2024 CUA-KCRNC Expert Report: Management of non-clear cell renal cell carcinoma

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INTRODUCTION

In 2023, approximately 8600 Canadians were diagnosed with kidney cancer.[1] At the time of diagnosis, up to 85% of patients present with localized or locally advanced renal cell carcinoma (RCC), while the remainder have metastatic disease.[2,3] Clear cell histology (ccRCC) accounts for most RCC cases, but approximately 25% are classified as non-clear cell RCC (nccRCC), also known as variant histology RCC.[4] Non-clear cell RCC represents a heterogeneous subgroup of tumors with distinct histopathologic origins, underlying genetic mutations, and oncologic outcomes. The two most common nccRCC pathologic subtypes are papillary and chromophobe RCC.[5]

The presence of variant histology carries significant prognostic and therapeutic implications in the management of RCC.[4] For instance, within localized RCCs, certain subtypes, such as SMARCB1-deficient medullary RCC or collecting duct RCC, exhibit more aggressive behavior and require more intensive management. In the context of metastatic RCC, most randomized clinical trials primarily included patients with ccRCC, creating uncertainty when extrapolating these findings to the management of patients with nccRCC. Consequently, physicians may face challenges in applying evidence developed in ccRCC to nccRCC cases, highlighting the need for further research and personalized approaches tailored toward specific histologic subtypes.

Acknowledging the prevailing uncertainty and the limitations of available data, this Expert Report aims to summarize current evidence and provide Canadian healthcare professionals with comprehensive guidance on managing nccRCC, with an emphasis placed on papillary and chromophobe RCC management.

METHODS

During the 2024 Canadian Kidney Cancer Forum (CKCF) held from February 8–10, 2024, in Toronto, Ontario, Canada, a dedicated session convened an expert panel comprising urologic and medical oncologists, other healthcare professionals, and patient advocates. The purpose of this session was to facilitate a discussion on the management of nccRCC and to develop consensus statements based on the best available evidence. These statements are intended to provide practical guidance to healthcare professionals and medical practitioners in their clinical practices.

Prior to the session, draft topic statements were generated by two authors (JG, PR) and subjected to review for clarity and completeness by board members of the Kidney Cancer Research Network of Canada (NB, RB, TF, ST, and LW), as detailed in Table 1. These topics spanned diagnostic imaging, pathologic classification, and genetic considerations, as well as treatment options for patients with localized and metastatic nccRCC, with a focus on papillary and chromophobe RCC.

Each topic statement was presented during the session, followed by a period for panel members to

suggest additional items and engage in open discussion. Adjustments to the statements were made in real-time to ensure they accurately represented the expert consensus. Following each discussion, participants were asked to vote either "agree" or "disagree" with the statements, with the option to abstain if appropriate. Consensus was predefined as follows: >75% agreement constituted a consensus, 50–75% agreement indicated near consensus, and <50% agreement meant no consensus was reached. This process was consistent with the methodology of a prior CKCF Consensus Statement.[6]

In total, 41 experts participated in the voting process, including 14 urologists, 22 medical oncologists, one pathologist, one radiation oncologist, one geneticist, and two patient advocates. After the meeting, an initial draft of the consensus statements was prepared by JG and PR and subsequently distributed to all co-authors for feedback. The final draft was then collaboratively reviewed and approved by all authors (Table 1).

RESULTS

STATEMENT 1

nccRCC tumors should be classified according to the World Health Organization Classification of Tumors, 5th Edition ***(consensus achieved: 100%)***.

In 2022, the World Health Organization's (WHO) publication on urinary and male genital tumors released its fifth edition, which has significantly enhanced our understanding of RCC through detailed morphologic, immunohistochemical, and molecular characteristics.[7] This latest edition introduced major nomenclature and terminology changes to the classification of existing renal tumors and incorporated several new tumor entities. In addition, the updated classification includes, for the first time, a category of molecularly defined RCC, incorporating several distinct RCC subtypes that may require molecular testing for diagnostic confirmation in a subset of cases.

New entities in the fifth edition include eosinophilic solid and cystic RCC, ALK-rearranged RCC, and ELOC (formerly TCEB1)-mutated RCC. Notable nomenclature changes include fumarate hydratase (FH)-deficient RCC (formerly known as hereditary leiomyomatosis RCC syndrome-associated RCC), SMARCB1-deficient medullary RCC (formerly known as medullary carcinoma RCC) and *TFEB*-altered RCC (to incorporate both TFEB-rearranged and TFEB-amplified tumors). Clear cell papillary renal cell tumor (replacing clear cell papillary renal cell carcinoma) was also introduced as a name change to better reflect the generally indolent behavior of this tumor type.[8] While a comprehensive review of all the changes falls beyond the scope of this report, we aim to highlight some key updates relevant to the classification of papillary and oncocytic/chromophobe tumors.

In the latest guidelines for papillary renal tumors, the WHO has moved away from the traditional subclassification into type 1 and type 2. Traditionally defined type 1 tumors are now regarded as "classic" papillary RCC. This change was prompted by poor reproducibility of subclassification and the recognition that previously labelled type 2 tumors exhibit significant heterogeneity in terms of pathologic features and clinical behavior. Importantly, several tumors previously categorized as type 2 papillary RCC are now identified as distinct molecularly defined entities, including FH-deficient RCC, TFE3-rearranged RCC, and *ALK*-rearranged RCC.[9] There is also evidence to support the prognostic value of WHO/International Society of Urological Pathology (ISUP) grade, tumor architecture and emerging biomarkers to risk-stratify papillary RCC and this is an area of ongoing investigation.[10-12]

In the spectrum of oncocytic/chromophobe tumors, the updated classification introduced a new category labelled "other oncocytic tumors of the kidney" to describe a heterogeneous group of tumors that are not classifiable as oncocytoma or chromophobe RCC. This subcategory encompasses two emerging entities, low-grade oncocytic tumor (LOT) and eosinophilic vacuolated tumor (EVT), with studies to date indicating that these tumors have benign behavior.[13,14] It also incorporates tumors with intermediate/overlapping features between oncocytoma and chromophobe RCC. The term "hybrid oncocytic chromophobe tumors" (HOCT) has been proposed for such tumors arising in the context of Bird-Hogg-Dube (BHD) or other hereditary syndromes, while the preferred terminology in the sporadic setting is "oncocytic renal neoplasm of low malignant potential NOS." It is also important to recognize the diagnostic challenges posed by the similarities between oncocytoma, chromophobe RCC, and the heterogeneity of other oncocytic tumors with intermediate features. Accordingly, the WHO 2022 classification cautions against a definite diagnosis of oncocytoma based on renal mass biopsy histology, a challenge also highlighted by Lavallée et al in the KCRNC consensus document on the role of renal mass biopsy.[15]

It is important to note that given the rarity of some nccRCC subtypes and the evolving pathologic classifi-

cation, consideration should be given to a dedicated re-review by a pathologist with expertise in renal tumor pathology.

STATEMENT 2

Patients diagnosed with nccRCC following renal mass biopsy should receive similar preoperative investigations and staging as those with ccRCC *(consensus achieved: 97%)*.

