doi.org/10.58931/cot.2025.2343

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Current Issues in the Management of Sporadic Non-clear Cell Renal Cell Carcinoma (Non-ccRCC)

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Introduction

Renal cell carcinoma (RCC) is the 10th most common cancer type in Canada. Numerous developments in the management of RCC over the last decade have led to improved outcomes, though these have mostly focused on the ~80% of patients with clear cell renal cell carcinoma (ccRCC). The remaining 20% of cases are labelled non-clear cell renal cell carcinoma (non-ccRCC) and represent a biologically and clinically heterogeneous group of diseases that are rare entities.[1] Historically, non-ccRCC has been managed similarly to clear cell tumours. Localized non-ccRCC has better outcomes than ccRCC[2]; however, survival of metastatic non-ccRCC is inferior to ccRCC (median overall survival [OS] of metastatic non-ccRCC reported as 39.2 months compared to 81.1 months for ccRCC).[3]

This has led to interest within the RCC scientific and patient communities to further improve outcomes for patients with non-ccRCC. This article describes the current management of patients with non-ccRCC and discusses future areas of interest in the field.

Molecular Classification of Non-clear Cell RCC

Non-ccRCC represents a group of rare, distinct diseases with differing characteristics, as reflected by the World Health Organization (WHO) Classification of Renal Tumors published in 2022.[4] The WHO has separated non-ccRCC into 6 distinct groups: papillary renal cell carcinoma, oncocytic and chromophobe renal tumours, collecting duct carcinoma, other renal tumours, and molecularly defined tumours.[5] Molecularly defined tumours comprise 11 subtypes, including *TFE3-3*-rearranged RCC, *TFEB*-altered RCC, *ELOC*-mutated RCC and fumarate hydratase-deficient RCC. The most common subtypes of non-ccRCC are papillary RCC (10–15%), chromophobe RCC (5%), and collecting duct (1%), medullary (1%), and translocation-associated tumours (1-4%).[3] Papillary RCC are associated with *MET* alterations, chromophobe RCC are associated with *TP53*, *PTEN*, and *TERT* alterations. Some non-ccRCC subtypes have a worse prognosis, such as *SMARCB1*-deficient medullary RCC or collecting duct RCC.[1]

The evidence base for management of specific tumours is limited due to a paucity of trial data. Therefore, these represent orphan tumours, and patients with these tumours would be best managed either within large-volume centres or within clinical trials.

Oncological Management of Early Non-ccRCC

Less than 2%[6] of patients have metastatic disease at diagnosis; however, 20–40% of patients recur after surgical excision. Recurrence is most likely after the first 5 years and can be predicted using the International Metastatic RCC Database Consortium (IMDC) Risk Stratification criteria for metastatic disease. The IMDC Risk Stratification has been validated in papillary and chromophobe carcinomas.

To reduce the risk of relapse, pembrolizumab is licensed in the adjuvant setting for patients at high risk of recurrence (including patients with pT4 tumours, lymph node involvement, high-grade tumours, and the presence of sarcomatoid lesions). Data from the KEYNOTE-564 trial[7], which included only patients with cc-RCC, demonstrated an improvement in 48-month OS from 86% in the placebo group to 91.2% in the pembrolizumab group (p=0.005). Uptake of pembrolizumab in Canada is limited to patients with ccRCC due to a lack of data and federal funding for the use of pembrolizumab in non-ccRCC.

The EVEREST trial included a subgroup of non-ccRCC (109 patients with papillary RCC and 99 with chromophobe RCC) at high risk of relapse following nephrectomy.[8] This trial evaluated everolimus versus placebo and did not detect an improvement in recurrence-free survival (RFS) or OS in non-ccRCC. There were unsurprisingly significantly higher levels of grade 3 toxicity with everolimus vs. placebo. Thus, everolimus is not recommended in the adjuvant setting for non-ccRCC.

The PROSPER-RCC trial included a cohort of patients with non-ccRCC and evaluated neoadjuvant nivolumab with surveillance alone.[9] The trial was curtailed early for futility, indicating there is no data supporting adjuvant nivolumab in non-ccRCC.

