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Original Research

# Addressing the best treatment for non-clear cell renal cell carcinoma: A meta-analysis of randomised clinical trials comparing VEGFR-TKis versus mTORi-targeted therapies

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Everolimus

**Abstract** ***Aim:*** Non-clear cell renal cell carcinoma (nccRCC) tumours include a heterogeneous group of malignancies that profoundly differ in terms of morphology, genetic profile, clinical behaviour and prognosis. The optimal treatment algorithm for nccRCC is still unknown and derived mainly from evidence available for ccRCC, being therefore represented by targeted agents against vascular endothelial growth factor and mammalian target of rapamycin (mTOR) pathways.

We aimed to compare the efficacy of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKis) and mTOR inhibitors (mTORi) for the treatment of nccRCC patients.

***Methods:*** Searching the MEDLINE/PubMed, Cochrane Library and American Society of Clinical Oncology Meeting abstracts prospective studies were identified. Data extraction was conduced according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

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The measured outcomes were progression-free survival (PFS), overall survival (OS) and the overall response rate (ORR).

***Results:*** Four randomised controlled trials were selected for final analysis, with a total of 332 patients evaluable for PFS. Treatment with TKi significantly reduced the risk of progression compared with mTORi (hazard ratio [HR] = 0.71; 95% confidence interval [CI] 0.60–0.84; $p < 0.0001$). This difference remained significant when sunitinib was compared with everolimus in first-line setting (HR = 0.67; 95% CI, 0.56–0.80; $p < 0.00001$). In the 332 patients evaluable for OS, no significant difference was found between TKi and mTORi (HR = 0.86; 95% CI, 0.67–1.12; $p = 0.27$). In the 176 evaluable patients, TKis therapy did not improve the ORR when compared with mTORi (relative risk [RR] = 2.21; 95% CI, 0.87–5.60; $p = 0.09$), even if treatment with sunitinib doubled the probability of achieving a tumour response.

***Conclusions:*** Treatment with TKis significantly improves PFS, but not OS, when compared with mTORi. Moreover, sunitinib as first-line therapy reduces the risk of progression compared with everolimus; therefore, supporting the standard treatment paradigm broadly used for ccRCC patients. The relatively modest efficacy of available targeted therapies reinforces the need of future histology based, molecular driven therapeutic paradigm.


## 1. Introduction

Renal cell carcinoma (RCC) represents the most frequent renal epithelial tumour (approximately 85%). Clinicians generally classify RCC based on tumour histology, distinguishing the predominant ccRCC histotype (which accounts singly for about 70–85% of RCC cases) from all the other RCC subtypes, which are collectively grouped as non-clear cell RCC (nccRCC). The heterogeneous container of nccRCC includes a mixture of malignancies that profoundly differ in terms of morphology, immunohistochemical features, genetic profile, clinical behaviour and prognosis. Among nccRCC, papillary RCC (pRCC, 10–15% of RCC) and chromophobe RCC (chRCC, 4–5%) are listed as the most common histotypes [1–3]. In terms of prognosis, although targeted agents have considerably improved nccRCC patients' outcome, the survival of nccRCC patients is significantly inferior compared with ccRCC patients [4].

nccRCC patients are generally excluded or underrepresented in pivotal randomised clinical trials (RCTs) testing vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKis) and mTOR-inhibitors (mTORi) in the ccRCC population. Clinical data supporting the efficacy of targeted agents in nccRCC are limited and based mainly on retrospective analyses, expanded access programs (EAPs) and single-arm phase II trials. Therefore, the optimal treatment algorithm for nccRCC remains uncertain and is mainly borrowed from evidence available for ccRCC [5].

Recently, a systematic review comparing clinical outcomes of nccRCC patients enrolled in pivotal RCTs with the ccRCC population included in the same trials showed a significant less efficacy of systemic treatments for nccRCC with lower response rates and worse median progression-free survival (mPFS) and overall survival (OS) [6]. However, defining the relative benefits and detriments of each agent in the nccRCC population remains unclear. A substantial contribution comes from the results of two prospective phase II randomised trials (ESPN and ASPEN) enrolling only nccRCC patients and comparing the activity of VEGFR-targeted therapy (sunitinib) with the mTOR-inhibitor everolimus [7,8]. Both studies showed a prolonged PFS for first-line sunitinib (mPFS 8.3 versus 5.6 months and 6.1 versus 4.1 months in the ASPEN and ESPN trials, respectively), albeit both agents demonstrated modest efficacy, underlining the need for identifying the optimum treatment in nccRCC. Therefore, first-line treatment with anti-VEGFR is, at present, the most recommended option, and sunitinib has the largest evidence compared to other TKis (even if statistics supporting this statement are not yet entirely reliable) [9].

In the present study, we perform a systematic review and meta-analysis of the available data to investigate the antitumour efficacy of VEGFR-TKis compared with mTORi in the treatment of nccRCC.

## 2. Patients and methods

### 2.1. Definition of outcomes

For each trial, treatment with mTORi (everolimus and temsirolimus) was considered as the control therapy, whereas VEGFR-TKi therapy (sunitinib or sorafenib) as the experimental one. OS and PFS were evaluated in the experimental arm over the control arm based on the hazard ratios (HRs) and relative 95% confidence intervals (CIs) set out in selected studies. Results were reported for the entire cohort and for patients treated in