Patients diagnosed with nccRCC following a renal mass biopsy should undergo preoperative investigations and staging similar to those for ccRCC. According to the 2022 Canadian Urological Association (CUA) guidelines on the management of localized small renal masses (i.e., solid mass ≤4 cm in diameter), these patients should have routine laboratory investigations, which at a minimum includes serum creatinine and glomerular filtration rate assessments. For patients with renal impairment who are being considered for invasive treatment, a urinalysis to screen for proteinuria is suggested. A urine albumin-to-creatinine ratio may also be considered.[16] Patients diagnosed with metastatic disease should also undergo routine baseline laboratory investigations, including complete blood count with differential and a corrected calcium test for prognostication purposes.

In addition to routine laboratory tests, these patients should undergo comprehensive imaging, including multiphasic, contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI), as well as chest imaging. For most patients with a small renal mass, a baseline chest X-ray is usually sufficient to screen for pulmonary metastases;[17,18] however, if any abnormalities are detected on the chest X-ray, a followup chest CT scan is recommended. Patients with larger or locally advanced tumors, or those diagnosed with more aggressive RCC subtypes, such as SMARCB1-deficient medullary RCC or collecting duct RCC, should be considered for a chest CT scan. This recommendation is due to the higher likelihood of pulmonary metastases in these cases and the greater sensitivity of CT imaging compared to chest X-ray.

Bone scintigraphy and brain imaging should be performed for patients exhibiting symptoms suggestive of metastases, as most bone and brain metastases are symptomatic at diagnosis.[19] Renal scintigraphy may be useful for patients with renal impairment or when radical nephrectomy is considered, particularly if an assessment of differential renal function could alter management.[17]

Table 1. Consensus topic statements and results as voted at the CKCF Meeting on February 10, 2024

Statement	Consensus
1. nccRCC tumors should be classified according to the WHO Classification of Tumors, 5th Edition.	Achieved: 100%
2. Patients diagnosed with nccRCC following renal mass biopsy should receive similar preoperative investigations and staging as those with ccRCC.	Achieved: 97%
3. For patients diagnosed with a ≤2 cm in diameter localized papillary or chromophobe RCC following renal mass biopsy, active surveillance is considered the preferred management option.	Achieved: 94%
4. For patients diagnosed with a 2–4 cm in diameter localized papillary or chromophobe RCC following renal mass biopsy, active surveillance or definitive treatment are considered the preferred management options.	Achieved: 97%
5. For patients diagnosed with >4 cm in diameter localized papillary or chromophobe RCC following renal mass biopsy, surgery (radical or partial nephrectomy, when feasible) is considered the preferred management option.	Achieved: 97%
6. In patients receiving definitive therapy for localized papillary or chromophobe RCC, postoperative surveillance should be similar to ccRCC.	Achieved: 94%
7. Patients with resected nccRCC should not be offered adjuvant systemic therapy, unless as part of a clinical trial.	Achieved: 100%
8. Most patients diagnosed with nccRCC should be offered germline genetic testing and/or counseling.	Achieved: 83%
9. Patients diagnosed with metastatic papillary or chromophobe RCC should be counseled and managed according to the IMDC prognostic model.	Achieved: 100%
10. Patients diagnosed with metastatic nccRCC should be offered the opportunity to participate in a clinical trial when available.	Achieved: 100%
11. In select patients with de novo metastatic papillary or chromophobe RCC, upfront cytoreductive nephrectomy may be considered after multidisciplinary discussion.	Achieved: 100%
12. Patients with de novo metastatic papillary or chromophobe RCC may be considered for deferred cytoreductive nephrectomy depending on the response to initial systemic therapy and after multidisciplinary discussion.	Achieved: 100%
13. For patients with oligometastatic papillary or chromophobe RCC, MDT may be considered.	Achieved: 100%
14. In patients with metastatic papillary or chromophobe RCC with favorable/intermediate-risk disease and low volume/asymptomatic or minimally symptomatic disease, active surveillance may be considered.	Achieved: 100%
15. Patients with metastatic papillary RCC who are not eligible for clinical trials and require systemic therapy should be offered ICI-based combination therapy or monotherapy with cabozantinib.	Achieved: 100%
16. In patients with metastatic chromophobe RCC who require systemic therapy, there is currently no standard of care, and these patients should be offered clinical trial enrollment when available.	Achieved: 100%
17. Patients with metastatic nccRCC (excluding SMARCB1-deficient renal medullary carcinoma and collecting duct RCC) with sarcomatoid or rhabdoid dedifferentiation should be offered combination ICI-based therapy.	Achieved: 100%

ICI: immune checkpoint inhibitor; IMDC: International Metastatic RCC Database Consortium; MDT: metastasis-directed therapy; nccRCC: non-clear cell renal cell carcinoma; WHO: World Health Organization.

STATEMENT 3

For patients diagnosed with a ≤2 cm in diameter localized papillary or chromophobe RCC following renal mass biopsy, active surveillance is considered the preferred management option *(consensus achieved: 94%)*.

STATEMENT 4

For patients diagnosed with a 2–4 cm in diameter localized papillary or chromophobe RCC following renal mass biopsy, active surveillance or definitive treatment are considered the preferred management options *(consensus achieved: 97%)*.

STATEMENT 5

For patients diagnosed with >4 cm in diameter localized papillary or chromophobe RCC following renal mass biopsy, surgery (radical or partial nephrectomy, when feasible) is considered the preferred management option *(consensus achieved: 97%)*.

For small renal masses, current evidence comparing different treatment options is of limited quality, and no single treatment has proven superior in randomized controlled trials (RCTs). Consequently, treatment decisions should be personalized, using a shared decision-making approach that aligns with each patient's values and preferences. A decision aid may help facilitate this process.[20]

The guidance document by Richard et al discusses CUA recommendations for the management of small renal masses.[17] The document highlights that given the high likelihood of benign histology (>20%), the slow growth rate of such tumors, especially for low-grade papillary RCC and chromophobe RCC compared to ccRCC,[21] and indolent nature of most malignancies ≤2 cm in diameter (>85% are low-grade),[22] active surveillance is recommended as the preferred strategy for localized papillary or chromophobe RCC ≤2 cm following a renal mass biopsy. Immediate, definitive treatments, such as surgery or percutaneous thermal ablation, remain viable options and should be discussed with patients to ensure they are well-informed of their options.

In patients with lesions measuring 2–4 cm, the CUA guideline reported no consensus on the preferred management strategy. Nearly 40% of panel members felt that definitive treatment should be considered. Therefore, both active surveillance and definitive treatment are considered viable management options. The guideline notes that the decision to proceed with active surveillance or definitive treatment may be influenced by several factors, including patient preferences and tumor characteristics, with the most important factor being patient preference. For more details, please refer to the CUA guideline on small renal masses.[17]

An important caveat to these two statements applies to more aggressive histologic subtypes, such as HLRCC-associated RCC, unclassified RCC, SMARCB1-deficient medullary RCC, collecting duct RCC, and tumors with a rhabdoid/sarcomatoid dedifferentiation. Given their more aggressive clinical behavior, upfront definitive treatment, or even systemic treatments in some cases (see section on management of SMARCB1-deficient medullary RCC), is recommended for localized tumors of these types.

For localized lesions measuring >4 cm, surgery is generally considered the preferred management strategy due to the higher risk of progression to metastatic disease, with a preference for nephron-sparing approaches whenever technically feasible and oncologically appropriate.[23]

STATEMENT 6

In patients receiving definitive therapy for localized papillary or chromophobe RCC, postoperative surveillance should be similar to ccRCC *(consensus achieved: 94%)*.