Despite the licensing of pembrolizumab in all RCC subgroups with intermediate or high risk of relapse, the role of pembrolizumab in non cc-RCC remains unclear. This is therefore an area for research and clinical trials. These datasets have led some to believe that adjuvant treatment in non-ccRCC is a data desert and that adjuvant treatment should not be offered to patients with non-ccRCC outside of a clinical trial.[1]

Management of Metastatic RCC

Much of the data regarding the management of non-ccRCC is derived from trials that predominantly evaluated ccRCC. The PAPMET trial, which included Canadian sites through the Canadian Cancer Trials Group (CCTG), evaluated tyrosine kinase inhibitors (TKI) in papillary RCC.[10] Papillary RCC are associated with upregulated *MET* signalling and thus TKI are of interest. Patients from Canada and the US with papillary RCC were randomized to receive either sunitinib as standard of care or cabozantinib, crizotinib, or savolitinib. Progression-free survival (PFS) was the primary outcome measure, and the savolitinib and crizotinib arms were closed early due to pre-defined futility. PFS was significantly higher in the cabozantinib group (9 months) than in the sunitinib group (5.6 months). Updated survival analysis from PAPMET indicated no significant increase in survival for those treated with cabozantinib compared with sunitinib.[11] However, this trial provides the only randomized data for treatment options in papillary RCC.

KEYNOTE-B61 was a single-arm trial in non-ccRCC evaluating lenvatinib and pembrolizumab in 158 patients.[12] This trial demonstrated a 49% objective response rate (ORR), a 12-month PFS of 63%, and an OS of 82%. Recently published 2-year follow-up data demonstrated a 51% ORR, with 13 patients having a complete response and 67% a partial response. The duration of response was 19.5 months across all subtypes.[13] Toxicity was as expected from immunotherapy and TKI combinations. The results were consistent across different histologies and with other trials involving checkpoint inhibitors. For example, KEYNOTE-427 evaluated single-agent pembrolizumab in 3 weekly doses for up to 24 months in non-ccRCC.[14] This trial demonstrated an ORR of 26.7%, and 59.7% of patients had a duration of response that lasted more than 12 months. The median PFS was 4.2 months, and the median OS was 28.9 months.

A single-centre study from Memorial Sloan Kettering evaluated 47 patients with non-ccRCC who were treated with nivolumab and cabozantinib.[15] This combination treatment was associated with an ORR of 47% in the

Subtype	Type of Treatment	Potential options
Papillary	• Targeted treatment • mTOR inhibitors • Immunotherapy • Combination strategies	• cabozantinib, savotinib, • everolimus, temsirolimus • pembrolizumab, nivolumab • pembrolizumab + axitinib, nivolumab + cabozantinib, nivolumab + ipilumumab, lenvatinib + pembrolizumab • erlotonib and Bevacizumab in non-FH deficient papillary RCC
Chromophobe	• Targeted treatment • mTOR inhibition • Combination strategies	• Sunitinib • everolimus, temsirolimus • pembrolizumab + axitinib, nivolumab + Cabozantinib
Collecting duct tumours	• Chemotherapy	• gemcitabine + cisplatin/carboplatin, paclitaxel + carboplatin
***SMARCB1*-deficient renal medullary carcinoma**	• Chemotherapy	• Platinum-based chemotherapy

Table 1. Management Options in non-ccRCC based on subtype; *summarized from Nepali et al.*[28]

cohort, including papillary RCC, unclassified, or translocation-associated RCC. In the cohort consisting of patients with chromophobe RCC, no responses were identified. This indicates a differential response dependent on histology. A cohort of patients with non-ccRCC treated with ipilimumab and pembrolizumab was evaluated as part of the CheckMate 920 trial,[16] and no new safety signals were identified. Fifty-two patients were evaluated, of whom 42.3% had unclassified histology, 34.6% papillary, 13.5% chromophobe, 3.8% translocation-associated, 3.8% collecting duct, and 1.9% renal medullary tumours. The ORR in this cohort was 19.6%, with a 12-month PFS of 22.7%. Recently, the DRON1 retrospective multicentre study evaluated immunotherapy and checkpoint inhibitor combinations in 56 centres in 17 countries. This study evaluated lenvatinib and pembrolizumab, pembrolizumab and axitinib, nivolumab and cabozantinib, and ipilimumab and nivolumab. The ORR were significantly higher for lenvatinib and pembrolizumab (p=0.047), and it appeared response rates were lowest for ipilimumab and nivolumab.[17]

SUNNIFORECAST[18] is a recently reported phase II trial assessing ipilimumab and nivolumab versus the physician's choice of treatment, which were overwhelmingly TKI options. The 12-month OS was significantly higher in the ipilimumab and nivolumab arm compared to TKI (78% vs. 68%). The ORR was also significantly higher in the experimental arm than the standard of care (33% vs. 20%). This trial suggested that the ipilimumab and nivolumab combination is an attractive option in non-ccRCC.

Current National Clinical Trials Network (NCTN) guidelines recommend cabozantinib as a single agent, cabozantinib and nivolumab, or lenvatinib and pembrolizumab as first-line agents in non-ccRCC. There is no current data to determine the best of these options in this setting.

