UroCCR
RÉSEAU FRANÇAIS DE RECHERCHE SUR LE CANCER DU REIN

Fiche de soumission de projet au Comité Scientifique et Ethique

TITRE DU PROJET : Transcriptomic Analysis of advanced renal cell carcinoma to identify Key genomic signatures predicting clinical response to next-generation anti-VEGFR Therapy and dual Immune Checkpoint inhibition
Acronyme : **TAKTIC**
UroCCR n°269

PROMOTEUR / RESPONSABLE DE TRAITEMENT :

☑ ACADEMIQUE ❒ INDUSTRIEL

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PROJET

☑ RETROSPECTIF ❒ PROSPECTIF

Date de début des inclusions : NA
Date de fin des inclusions : NA
Période d'étude : 2018 à aujourd'hui

Partenaires (équipes) associés au projet : oui
National : IntegraGen
International : -

DESCRIPTION / JUSTIFICATION SCIENTIFIQUE DU PROJET

Contexte :
Management of clear cell renal cell carcinoma (ccRCC) has been revolutionized in recent years by the introduction of new-generation VEGFR tyrosine kinase inhibitors (TKIs) and immunotherapy (IO) targeting PD1/PDL1 and CTLA4. Current standard of care in the first-line metastatic or advanced setting is based on either dual IO with nivolumab + ipilimumab, following the results of the CheckMate-214 trial that demonstrated an improvement in overall survival compared with sunitinib, or a combination of TKI + IO. Three TKI+IO combinations have received first-line approval: axitinib–pembrolizumab (KEYNOTE-426), cabozantinib–nivolumab (CheckMate-9ER), and lenvatinib–pembrolizumab (CLEAR). All of these regimens were compared to sunitinib in the respective clinical trials, but no head-to-head comparison has been conducted between these four therapeutic options. While all patients will receive an IO agent (nivolumab or pembrolizumab), the choice of combination with ipilimumab or a TKI is left to the physician in the absence of validated predictive biomarkers.

Bulk RNA sequencing performed by Beuselink et al. in 2015 identified four molecular subtypes of ccRCC (ccRCC1–4), each with distinct sensitivity to sunitinib and distinct immune and angiogenesis-related signatures. The BIONIKK clinical trial demonstrated the feasibility of using these molecular signatures to guide treatment choice between sunitinib and IO in a prospective setting, showing potential clinical applicability, though statistical significance was not reached, this was likely due to limited patient numbers.

In parallel, Motzer et al. extended this classification by performing transcriptomic profiling of 823 patients from the IMmotion151 trial, which compared atezolizumab (anti-PDL1 antibody) + bevacizumab (anti-VEGF antibody) versus sunitinib. Their analysis identified seven molecular subgroups instead of four. Patients in clusters 1 and 2, characterized by strong angiogenic signatures, had better prognosis for atezolizumab + bevacizumab and sunitinib, with no significant difference in progression-free survival (PFS) between the two regimens. Most patients in those groups had a favorable IMDC prognosis. In contrast, clusters 4 and 5, defined by low angiogenesis but strong immune or cell-cycle signatures, showed poorer outcomes under sunitinib. In these subsets, atezolizumab + bevacizumab significantly improved objective response rates and PFS compared with sunitinib.

These seven molecular profiles were re-employed in 2024 by Saliby et al. to classify patients from the JAVELIN Renal 101 trial, which tested axitinib + avelumab (anti PDL1 antibody) versus sunitinib. In this trial, axitinib + avelumab tended to improve patient outcomes across all molecular subtypes9. Despite validation of the 7 ccRCC subtypes, this study was unable to demonstrate predictive value of those signatures for selecting TKI+IO versus TKI alone.

Despite the large number of patients analyzed, these studies have limitations: Sunitinib was consistently used as the comparator arm, yet it is no longer recommended as first-line therapy, having been replaced by new-generation TKIs. Moreover, current treatment decisions are made between IO-IO and TKI-IO, rather than between TKI and TKI-IO, limiting the applicability of these findings to present-day clinical practice.

In clinical practice, some patients present durable responses to IO-IO, while others show primary resistance (around 20%) and would potentially have benefited more from first-line TKI-IO, which generally induces higher response rates. This highlights a strong unmet need to identify predictive biomarkers to guide treatment choice between IO-IO and TKI-IO in the first-line setting, to avoid loss of therapeutic opportunity in IO refractory patients.

In practice, patients with metastatic ccRCC who received IO-IO as first-line therapy could be classified into three groups :
- Group 1: sensitive to IO-IO (treatment duration more than 12 months, according to Checkmate 214 trial) but resistant to subsequent TKI (progression within 6 months)
- Group 2: resistant to IO-IO (progression within 6 months) but sensitive to subsequent TKI (treatment duration more than 12 months, according to the CABOPOINT study)
- Group 3: resistant to both IO-IO and subsequent TKI

Objectifs Principal :

The objective of our study is to identify predictive signatures of response to IO-IO and to next-generation TKIs in ccRCC, through tumor bulk RNA sequencing of a patient cohort, to support personalized selection of optimal therapeutic combinations.