Risk-adapted followup strategies after definitive treatment for localized disease are extensively discussed in the CUA guideline for followup of patients after treatment of non-metastatic RCC.[24] While there is currently no evidence suggesting that these strategies should differ based on histologic subtypes, the presence of sarcomatoid features has been shown to increase the risk of progression and may warrant more intensive surveillance.[25-28] As well, more aggressive histologic subtypes, such as SMARCB1-deficient medullary RCC and collecting duct RCC, may warrant more intensive surveillance. Conversely, more indolent subtypes, such as eosinophilic vacuolated tumor and low-grade oncocytic tumor, may require less intensive followup.

Typically, a routine chest X-ray is recommended for detecting recurrence in the lungs; however, for patients at higher risk, a chest CT scan is preferred due to its greater sensitivity. CT or MRI scans of the abdomen and pelvis are recommended for detecting abdominal recurrences, especially for patients at increased risk of recurrence. Patients with lower risk (pT1 and pT2) may be suitable for abdominal ultrasound. Postoperatively, an optional abdominal CT scan or MRI at 3–12 months can be considered for patients who underwent partial nephrectomy to evaluate the residual baseline renal appearance. For patients who have undergone ablation,

given the higher risk of incomplete ablation compared to surgery,[29] contrast-enhanced abdominal CT or MRI is suggested at three, six, and 12 months post-ablation and then annually thereafter for up to five years. Routine head imaging or bone scintigraphy are not recommended unless specific clinical symptoms or indications are present. According to the CUA guideline, routine imaging should be performed for a period of at least five years and can be risk-adjusted thereafter.[24]

STATEMENT 7

Patients with resected nccRCC should not be offered adjuvant systemic therapy unless as part of a clinical trial ***(consensus achieved: 100%).***

There is limited data on the role of adjuvant systemic therapy in patients with nccRCC, including papillary and chromophobe RCC. Evidence from the Keynote-564 trial supports the use of pembrolizumab based on improvements in disease-free survival and overall survival (OS) in high-risk patients with clear cell histology;[30] however, this trial did not enroll patients with pure nccRCC histology. Among adjuvant RCC trials,[30-34] only the PROSPER-RCC trial allowed for a subset of nccRCC patients with ≥pT2, any N, M0 or oligometastatic M1 planned for definitive resection. In this study, patients were randomized to receive either a placebo or nivolumab. At an interim analysis, with a median followup of 16 months, the Data and Safety Monitoring Committee halted the trial for futility due to the absence of relapse-free survival (hazard ratio [HR] 0.9, 95% confidence interval [CI] 0.74–1.28%, one-sided p=0.43).[34] Consequently, in the absence of supporting evidence, adjuvant systemic therapy should not be offered to patients with pure nccRCC post-nephrectomy unless as part of a clinical trial.

STATEMENT 8

Most patients diagnosed with nccRCC should be offered germline genetic testing and/or counseling ***(consensus achieved: 83%).***

It has been reported that approximately 5–8% of patients with RCC have a hereditary predisposition, and this figure is likely an underestimate.[35] Common genes associated with nccRCC include *FLCN* (BHD syndrome), *FH* (FH-deficient RCC), *TSC1/2* (tuberous sclerosis complex), *MET* (hereditary papillary RCC), and *SDHB* (succinate dehydrogenase [SDH]-deficient RCC). Therefore, there appears to be enrichment for germline mutations in patients with nccRCC.

The current CUA guideline recommends genetic assessment for patients who present with early-onset (≤45 years of age), bilateral or multifocal tumors, a first or second-degree relative with any renal tumor or a history of RCC-associated hereditary syndrome, or features indicative of hereditary syndromes.[36] Similar guidelines have been issued by the National Comprehensive Cancer Network[37] and the American College of Medical Genetics;[38] however, it is important to emphasize that up to one-third (36%) of patients diagnosed with an RCC-related germline variant do not meet these criteria.[39] Additionally, research by Nguyen et al found that a personal history of cancer and a family history of RCC or other cancers were not necessarily predictive of a positive germline test.[40]

There was consensus that most patients diagnosed with nccRCC, particularly those with bilateral/multifocal tumors and metastatic disease, should be offered germline genetic testing.[41] Certain jurisdictions in Canada allow for germline testing for any patient with nccRCC, but funding may differ between provinces. The group also recognizes the urgent need for research aimed at optimizing genetic evaluation criteria to better identify patients who may carry germline alterations, given their potential therapeutic and familial implications.

STATEMENT 9

Patients diagnosed with metastatic papillary or chromophobe RCC should be counseled and managed according to the International Metastatic RCC Database Consortium prognostic model ***(consensus achieved: 100%).***

The treatment approach for metastatic RCC has evolved significantly over the past 20 years. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) provides risk factors that help estimate an individual patient's OS.[42] Although the original prognostic model was developed primarily for patients with ccRCC, with only 12% of the cohort representing nccRCC, subsequent studies demonstrated that this risk classification correlates with survival outcomes for both papillary and chromophobe RCC histologies.

For instance, in a study by Wells et al involving a large cohort of 466 patients with metastatic papillary RCC, the IMDC prognostic model successfully stratified patients into favorable (OS=34.1 months), intermediate (OS=17.0 months), and poor risk groups (OS=6.0 months);[43] however, the authors also noted that irrespective of the risk group, survival outcomes for patients with metastatic papillary RCC were inferior to those with ccRCC.

Likewise, using the same database, Yip et al demonstrated that the IMDC risk factors were equally able to stratify patients with chromophobe RCC (n=109).[44] With the caveat that this study was conducted prior to the immune checkpoint inhibitors (ICI) era, the authors demonstrated that patients with metastatic chromophobe RCC had similar OS rates to those with ccRCC (23.8 months, 95% CI 16.7–28.1 vs. 22.4 months, 95% CI 21.4–23.4, respectively [p=0.09]). Notably, the distribution of IMDC risk categories — favorable (18%), intermediate (59%) and poor (23%) — correlated with median OS of 31.4, 27.3, and 4.8 months, respectively.

Despite these findings, the applicability of the IMDC risk factors for prognostication in other variant histologies has yet to be established. Therefore, their use in nccRCC should be limited to metastatic cases with either papillary or chromophobe RCC.

■ STATEMENT 10

Patients diagnosed with metastatic nccRCC should be offered the opportunity to participate in a clinical trial when available ***(consensus achieved: 100%)***.

Given the absence of large phase 3 randomized trials in this population, no standard therapeutic approach exists. In the absence of robust comparative data, priority should be placed on enrolling patients in clinical trials whenever feasible.

■ STATEMENT 11

In select patients with de novo metastatic papillary or chromophobe RCC, upfront cytoreductive nephrectomy may be considered after multidisciplinary discussion ***(consensus achieved: 100%)***.

While cytoreductive nephrectomy (CN) was widely used in the past, its role has been called into question by the results of the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) study.[45] This study randomized patients with metastatic ccRCC to receive either upfront CN followed by sunitinib therapy or sunitinib therapy alone. Eligible patients were stratified according to their Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic risk — intermediate vs. poor. The findings demonstrated the non-inferiority of sunitinib alone compared to the combination of nephrectomy followed by sunitinib in terms of OS.[45]

Several observational studies have investigated the role of CN in both the vascular endothelial growth factor (VEGF)-targeted and immune-checkpoint inhibitor eras and identified a survival advantage with CN.[46-61] Although observational studies have inherent selection biases and limitations, the overall evidence suggests a potential survival benefit from CN in appropriately selected patients.