The current Canadian guidelines suggest a personalized approach, reflecting the differential outcomes observed for the various subtypes.[1] **Table 1** summarizes potential treatment options for non-ccRCC. For patients with *de novo* metastatic papillary and chromophobe RCC, cytoreduction is recommended based on data from ccRCC. Furthermore, in these subtypes, it is recommended that localized techniques, such as surgery, radiofrequency ablation, and radiotherapy techniques such as stereotactic ablative radiotherapy, be considered for patients with oligometastatic disease (5 or fewer metastases). Surveillance is the recommended treatment option for individuals with low-volume/favourable-risk papillary and chromophobe RCC, as these conditions can be indolent.

Canadian guidelines for symptomatic/high-volume RCC reflect the National Comprehensive Cancer Network (NCCN) guidelines - recommending cabozantinib as a single agent or a checkpoint inhibitor in combination with a TKI. For those with metastatic chromophobe carcinoma, given the absence of

trial data supporting interventions in this setting, recruitment into clinical trials is recommended.[1]

Specific Subsets of Non-ccRCC

Chromophobe RCC generally has a good prognosis and has not been found to be impacted by risk factors such as obesity and smoking. Up to 10% of cases will metastasize, with a subset having sarcomatoid differentiation, which is associated with poor prognosis. Chromophobe RCC generally has poor response rates, with limited data available on treatment efficacy. However, a single-arm, phase II study evaluated the combination of lenvatinib with everolimus in patients with newly diagnosed non-ccRCC. Among nine patients with chromophobe RCC, the ORR was 44% with the combination. The lenvatinib/pembrolizumab study included more patients with chromophobe RCC (29 patients) and the ORR within this subset was 28%.

SMARCB1-deficient RCC is a rare, aggressive subtype with poor outcomes, representing <1% of RCC. MD Anderson has published the largest series of *SMARCB1*-deficient RCC cases. These tumours are associated with sickle hemoglobinopathies and are more frequent in males. The authors of this publication recommends platinum-based chemotherapy, such as carboplatin and paclitaxel, in the first line, followed by gemcitabine and doxorubicin or erlotinib.[19] Immunotherapy has not been shown to be beneficial for this population.[1]

Collecting duct tumours represent around 1% of RCC, and over 50% of patients with collecting duct tumours have metastatic disease. Patients with metastatic collecting duct tumours have a median OS of 7 months.[20] Given their rarity, data regarding the optimal management is limited. The GETUG phase II trial evaluated 23 patients with collecting duct tumours and found that gemcitabine and cisplatin treatment was associated with a PFS of 7.1 months and an OS of 10.5 months.[21] These data suggested that gemcitabine and cisplatin can be used to treat metastatic collecting duct tumours.[1]

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is associated with inherited fumarate hydratase (*FH*) mutations. Srinivasan et al. published a phase II trial assessing bevacizumab and erlotonib in 43 patients with HLRCC and 40 patients with sporadic papillary RCC.[22] The ORR was 72% with HLRCC-associated papillary renal-cell carcinoma, the median PFS was 21.1 months (95% CI: 15.6–26.6), and the median OS was 44.6 months (95% CI: 32.7-not estimated). A confirmed response occurred in 14 patients (35%; 95% CI: 22–51) with sporadic papillary renal-cell carcinoma (those without *FH* mutations), with a median PFS of 8.9 months (95% CI: 5.5–18.3) and a median OS of 18.2 months (95% CI: 12.6–29.3). These data have led to the inclusion of this combination of erlotinib and bevacizumab in HLRCC in the NCCN guidelines.

A retrospective study of non-ccRCC from China was presented at the American Society of Clinical Oncology's annual Genitourinary Cancers Symposium (ASCO GU).[23] This study evaluated 77 patients, including 70 HLRCC cases and seven case with somatic *FH*-loss. Recurrent pathogenic alterations were found in *NF2* (6/57, 11%), *CDH1* (6/57, 11%), *PIK3CA* (6/57, 11%), and *TP53* (5/57, 8.8%) genes. Sixty-seven patients were evaluable for response to first-line systemic therapy with bevacizumab and erlotonib (n=12), TKI monotherapy (n=29), or immune checkpoint inhibitor (ICI)/TKI (n=26). ICI/TKI combination therapy was associated with a more favourable OS (hazard ratio [HR]: 0.19, 95% CI: 0.04–0.90) and PFS as first-line therapy (HR: 0.22, 95% CI: 0.07–0.71) compared to bevacizumab and erlotonib combination therapy. This led to a phase II single centre trial in China evaluating lenvatinib plus tislelizumab, which was presented at ASCO GU in 2025.[24] Seventeen patients with either germline *FH* mutations or bilallelic somatic *FH* mutations were included in the study. The ORR in this study was 93% with a 20% complete response rate, suggesting this combination requires further study.