Objectifs Secondaires :
Identify a specific transcriptomic signature for group 2.

Critères de jugement :
PFS (IO-IO) and PFS (TKI).

Hypothèse :
Patients in Group 2 would likely have benefited from first-line IO-TKI instead of IO-IO, given their sensitivity profile: we expect to identify a transcriptomic signature able to identify this patient population among others.

Critères d'inclusion :
Age > 18 years;
Patients with metastatic ccRCC who received 1st line IO-IO therapy, and a subsequent line with new generation TKI.

Critères d'exclusion :
Patients treated for a second neoplasia in parallel.

Analyses statistiques :
Survival curves will be estimated using the Kaplan–Meier method, compared using the log-rank test, and assessed in multivariate analysis using Cox regression.
Transcriptomic analysis: Bulk RNA sequencing (Illumina, total RNAseq) will be performed on FFPE archival tissue from 40 patients (13-14 patients from each group), in collaboration with the French Integragen plaform. After mapping and quality control, differential expression analysis will be carried out between groups in collaboration with the bioinformatics unit of Bordeaux University Hospital, using the R software (DESeq2 package). We will also assess expression of the seven ccRCC molecular subtypes described by Motzer et al. in our cohort, using enrichment analysis methods such as GSVA or ssGSEA.

Résultats attendus :
We aim to identify transcriptomic signatures associated with each patient group, particularly for group 2 as such signatures could guide this population towards first-line TKI-IO rather than IO-IO. Predictive signatures of sensitivity or resistance to IO-IO and TKI will initially be validated against published datasets (e.g., TCGA or JAVELIN Renal 101). If a signature emerges from the group 2, it could be further validated in an independent cohort of patients from Bordeaux University hospital, who received first-line TKI-IO.
A key strength of our study is that we have both IO-IO and subsequent TKI sensitivity profiles for each patient—an element lacking in previous transcriptomic studies where subsequent line sensitivity was not considered. This approach limits inter-individual heterogeneity and enables optimal patient selection.

Bibliographie :
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Rini, B. I. et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N. Engl. J. Med. 380, 1116–1127 (2019).

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Beuselinck, B. et al. Molecular subtypes of clear cell renal cell carcinoma are associated with sunitinib response in the metastatic setting. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 21, 1329–1339 (2015).

Vano, Y.-A. et al. Nivolumab, nivolumab-ipilimumab, and VEGFR-tyrosine kinase inhibitors as first-line treatment for metastatic clear-cell renal cell carcinoma (BIONIKK): a biomarker-driven, open-label, non-comparative, randomised, phase 2 trial. Lancet Oncol. 23, 612–624 (2022).

Motzer, R. J. et al. Molecular Subsets in Renal Cancer Determine Outcome to Checkpoint and Angiogenesis Blockade. Cancer Cell 38, 803-817.e4 (2020).

Saliby, R. M. et al. Impact of renal cell carcinoma molecular subtypes on immunotherapy and targeted therapy outcomes. Cancer Cell 42, 732–735 (2024).

DONNEES CLINIQUES ET RESSOURCES BIOLOGIQUES :

Description des données nécessaires :
Age au diagnostic, type histologique, sites métastatiques au diagnostic, dates de début et fin de traitement par IO-IO, date de progression sous IO-IO, meilleure réponse obtenue sous IO-IO, sites en progression au moment de la progression, date de début de la 2nde ligne par TKI, nom du traitement par TKI, date de fin de traitement par TKI, meilleure réponse sous TKI.

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

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

*** Type : blocs FFPE de tissus tumoraux pré-ttt IO-IO**
*** Quantité : 1 bloc par patient**
*** Autres précisions :**

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 ? :

CALENDRIER

Soumission Comité Scientifique et Ethique UroCCR : 12/2025

Revue des données : 01/2026

Cession des échantillons : 02/2026

Analyses statistiques : 03/2026

Soumission abstract congres : à définir

Article soumis : à définir

Revue ciblée : à définir

Le projet a-t-il déjà bénéficié d'une évaluation scientifique positive ?

☑ OUI (joindre la copie) ❒ NON
Date : Septembre 2025
Par qui (citer l'institution évaluatrice et fournir la copie des expertises) : Obtention d'une bourse de recherche GETUG-EISAI, avis favorable du comité éthique du CHU de Bordeaux.

Cadre réservé à l'équipe coordinatrice UroCCR (ou UroCCR-Chain si données chainées)
_____ Faisabilité et Evaluation scientifique et éthique _____

Disponibilité des données :

Date : 02/12/2025 Oui : ☑ Non : ☐
Effectifs : 63 patients éligibles (sous réserve de la validation des critères d'inclusion)

Disponibilité des ressources biologiques dans la biocollection virtuelle :

Date : Oui : ☐ Non : ☐ NA : ☑
Commentaires :

AVIS DU COMITÉ SCIENTIFIQUE ET ETHIQUE :
Date : 02/12/2025
Evaluation du projet :
Positif : ☑ Négative : ☐