It is important to note that most of these studies have been limited to patients with metastatic ccRCC, with only a handful of observational studies including nccRCC patients.[62-68] For example, a retrospective study done through the IMDC database demonstrated a survival advantage for CN in metastatic papillary RCC (median OS with CN 16.3 months vs. 8.6 months without CN, p<0.0001).[68] The generalizability of trial data (i.e., CARMENA) derived in ccRCC to nccRCC patients remains uncertain. Given the totality of evidence, the authors believed it is reasonable to offer CN to select patients with advanced papillary and chromophobe RCC, especially considering that systemic therapy is generally less effective for these types when compared to ccRCC.[69,70]

Our group extensively addressed the role of CN in ccRCC and patient selection in a separate report.[70] Briefly, our current recommendation is that most patients with metastatic nccRCC should initially be offered systemic therapy; however, upfront CN may be considered in appropriately selected patients with favorable/intermediate IMDC risk chromophobe/papillary RCC and limited metastatic burden following multidisciplinary discussion. Candidates eligible for upfront CN should meet the following criteria: good performance status, minimal symptoms related to metastases, resectable primary tumor with acceptable morbidity, and a limited burden of metastatic disease.

Patients who undergo upfront CN should be offered postoperative metastases-directed therapy (MDT), a period of active surveillance, or systemic therapy.[6,69,70] Lastly, symptomatic disease remains an important indication for CN, particularly for patients who are unable to receive systemic treatment or who require hospitalization due to their symptoms. For patients who are not suitable candidates for surgery, alternatives such as angioembolization or stereotactic body radiotherapy (SBRT) may also be considered for symptom palliation.

■ STATEMENT 12

Patients with de novo metastatic papillary or chromophobe RCC may be considered for deferred cytoreductive nephrectomy depending on the response to initial systemic therapy after multidisciplinary discussion ***(consensus achieved: 100%)***.

The SURTIME randomized trial explored whether the use of sunitinib therapy before CN (deferred CN)

would improve outcomes compared with immediate CN followed by sunitinib in ccRCC.[71] The deferred CN approach did not improve the primary end point of 28-week progression-free survival (PFS). With the deferred approach, more patients received sunitinib, with improved OS results. In the CARMENA trial, although a smaller cohort (n=40) underwent delayed CN, these patients derived an OS benefit compared to patients who did not (48.5 months vs. 15.7 months, p<0.01).[72] Recent observational studies also support this delayed approach, specifically in ccRCC.[54,73-78]

Although the SURTIME and CARMENA trials were limited to ccRCC, we believe that select patients with metastatic nccRCC (primarily papillary or chromophobe RCC) who achieve a complete or durable partial response after systemic therapy may be considered for deferred CN following a multidisciplinary discussion. Lastly, it is important to emphasize that instances of complete response are most often observed in patients who previously underwent nephrectomy.[75,76,79,80]

STATEMENT 13

For patients with oligometastatic papillary or chromophobe RCC, metastasis-directed therapy may be considered ***(consensus achieved: 100%).***

Oligometastatic disease typically describes patients with a limited number of detectable metastatic lesions, generally five or fewer.[81]

Several observational and small prospective studies in ccRCC have demonstrated that MDT is feasible, safe, and may delay the need for systemic therapy. Patients who have successfully completed MDT may enter a period of surveillance with close monitoring and deferred initiation of systemic therapy.[82-84]

In mRCC, the primary modalities for MDT include surgical metastasectomy and SBRT. Additionally, conventional external beam radiotherapy (when SBRT is not feasible) or percutaneous thermal ablation may also be employed.[17] Metastatic sites amenable to MDT include lung, liver, brain, pancreatic, thyroid, bone, and locoregional recurrences. In ccRCC, a longer disease-free interval (>1 year from diagnosis to metastatic disease) was associated with better outcomes with MDT. Given that no single approach (i.e., surgical metastasectomy vs. SBRT) has been definitively proven to be superior, patients with nccRCC being considered for MDT should be discussed at multidisciplinary rounds.[83,85-87]

Although most of the evidence supporting MDT is focused on ccRCC, patients with oligometastatic papillary or chromophobe RCC should be considered for MDT after multidisciplinary discussion. Consideration for MDT is especially appealing in patients with oligometastatic chromophobe RCC, given lower response rates to systemic therapies compared to ccRCC. In these cases, MDT ± CN followed by close active surveillance is a reasonable strategy. In patients with nccRCC who have successfully completed MDT and are rendered no evidence of disease (NED) within one year of nephrectomy, we suggest not proceeding with one year of pembrolizumab, as per the Keynote-564 trial.[30] As referenced in Statement 7, this trial did not include patients with non-clear cell histology and the benefit of adjuvant therapy in this group remains unproven.

It is important to monitor these patients before proceeding with MDT to ensure that the disease is not progressing rapidly. Patients with rapidly progressing oligometastatic disease, poor-risk IMDC stratification, or more aggressive RCC histologies (i.e., SMARCB1-deficient medullary RCC) are generally not suitable candidates for MDT alone and should receive upfront systemic therapy.[88]

STATEMENT 14

In patients with metastatic papillary or chromophobe RCC with favorable/intermediate-risk disease and low-volume/asymptomatic or minimally symptomatic disease, active surveillance may be considered ***(consensus achieved: 100%).***

It has been well-documented that there exists a subset of patients with asymptomatic metastatic RCC who display a more indolent disease biology, including those with low-volume/slow-growing metastases. In this group, close clinical and radiographic surveillance with deferral of systemic therapy can be considered. This includes patients with oligometastatic disease following the completion of MDT. There is no standardized surveillance schedule, but it should involve routine chest and abdominal imaging and clinical assessments, with treatment based on radiographic or clinical signs of progression.

Although the indication for active surveillance is largely derived from data in metastatic ccRCC, there are studies on active surveillance that included patients with non-ccRCC, including papillary and chromophobe histologies. For instance, the phase 2 trial by Rini et al enrolled a small proportion of patients with chromophobe RCC.[89] In the overall population, the median time on surveillance was 14.9 months. Additionally, two large observational studies on active surveillance included patients with nccRCC.

Although histology-specific subgroups were not reported in these studies, we believe it is reasonable to generalize these findings to appropriately selected patients with nccRCC. This approach may be particularly attractive in metastatic chromophobe RCC, which typically displays a more indolent phenotype and where effective systemic therapy options are limited.[89-91]

STATEMENT 15

Patients with metastatic papillary RCC who are not eligible for clinical trials and require systemic therapy should be offered immune checkpoint inhibitors-based combination therapy or monotherapy with cabozantinib ***(consensus achieved: 100%).***

The evidence for the systemic treatment of advanced papillary RCC comes from several sources, including small phase 2 RCTs and single-arm prospective trials, as well as retrospective observational studies. The therapeutic options can be broadly divided into the following categories: targeted tyrosine kinase inhibitor (TKI) monotherapy, ICI monotherapy, ICI-ICI combination therapy, and ICI/TKI combination therapy. Table 2 summarizes several key trials in papillary RCC.