Future Developments

The benefit of adjuvant pembrolizumab in non-ccRCC remains unclear despite FDA approval in this setting, emphasizing the need for further clinical trials. The RAMPART study will provide important information on the role of durvalumab with or without tremelimumab across several cancer subtypes. This trial includes an active surveillance arm.[25]

In the metastatic setting, there is a concerted effort to improve outcomes as non-ccRCC has been somewhat neglected compared to ccRCC. There have been single-arm phase II trials such as KEYNOTE-B61; however, single-arm trials do

not produce data of sufficient quality to change practice. The SAMETA trial evaluates durvalumab versus durvalumab and sunitinib versus sunitinib alone versus durvalumab alone.[26] PAPMET-2 also combines immunotherapy (atezolizumab) with cabozantinib compared to cabozantinib alone, using PFS as an endpoint.[27] Both these trials are currently accruing patients. Given the relative lack of developments in non-ccRCC, other treatments are being considered. CCTG is developing a phase I trial in non-ccRCC assessing chimeric antigen receptor (CAR) T-cell therapy directed against GPNMB-1, as this protein is overexpressed in some types of non-ccRCC. Other areas of interest in non-ccRCC are determining genomic, proteomic, transcriptomic, or metabolomic signatures to enable personalized prognostication, treatment, and follow-up of non-ccRCC.

Conclusion

Outcomes of non-ccRCC remain poor compared to ccRCC, and robust data to help make clinical decisions are lacking. Management of non-ccRCC is challenging due to their heterogeneous clinical and biological behaviour. Personalized medicine involving assessment of genetic alterations and the tumour microenvironment is of particular interest in non-ccRCC. A better understanding of these factors may enable the development of novel treatments. Currently, it is strongly recommended that patients with non-ccRCC participate in clinical trials to strengthen the evidence base for therapeutic interventions.

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Financial Disclosures

M.J.: None declared.

References

1. Graham J, Ahmad AE, Basappa NS, Bernhard JC, Bhindi B, Bossé D, et al. 2024 CUA-KCRNC Expert Report: Management of non-clear cell renal cell carcinoma. Can Urol Assoc J. 2024;18(11):E371-e86.
2. Gulati S, Philip E, Salgia S, Pal SK. Evolving treatment paradigm in metastatic non clear cell renal cell carcinoma. Cancer Treat Res Commun. 2020;23:100172.
3. Urman D, Deshler L, Weise N, Shabaik A, Derweesh I, Bagrodia A, et al. Outcomes of patients with advanced renal cell carcinoma with non-clear cell histology treated with systemic therapy. Clin Genitourin Cancer. 2023;21(6):660-8.e1.
4. Goswami PR, Singh G, Patel T, Dave R. The WHO 2022 Classification of renal neoplasms (5th Edition): Salient updates. Cureus. 2024;16(4):e58470.
5. Moch H, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, et al. The 2022 World Health Organization Classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. Eur Urol. 2022;82(5):458-68.
6. Cardenas LM, Sigurdson S, Wallis CJD, Lalani A-K, Swaminath A. Advances in the management of renal cell carcinoma. CMAJ. 2024;196(7):E235-E40.
7. Powles T, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022;23(9):1133-44.
8. Gulati S, Tangen C, Ryan CW, Vaishampayan UN, Shuch BM, Barata PC, et al. Adjuvant everolimus in non–clear cell renal cell carcinoma: a secondary analysis of a randomized clinical trial. JAMA Netw Open. 2024;7(8):e2425288-e.
9. Allaf ME, Kim S-E, Master V, McDermott DF, Harshman LC, Cole SM, et al. Perioperative nivolumab versus observation in patients with renal cell carcinoma undergoing nephrectomy (PROSPER ECOG-ACRIN EA8143): an open-label, randomised, phase 3 study. Lancet Oncol 2024;25(8):1038-52.
10. Pal SK, Tangen C, Thompson IM, Jr., Balzer-Haas N, George DJ, Heng DYC, et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. Lancet. 2021;397(10275):695-703.
11. Barata P, Tangen C, Plets M, Thompson IM, Narayan V, George DJ, et al. Final Overall survival analysis of S1500: a randomized, phase ii study comparing sunitinib with cabozantinib, crizotinib, and savolitinib in advanced papillary renal cell carcinoma. J Clin Oncol. 2024;42(33):3911-6.

