ORRs between 31% and 49.4% (12, 13). Ongoing trials (PAPMET 2, SAMETA, STELLAR-304) are evaluating further combinations of immunotherapy and TKIs in RCC (14-16).
The aim of this retrospective study is to evaluate efficacy of first-line systemic treatments used for locally advanced and metastatic NCCRC and to assess the efficacy of immunotherapy compared to TKIs alone in these patients, across different NCCRC subtypes.

Objectifs Principal :
To identify clinical, biological, and histopathological factors associated with response to first-line systemic therapies (where response is defined as time to treatment failure (TTF)) in patients with advanced or metastatic nccRCC

Objectifs Secondaires :
(1) To compare the efficacy of different systemic approaches (TKI, immunotherapy, or combination) according to histological subtypes of nccRCC.

(2) To assess the objective response rate (ORR) when available according to RECIST v1.1.

(3) To identify prognostic and ~~predictive~~ factors associated with progression-free survival (PFS) and overall survival (OS) (IMDC score, histopathological subtypes, age, sex, performance status, and laboratory parameters).

(4) To explore molecular biomarkers associated with treatment outcomes (TTF, PFS, ORR, and OS) using multi-omics profiling.

Critères de jugement principal:
TTF = time from initiation of first-line systemic therapy to permanent treatment discontinuation for any reason (progression, toxicity, or death).
Patients still receiving treatment at the last available follow-up will be censored at the date of last contact.

Critères de jugement secondaire:
(1) Progression-free survival (PFS), Overall survival (OS). These outcomes will be compared across histological subtypes and type of systemic therapy.
→ PFS = time from initiation of first-line systemic therapy to disease progression or death from any cause.
→ OS = time from initiation of first-line systemic therapy to death from any cause.

(2) Overall response rate (ORR) according to RECIST v1.1 when available.

(3) Associations between baseline clinical, biological, and histopathological factors and treatment outcomes, defined as progression-free survival (PFS) and overall survival (OS)
(4) Associations between biological markers and treatment outcomes, defined TTF, PFS, ORR and OS.

Hypothèse :
Response to systemic therapies in NCCRC varies according to histopathological subtypes and clinical prognostic features (including IMDC criteria). Identifying predictive factors of response may help refine therapeutic strategies in this heterogeneous population.

Critères d'inclusion :
Patients are eligible for the study if they meet all of the following criteria :
- Age ≥18 years
- Locally advanced or metastatic NCCRC
- All patients initiating a first-line systemic therapy with ICI based treatment will be included, regardless of treatment discontinuation or early stop.

Critères d'exclusion :
- Patient's refusal to participate

Analyses statistiques :
Qualitative data will be described by their frequency, percentage and 95% confidence interval. Quantitative data will be described by their mean and standard deviation or median and interquartile range. The number of missing data will be presented.

Patients were followed until death or the data censorship date.

Principal : Kaplan-Meier curves to estimate TTF ; Cox proportional hazards models to identify factors associatied with TTF ; Hazard ratios (HRs) with 95% confidence intervals (CI95%) for each factor.

Secondaries :
(1) Kaplan–Meier curves to estimate PFS et OS by treatment group across histological subtypes; Log-rank test for (pairwise) comparisons ; Adjusted Cox models if necessary for confounding variables ; HRs (95% CI)
(2) Proportion of responders (CR + PR) between treatment groups and histological subtypes ; chi-² or Fisher exact test for subgroup comparisons; 95% CI for proportions.
(3) Kaplan-Meir curves to estimate PFS and OS per factor (baseline clinical, biological, histopathological factors) ; Cox proportional hazards models to identify independent prognostic factors; Multivariate analysis to adjust for confounding variables ; HRs (95% CI) .
(4) Univariate analysis : Cox models for time-to-event endpoints, logistic regression for ORR ; Multivariate exploratory analysis if population size allows ; Multiple testing correction (Bonferroni or FDR) ; descriptive analysis/visualization for multi-omics data

Résultats attendus :
- Identification of various response rate of TKI and/or ICI according to nccRCC subtype
- Validate the prognosis role of IMDC criteria in all histopathological subtypes
- Identify of novel biomarkers associated with response to TKI and/or immunotherapy

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DONNEES CLINIQUES ET RESSOURCES BIOLOGIQUES :

Description des données nécessaires :

Sociodemographic data, Performance Status, IMDC score,
Age and stage at diagnosis of NCCRC and baseline RCC characteristics
Details on metastatic treatments until third-line if available including type of treatment used, response rate, progression-free survival, duration and reason for cessation of therapy.
Overall survival data
Cause of death
For patients not enrolled in clinical trials, central histological review will be performed when available to confirm the non-clear cell subtype.

Recours données chaînées au SNDS (UroCCR-Chain) : ❒ OUI ☑ NON

Le projet a-t-il des besoins en ressources biologiques ? : ☑ OUI ❑ NON

The project will begin by clinical characterization of the whole cohort as planned. We will then select subset of samples for which material is available and treated for first-line setting by immunotherapy +/- TKI for multi-omics analysis.

*** Type : FFPE samples**
*** Quantité : 1 block in tumor front and 1 block in central tumor**
*** Autres précisions :**
*** Données associées :**

INCLUSION DES CENTRES PARTICIPANTS

Un nombre minimum de patients par centre est-il requis pour être inclus dans cette étude ? ❒ OUI ☑ NON
Si oui lequel ? :

Quelle est la donnée UroCCR indispensable à renseigner par les centres participants pour cette étude ?
All participating UroCCR centers will be contacted to retrospectively identify eligible patients, including deceased ones not yet entered in the UroCCR database, to strengthen sample size and representativeness.
A feasibility assessment will be conducted to evaluate potential linkage with SNDS data through the Health Data Hub (HDH) infrastructure.

CALENDRIER

Soumission au Comité Scientifique et Ethique UroCCR : November 2025

Sollicitations des centres : February 2026

Date recueil des données/Queries : May 2026 for clinical part

Dates statistiques faites : July-August 2026 for clinical part.
For translational part, the study will be done when the contract is finalized and the samples centralized for molecular profiling.

Soumission abstract congres : ASCO GU 2027 (deadline September 2026)

Article soumis : 2027

Revue ciblée : Non connue

Cadre réservé à l'équipe coordinatrice UroCCR (ou UroCCR-Chain si données chainées)

_____ Faisabilité et Evaluation scientifique et éthique _____

Disponibilité des données :

Date : décembre 2024 Oui : ☑ Non : ❒
Effectifs : 1530 patients (sous réserve de la validation de l'éligibilité par les centres participants)

Disponibilité des ressources biologiques dans la biocollection virtuelle :

Date : Oui : ❒ Non : ❒ NA : ☑
Commentaires :

AVIS DU COMITÉ SCIENTIFIQUE ET ETHIQUE :
Date : 09/03/2026
Evaluation du projet :
Positive : ☑ Négative : ☐