Cabozantinib is a multitargeted TKI and has demonstrated efficacy as a single-agent therapy in papillary RCC. In the PAPMET phase 2 randomized trial, cabozantinib achieved an objective response rate (ORR) of 23% and a median PFS of 9.0 months, compared to sunitinib, which had an ORR of 5% and a median PFS of 5.6 months.[92] This established cabozantinib as a potential first-line treatment for advanced papillary RCC. Monotherapy with ICIs has also shown activity in metastatic papillary RCC based on non-randomized phase 2 studies. Nivolumab demonstrated an ORR range of 5–11%,[93-95] while the phase 2 Keynote-427 study of single-agent pembrolizumab demonstrated an ORR of 29% and PFS of 5.5 months.[96]

Several ICI and TKI combinations have been explored in prospective, single-arm, phase 2 trials.[97-101] The largest study reported to date is the Keynote B61 trial, which examined the combination of lenvatinib and pembrolizumab in nccRCC (n=93 with papillary RCC). This trial demonstrated an ORR of 54% and PFS of 17.5 months in the papillary subgroup.[98] Other combinations have also shown activity with ORR ranging from 29–48% (Table 2).

Combination ICI therapy with nivolumab + ipilimumab has also been explored in papillary RCC.[102,104] A recently presented phase 2 RCT of nivolumab + ipilimumab vs. physician's choice demonstrated an ORR of 29% with the combination, with a complete response rate of 9.7%.[104]

Given the available data and the absence of robust comparative evidence, it is difficult to strongly recommend a specific treatment regimen. The combination of lenvatinib and pembrolizumab has the highest reported ORR, making it an attractive option for metastatic papillary RCC. As in ccRCC, it is important to evaluate the durability of responses to ICI-based therapies in papillary RCC, particularly with the ipilimumab-nivolumab combination. Based on the totality of existing data and current drug availability in Canada, we suggest ICI-based combination therapy (e.g., lenvatinib + pembrolizumab, cabozantinib + nivolumab, nivolumab + ipilimumab) or single-agent cabozantinib as preferred first-line options in metastatic papillary RCC. Alternative options include single-agent pembrolizumab (Table 2).

STATEMENT 16

In patients with metastatic chromophobe RCC who require systemic therapy, there is currently no standard of care, and these patients should be offered clinical trial enrollment when available ***(consensus achieved: 100%).***

Compared to papillary RCC, there is less data to guide systemic therapy recommendations in advanced chromophobe RCC. As such, clinical trial enrollment should be prioritized. As mentioned in Statement 13, in patients with oligometastatic chromophobe RCC, CN with MDT followed by active surveillance is a preferred approach in appropriately selected patients.

Existing evidence suggests that these tumors are less responsive to ICI therapy compared to papillary RCC, which is likely related to underlying differences in tumor biology (Table 3). The use of single-agent ICI therapy has been studied in chromophobe RCC with limited activity. Nivolumab demonstrated an ORR range of 0–29%,[93-95] while pembrolizumab has shown an ORR of 9.5% and a PFS of 3.9 months.[96]

A recently reported phase 2 RCT of nivolumab + ipilimumab vs. physician's choice in nccRCC demonstrated an ORR of 25.9% with the combination within the chromophobe subgroup (n=54), although the progressive disease rate was 29.6%.[104] Given the relatively small sample size and number of events in the chromophobe subgroup, these results should be interpreted with caution and longer followup is required to assess the durability of response.

Although data on TKI therapy in chromophobe RCC is relatively limited, cabozantinib has shown efficacy across RCC subtypes, suggesting potential benefit in

Table 2. Notable clinical trials with published results for papillary renal cell carcinoma

Trial	Enrollment criteria	Number of pRCC	Intervention	Results
Single-agent TKI				
NCT02761057 (PAPMET)[92]	Up to one prior systemic therapy excluding VEGF and MET inhibitor	147 (90 for cabozantinib vs. sunitinib)	Cabozantinib vs. sunitinib (savolitinib and crizotinib arms closed)	ORR: 23% vs. 4% (p=0.010) Median PFS: 9.0 vs. 5.6 m (HR 0.60, 95% CI 0.37–0.97, p=0.019) Median OS: 20.0 vs. 16.4 m (HR 0.84, 95% CI 0.47–1.51)
NCT03091192 (SAVOIR)[103]	MET driven, no prior therapy	Savolitinib 33 Sunitinib 27	Savolitinib vs. sunitinib	ORR: 27% (95% CI 13.3–45.5) vs. 7% (95% CI 0.9–24.3) PFS: 7.0 (95% CI 2.8 to not calculated [NC] m vs. 5.6 m [95% CI 4.1–6.9])
Single-agent ICI				
NCT02853344 (Keynote-427)[96]	No prior systemic therapy	118 (71.5%)	Pembrolizumab	ORR: 28.8% Median PFS: 5.5 m (95% CI 3.9–6.9) Median OS: 31.5 m (95% CI 25.5–NR)
NCT03117309 (HCRN GU16-260-Cohort B)[93]	No prior systemic therapy	19 (54%)	Nivolumab (part A), then with ipilimumab if refractory to monotherapy (part B)	ORR: 1/19 (5%) in part A
NCT02596035 (CheckMate 374)[94]	Prior systemic therapy allowed	24 (54.5%)	Nivolumab	ORR: 8.3%
NCT03012581 (AcSe)[95]	Prior systemic therapy allowed	pRCC type 2: 20 (41%), pRCC type I and unclassified 9 (18%)	Nivolumab	ORR: 10% (pRCC type 2: 5% pRCC type 1 and unclassified: 11%)
Combination ICI				
NCT02982954 CheckMate 920[102]	No prior systemic therapy	18 (34.6%)	Nivolumab with ipilimumab	ORR:27.8%* *Assuming all 18 were included in ORR (only 46/52 patients were included)
NCT03075423 SUNNIFORECAST[104]	No prior systemic therapy	178 (57.6%)	Nivolumab with ipilimumab	ORR: 29.2%
Combination ICI and TKI				
NCT03635892 (CA209-9KU)[97]	No prior ICIs	32	Cabozantinib with nivolumab	ORR: 48% (95% CI 30–64) Median PFS: 13 m (95% CI 7.9–16.9)
NCT04704219 (Keynote-B61)[98]	No prior therapy	93 (59%)	Pembrolizumab plus lenvatinib	ORR: 54% (95% CI 43–64) Median PFS: 17.5 m (15–NR)
NCT03170960 (COSMIC-021)[99]	No prior ICIs or MET inhibitors	15 (47%)	Cabozantinib with atezolizumab	ORR: 47% Median PFS: 8.1 m (95% CI 2.7–18.4) Median OS: 31.8 (95% CI 6.1–NR)
NCT02819596 (CALYPSO)[100]	No prior ICIs or MET inhibitors	41	Savolitinib with durvalumab	ORR: 29% (95% CI 16–46) Median PFS: 4.9 m (95% CI 2.5–10) Median OS: 14.1 m (95% CI 7.3–30.7)

CI: confidence interval; HR: hazard ratio; ICI: immune checkpoint inhibitors; NE: not evaluable; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor; VGEF: vascular endothelial growth factor.