12. Albiges L, Gurney H, Atduev V, Suarez C, Climent MA, Pook D, et al. Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2023;24(8):881-91.
13. Voss MH, Gurney H, Atduev V, Suarez C, Climent MA, Pook D, et al. First-line pembrolizumab plus lenvatinib for advanced non–clear-cell renal cell carcinoma: updated results from the phase 2 KEYNOTE-B61 trial. Eur Urol. 2025.
14. McDermott DF, Lee JL, Ziobro M, Suarez C, Langiewicz P, Matveev VB, et al. Open-label, single-arm, phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. J Clin Oncol. 2021;39(9):1029-39.
15. Lee C-H, Voss MH, Carlo MI, Chen Y-B, Zucker M, Knezevic A, et al. Phase II trial of cabozantinib plus nivolumab in patients with non–clear-cell renal cell carcinoma and genomic correlates. J Clin Oncol. 2022;40(21):2333-41.
16. Tykodi SS, Gordan LN, Alter RS, Arrowsmith E, Harrison MR, Percent I, et al. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 CheckMate 920 trial. J Immunother Cancer. 2022;10(2).
17. Massari F, Mollica V, Kopp RM, Grande E, Fiala O, Kanesvaran R, et al. Immune-based combinations in intermediate-/poor-risk patients with non–clear cell renal cell carcinoma: results from the ARON-1 study. Eur Urol Focus. 2025.
18. Bergmann L, Albiges L, Ahrens M, Gross-Goupil M, Boleti E, Gravis G, et al. Prospective randomized phase-II trial of ipilimumab/nivolumab versus standard of care in non-clear cell renal cell cancer - results of the SUNNIFORECAST trial. Ann Oncol. 2025;36(7):796-806.
19. Lebenthal JM, Kontoyiannis PD, Hahn AW, Lim ZD, Rao P, Cheng JP, et al. Clinical Characteristics, Management, and Outcomes of Patients with Renal Medullary Carcinoma: A Single-center Retrospective Analysis of 135 Patients. Eur Urol Oncol. 2025;8(2):315-23.
20. Suarez C, Marmolejo D, Valdivia A, Morales-Barrera R, Gonzalez M, Mateo J, et al. Update in collecting duct carcinoma: Current aspects of the clinical and molecular characterization of an orphan disease. Front Oncol. 2022;12:970199.
21. Oudard S, Banu, E, Vieillefond, A, Fournier, L, Priou, F, Medioni, J, Culine, S. Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Genitales) Study. J Urol. 2007;177:1698-702.
22. Srinivasan R, Gurram S, Singer EA, Sidana A, Al Harthy M, Ball MW, et al. Bevacizumab and erlotinib in hereditary and sporadic papillary kidney cancer. N Engl J Med. 2025;392(23):2346-56.
23. Xu Y, Kong W, Cao M, Wang J, Wang Z, Zheng L, et al. Genomic Profiling and Response to immune checkpoint inhibition plus tyrosine kinase inhibition in FH-deficient renal cell carcinoma. Eur Urol. 2023;83(2):163-72.
24. Kong W, Wu G, Xu Y, Wang Z, Zhang J. Lenvatinib plus tislelizumab as first-line therapy for advanced fumarate hydratase-deficient renal cell carcinoma: A single-center, single-arm, phase II study. J Clin Oncol. 2025;43(5_suppl):443-.
25. Oza B, Frangou E, Smith B, Bryant H, Kaplan R, Choodari-Oskooei B, et al. RAMPART: A phase III multi-arm multi-stage trial of adjuvant checkpoint inhibitors in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse. Contemp Clin Trials. 2021;108:106482.
26. Choueiri TK, Xu W, Poole L, Telaranta-Keerie A, Hartmaier R, Powles T. SAMETA: An open-label, three-arm, multicenter, phase III study of savolitinib + durvalumab versus sunitinib and durvalumab monotherapy in patients with MET-driven, unresectable, locally advanced/metastatic papillary renal cell carcinoma (PRCC). J Clin Oncol. 2022;40(16_suppl):TPS4601-TPS.
27. Maughan BL, Plets M, Pal SK, Ged Y, Tangen C, Vaishampayan UN, et al. SWOG S2200 (PAPMET2): A phase II randomized trial of cabozantinib with or without atezolizumab in patients with advanced papillary renal cell carcinoma (PRCC). J Clin Oncol. 2024;42(4_suppl):TPS493-TPS.
28. Nepali PR, Eraky A, Okhawere KE, Dogra N, Mehrazin R, Badani K, et al. Molecular and therapeutic landscape of non-clear cell renal carcinoma. Nat Rev Urol. 2025.