Table 2 (cont'd). Notable clinical trials with published results for papillary renal cell carcinoma

Trial	Enrollment criteria	Number of pRCC	Intervention	Results
Combination TKI and mTOR inhibitor				
NCT01108445 (ASPEN)[101]	No prior systemic treatment	Everolimus: 37 (65%) Sun: 33 (65%)	Everolimus plus lenvatinib vs. sunitinib	ORR: Everolimus: 2 (5%) Sun: 8 (24%)
NCT02915783[105]	No prior systemic treatment	20 (65%)	Lenvatinib Plus Everolimus	ORR: 15% Median PFS: 9.2 m (95% CI 3.5–NE) Median OS: 11.7 m (95% CI 8.1–NE)
Combination ICI and anti-angiogenic				
NCT02724878[106]	Prior systemic therapy allowed but not ICI or bevacizumab	12 (35%)	Atezolizumab with bevacizumab	ORR: 25% (0.039–0.539)

CI: confidence interval; HR: hazard ratio; ICI: immune checkpoint inhibitors; NE: not evaluable; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor; VGEF: vascular endothelial growth factor.

chromophobe RCC based on its mechanism of action and performance in broader RCC populations.[92]

The combination of pembrolizumab and lenvatinib has also shown promising results in chromophobe RCC, with ORR of about 28% and a PFS of 12.5 months; however, distinguishing the contributions of pembrolizumab vs. lenvatinib alone remains challenging due to the single-arm nature of these studies.[98]

Additional combinations, such lenvatinib and the mTOR inhibitor everolimus, have been explored, with an ORR range of 33–44% with the combination (n=6–9) compared to 10% for patients treated with sunitinib (n=10).[101,105]

Based on the totality of data in metastatic chromophobe RCC and current drug availability in Canada, preferred first-line options include combination ICI and TKI therapy (pembrolizumab + lenvatinib) or the combination of lenvatinib and everolimus. Alternative options include single-agent TKI therapy (cabozantinib, sunitinib) and nivolumab + ipilimumab. As emphasized above, clinical trial enrollment is preferred (Table 3).

■ STATEMENT 17

Patients with metastatic nccRCC (excluding SMARCB1-deficient renal medullary carcinoma and collecting duct RCC) with sarcomatoid or rhabdoid dedifferentiation should be offered combination immune checkpoint inhibitor-based therapy ***(consensus achieved: 100%).***

Sarcomatoid or rhabdoid dedifferentiation has been associated with enhanced sensitivity to ICI-based therapy and is emerging as a predictive biomarker in RCC. These pathologic features can be seen across all RCC histologic subtypes, including chromophobe and papillary RCC. The positive association between sarcomatoid/rhabdoid dedifferentiation[106] and improved outcomes with ICI therapy is most notable in ccRCC, with complete responses seen in approximately 20% of patients treated with the combination of ipilimumab and nivolumab.[107]

The data on this association in nccRCC is limited due to the rarity of these pathologic subtypes; however, case reports of papillary RCC with sarcomatoid dedifferentiation demonstrated favorable responses to the ipilimumab and nivolumab combination.[108] Therefore, it is reasonable to extrapolate these findings to nccRCC histologies and to select ICI-based therapies, particularly ipilimumab plus nivolumab, in those with sarcomatoid or rhabdoid dedifferentiation.

Special consideration: Management of metastatic collecting duct RCC and SMARCB1-deficient medullary RCC

Although the management of metastatic collecting duct RCC and SMARCB1-deficient medullary RCC was not formally voted on during the consensus meeting, it was discussed during the meeting and when writing and reviewing the final document. Therefore, it is important to briefly review the treatment approaches for these rare yet aggressive RCC subtypes.

Collecting duct carcinoma accounts for approximately 1% of all renal tumors, with nearly 50% of patients being metastatic at diagnosis.[109] Given its rarity, other malignancies should be excluded before confirming its diagnosis. Due to limited data, it is chal-

Table 3. Notable clinical trials with published results for chromophobe RCC

Trial	Enrollment criteria	Number with chromophobe RCC	Intervention	Results
Single-agent ICI				
NCT02853344 (Keynote-427)[96]	No prior systemic therapy	21 (12.7%)	Pembrolizumab	ORR: 9.5% (95% CI 1.2–30.4) Median PFS: 3.9 m (95% CI 2.6–6.9) Median OS: 23.5 m (95% CI 9.3–NR)
NCT03117309 (HCRN GU16-260)[93]	No prior systemic therapy	6 (17%)	Nivolumab (part A), then with ipilimumab if refractory to mono-therapy (part B)	ORR: 1/6 (17%)
NCT02596035 (CheckMate 374)[94]	Prior systemic therapy allowed	7 (15.9%)	Nivolumab	ORR: 28.6%
NCT03012581 (AcSe)[95]		9 (18%)	Nivolumab	ORR: 0
Single-agent mTOR inhibitor/TKI				
NCT01185366 (ESPN)[107]	No prior systemic therapy	Everolimus: 6 (17%) Sun: 6 (18%)	Everolimus vs. sunitinib	ORR: Everolimus: 1 (3%) Sun: 2 (6%) Median PFS: Everolimus: NA Sun: 8.9 m (95% CI 2.9–20.1) Median OS: Everolimus: 25.1 (95% CI 4.7–NA) Sun: 31.6 m (95% CI 14.2–NA)
Combination TKI and mTOR inhibitor				
NCT01108445 (ASPEN)[101]	No prior systemic treatment	Everolimus: 6 (10%) Sun: 10 (20%)	Everolimus plus lenvatinib vs. sunitinib	ORR: Everolimus: 2 (33%) Sun: 1 (10%)
NCT02915783[105]	No prior systemic treatment	9 (29%)	Lenvatinib plus everolimus	ORR: 44% Median PFS: 13.1 m (95% CI 0.5–NE) Median OS: NE m (95% CI 0.5–NE)
Combination ICI				
NCT02982954 CheckMate 920[102]	No prior systemic therapy	7 (13.5%)	Nivolumab with ipilimumab	ORR: 0%
NCT03075423 SUNNIFORECAST[104]	No prior systemic therapy	60 (19.4%)	Nivolumab with ipilimumab	ORR: 25.9%
Combination ICI and TKI				
NCT03635892 (CA209-9KU)[108]	No prior ICIs	7	Cabozantinib with nivolumab	ORR: 0%
NCT04704219 (Keynote-B61)[98]	No prior therapy	29 (18%)	Pembrolizumab plus lenvatinib	ORR: 28% (95% CI 13–47) Median PFS: 12.5 m (3.9–NR)
NCT03170960 (COSMIC-021)[99]	No prior ICIs or MET inhibitors	8 (25%)	Atezolizumab with cabozantinib	ORR: 11%
Combination ICI and anti-angiogenic				
NCT02724878[106]	Prior systemic therapy Allowed but not ICI or bevacizumab	10 (29%)	Atezolizumab with bevacizumab	ORR: 10%

CI: confidence interval; HR: hazard ratio; ICI: immune checkpoint inhibitors; NA: not available; NE: not evaluable; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor; VGEF: vascular endothelial growth factor.

lenging to determine the optimal treatment for this subtype. The current standard of care for advanced cases is platinum-based cytotoxic chemotherapy, including gemcitabine plus cisplatin or carboplatin plus paclitaxel. The addition of bevacizumab to platinum-based chemotherapy may enhance treatment outcomes, but its potential benefits could be offset by the increased toxicity.[110]

Reports have also shown partial responses to mTOR inhibitors or TKI agents, such as everolimus[111] and sunitinib.[112] A small phase 2 study (n=23) showed encouraging results with cabozantinib (ORR 35%, 95% CI,16–57%).[113] Immuno-oncology (IO) agents have also shown modest activity in a number of case reports, with partial responses observed with nivolumab. A phase 2 trial examining the role of pembrolizumab and enfortumab vedotin (EV) is currently underway in Italy.[114]

SMARCB1-deficient medullary RCC is a rare (representing ≤0.5% of all RCCs) and highly aggressive form of nccRCC (median OS of 13 months). It is predominantly diagnosed in young adults with sickle cell trait/disease.[115,116] The majority of patients will present with nodal or visceral metastases.[116,117] Consequently, even patients with small, localized tumors should be strongly considered for systemic treatment, apart from patients presenting with localized tumors ≤4 cm, which may be treated with upfront surgical resection. Given the infiltrative nature of this subtype, if surgery is warranted, radical nephrectomy is usually preferred over partial nephrectomy.

For patients receiving systemic therapies, the current standard is platinum-based chemotherapies, such as carboplatin plus paclitaxel. Unfortunately, responses to chemotherapy are relatively low (<30%) and often short-lived,[116] but durable complete responses have been noted with carboplatin and paclitaxel.[116] Other chemotherapeutic agents, such as doxorubicin and gemcitabine,[118] or agents targeting the epidermal growth factor receptor (EGFR) pathway have shown activity in patients refractory to platinum-based therapy.[119]

ICI-based therapies have shown very limited efficacy, with a clinical trial of nivolumab plus ipilimumab being stopped early for futility.[120] The SMARCB1-deficient medullary RCC cohort of a basket trial evaluating pembrolizumab monotherapy was also terminated early due to rapid disease progression observed in the first five patients enrolled.[121]As with other rare RCC subtypes, these patients should be considered for clinical trials whenever possible, and several trials are currently ongoing.[122,123]

CONCLUSIONS

This Expert Report document provides guidance on the management of nccRCC, emphasizing the importance of histologic classification in treatment decision-making. We focused primarily on papillary and chromophobe RCC and discussed management strategies for localized and metastatic disease. The consensus statements included were designed to standardize care and hopefully improve patient outcomes while underscoring the need for ongoing research to further refine treatment strategies in variant RCC subtypes. Through the KCRNC, Canada is well-positioned to promote future research efforts in rare RCC subtypes.

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In addition to the authors listed, the following experts participated in the consensus decisions listed herein and should be acknowledged.

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REFERENCES

1. Kidney cancer statistics | Canadian Cancer Society. Available at: https://cancer.ca/en/cancer-information/cancer-types/kidney/statistics. Accessed April 15, 2024.
2. Herbert A, Barclay ME, Koo MM, et al. Stage-specific incidence trends of renal cancers in the East of England, 1999-2016. *Cancer Epidemiol* 2021;71(Pt A). https://doi.org/10.1016/j.canep.2020.101883
3. Tajzler C, Tanguay S, Mallick R, et al. Determining generalizability of the Canadian Kidney Cancer information system (CKCis) to the entire Canadian kidney cancer population. *Can Urol Assoc J* 2020;14:E499-506. https://doi.org/10.5489/cuaj.6716
4. Patard JJ, Leray E, Rioux-Leclercq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: A multicenter experience. *J Clin Oncol* 2005;23:2763-71. https://doi.org/10.1200/JCO.2005.07.055
5. Salgia NJ, Zengin ZB, Pal SK, et al. Renal cell carcinoma of variant histology: New biologic understanding leads to therapeutic advances. *ASCO Ed Book* 2024;44. https://doi.org/10.1200/EDBK_438642
6. Lalani AKA, Kapoor A, Basappa NS, et al. Adjuvant therapy for renal cell carcinoma: 2023 Canadian Kidney Cancer Forum consensus statement. *Can Urol Assoc J* 2023;17:E154-63. https://doi.org/10.5489/cuaj.8381
7. International Agency for Research on Cancer. Urinary and Male Genital Tumours. Vol 8. (Moch H, ed.). International Agency for Research on Cancer; 2022. Available at: https://tumourclassification.iarc.who.int. Accessed April 24, 2024.
8. Diolombi ML, Cheng L, Argani P, et al. Do clear cell papillary renal cell carcinomas have malignant potential? *Am J Surg Pathol* 2015;39:1621-34. https://doi.org/10.1097/PAS.0000000000000513
9. Linehan WM, Spellman PT, Ricketts CJ, et al. Comprehensive molecular characterization of papillary renal cell carcinoma. *N Engl J Med* 2016;374:135-45. https://doi.org/10.1056/NEJMoa1505917
10. Saleeb RM, Brimo F, Gao Y, et al. ABCC2 expression in papillary renal cell carcinoma provides better prognostic stratification than WHO/ISUP nucleolar grade. *Hum Pathol* 2022;120:57-70. https://doi.org/10.1016/j.humpath.2021.12.006
11. Yang C, Shuch B, Kluger H, et al. High WHO/ISUP grade and unfavorable architecture, rather than typing of papillary renal cell carcinoma, may be associated with worse prognosis. *Am J Surg Pathol* 2020;44:582-93. https://doi.org/10.1097/PAS.0000000000001455
12. Murugan P, Jia L, Dinatale RG, et al. Papillary renal cell carcinoma: A single institutional study of 199 cases addressing classification, clinicopathologic and molecular features, and treatment outcome. *Mod Pathol* 2022;35:825-35. https://doi.org/10.1038/s41379-021-00990-9
13. He H, Trpkov K, Martinek P, et al. "High-grade oncocytic renal tumor": Morphologic, immunohistochemical, and molecular genetic study of 14 cases. *Virchows Arch* 2018;473:725-38. https://doi.org/10.1007/s00428-018-2456-4
14. Choiniere R, Al Qa'qa' S, Cheung CC, et al. Frequency and clinicopathologic features of renal low-grade oncocytic tumour and eosinophilic vacuolated tumor: Reclassification of 605 eosinophilic tumors including patients managed with active surveillance. *J Clin Pathol* 2024; Epub ahead of print. https://doi.org/10.1136/jcp-2024-209711
15. Lavallée LT, McAlpine K, Kapoor A, et al. Kidney Cancer Research Network of Canada (KCRNC) consensus statement on the role of renal mass biopsy in the management of kidney cancer. *Can Urol Assoc J* 2019;13(:377-83. https://doi.org/10.5489/cuaj.6176
16. Bhindi B, Lohse CM, Schulte PJ, et al. Predicting renal function outcomes after partial and radical nephrectomy. *Eur Urol* 2019;75:766-72. https://doi.org/10.1016/j.eururo.2018.11.021
17. Richard PO, Violette PD, Bhindi B, et al. Canadian Urological Association guideline: Management of small renal masses - Summary of recommendations. *Can Urol Assoc J* 2022;16:24-5. https://doi.org/10.5489/cuaj.7760
18. Canvasser NE, Stouder K, Lay AH, et al. The usefulness of chest X-Rays for T1a renal cell carcinoma surveillance. *J Urol* 2016;196:321-6. https://doi.org/10.1016/j.juro.2016.02.068
19. Suarez-Sarmiento A, Nguyen KA, Syed JS, et al. brain metastasis from renal-cell carcinoma: An institutional study. *Clin Genitourin Cancer* 2019;17:e1163-70. https://doi.org/10.1016/j.clgc.2019.08.006
20. McAlpine K, Breau RH, Stacey D, et al. Shared decision-making for the management of small renal masses: Development and acceptability testing of a novel patient decision aid. *Can Urol Assoc J* 2020;14:385-91. https://doi.org/10.5489/cuaj.6575
21. Finelli A, Cheung DC, Al-Matar A, et al. Small renal mass surveillance: Histology-specific growth rates in a biopsy-characterized cohort. *Eur Urol* 2020;78:460-7. https://doi.org/10.1016/j.eururo.2020.06.053
22. Bhindi B, Thompson RH, Lohse CM, et al. The probability of aggressive versus indolent histology based on renal tumor size: Implications for surveillance and treatment. *Eur Urol* 2018;74:489-97. https://doi.org/10.1016/j.eururo.2018.06.003
23. Thompson RH, Hill JR, Babayev Y, et al. Metastatic renal cell carcinoma risk according to tumor size. *J Urol* 2009;182:41-5. https://doi.org/10.1016/j.juro.2009.02.128
24. Kassouf W, Monteiro LL, Drachenberg DE, et al. Canadian Urological Association guideline for followup of patients after treatment of non-metastatic renal cell carcinoma. *Can Urol Assoc J* 2018;12:231-8. https://doi.org/10.5489/cuaj.5462
25. Alevizakos M, Gaitanidis A, Nasioudis D, et al. Sarcomatoid renal cell carcinoma: Population-based study of 879 patients. *Clin Genitourin Cancer* 2019;17:e447-53. https://doi.org/10.1016/j.clgc.2019.01.005
26. Leibovich BC, Lohse CM, Cheville JC, et al. Predicting oncologic outcomes in renal cell carcinoma after surgery. *Eur Urol* 2018;73:772-80. https://doi.org/10.1016/j.eururo.2018.01.005
27. Pieretti AC, Westerman ME, Childs A, et al. Sarcomatoid features and lymph node-positive disease in chromophobe renal cell carcinoma. *Urol Oncol Semin Orig Investig* 2021;39:790.e17-23. https://doi.org/10.1016/j.urolonc.2021.06.016
28. Arenovich E, Breau RH, Mallick R, et al. Management, outcomes and predictors of recurrence in chromophobe renal cell carcinoma: Results from the Canadian Kidney Cancer information system (CKCis). *J Clin Urol* 2024;42(4_suppl):389-389. https://doi.org/10.1200/JCO.2024.42.4_suppl.389
29. Kachura J, Baldassarre F, Kielar A, et al. Focal Tumour Ablation for Renal Cell Carcinoma. Cancer Care Ontario. 2016;Program in.
30. Choueiri TK, Tomczak P, Park SH, et al. Overall survival with adjuvant pembrolizumab in renal cell carcinoma. *N Engl J Med* 2024;390:1359-71. https://doi.org/10.1056/NEJMoa2312695
31. Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab vs. placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): A multicenter, randomized, double-blind, phase 3 trial. *Lancet* 2022;400:1103-16. https://doi.org/10.1016/S0140-6736(22)01658-0
32. Motzer RJ, Russo P, Grünwald V, et al. Adjuvant nivolumab plus ipilimumab vs. placebo for localized renal cell carcinoma after nephrectomy (CheckMate 914): A double-blind, randomized, phase 3 trial. *Lancet* 2023;401:821-32. https://doi.org/10.1016/S0140-6736(22)02574-0
33. Lara PN, Tangen C, Heath EI, et al. Adjuvant Everolimus in patients with completely resected, very high-risk renal cell carcinoma of clear cell histology: Results from the phase 3 placebo-controlled SWOG S0931 (EVEREST) trial. *Eur Urol* 2024; Epub ahead of print. https://doi.org/10.1016/j.eururo.2024.05.012
34. Allaf M, et al. LBA67 - phase 3 randomized study comparing perioperative nivolumab (nivo) vs. observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. *Ann Oncol* 2022;33:S808-69. https://doi.org/10.1016/j.annonc.2022.08.072

35. Shuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: Implications for germline and somatic mutation testing and clinical management. *J Clin Oncol* 2014;32:431-7. https://doi.org/10.1200/JCO.2013.50.8192
36. Reaume MN, Graham GE, Tomiak E, et al. Canadian guideline on genetic screening for hereditary renal cell cancers. *Can Urol Assoc J* 2013;7:319. https://doi.org/10.5489/cuaj.1496
37. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw* 2022;20:71-90. https://doi.org/10.6004/jnccn.2022.0001
38. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: Referral indications for cancer predisposition assessment. *Genet Med* 2015;17:70-87. https://doi.org/10.1038/gim.2014.147
39. Carlo MI, Mukherjee S, Mandelker D, et al. Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma. *JAMA Oncol* 2018;4:1228-35. https://doi.org/10.1001/jamaoncol.2018.1986
40. Nguyen KA, Syed JS, Espenschied CR, et al. Advances in the diagnosis of hereditary kidney cancer: Initial results of a multigene panel test. *Cancer* 2017;123:4363-71. https://doi.org/10.1002/cncr.30893
41. Nguyen CB, Knaus C, Li J, et al. Pathogenic germline mutational landscape in patients with renal cell carcinoma and associated clinicopathologic features. *JCO Prec Oncol* 2023;7. https://doi.org/10.1200/PO.23.00168
42. Ko JJ, Xie W, Kroeger N, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: A population-based study. *Lancet Oncol* 2015;16:293-300. https://doi.org/10.1016/S1470-2045(14)71222-7
43. Wells CJ, Donskov F, Fraccon AP, et al. Characterizing the outcomes of metastatic papillary renal cell carcinoma. *Cancer Med* 2017;6:902-9. https://doi.org/10.1002/cam4.1048
44. Yip SM, Ruiz Morales JM, Donskov F, et al. Outcomes of metastatic chromophobe renal cell carcinoma (chrRCC) in the targeted therapy era: Results from the International Metastatic Renal Cell Cancer Database Consortium (IMDC). *Kidney Cancer* 2017;1:41-7. https://doi.org/10.3233/KCA-160002
45. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med* 2018;379:417-27. https://doi.org/10.1056/NEJMoa1803675
46. Mori K, Quhal F, Yanagisawa T, et al. The effect of immune checkpoint inhibitor combination therapies in metastatic renal cell carcinoma patients with and without previous cytoreductive nephrectomy: A systematic review and meta-analysis. *Int Immunopharmacol* 2022;108:108720. https://doi.org/10.1016/j.intimp.2022.108720
47. Bakouny Z, El Zarif T, Dudani S, et al. Upfront cytoreductive nephrectomy for metastatic renal cell carcinoma treated with immune checkpoint inhibitors or targeted therapy: An observational study from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol* 2023;83:145-51. https://doi.org/10.1016/j.eururo.2022.10.004
48. Conti SL, Thomas IC, Hagedorn JC, et al. Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. *Int J Cancer* 2014;134:2245-52. https://doi.org/10.1002/ijc.28553
49. Bamias A, Tzannis K, Papatsoris A, et al. Prognostic significance of cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma treated with first-line sunitinib: A European multi-institutional study. *Clin Genitourin Cancer* 2014;12:373-83. https://doi.org/10.1016/j.clgc.2014.03.012
50. Abern MR, Scosyrev E, Tsivian M, et al. Survival of patients undergoing cytoreductive surgery for metastatic renal cell carcinoma in the targeted-therapy era. *Anticancer Res* 2014;34:2405-11.
51. You D, Jeong IG, Ahn JH, et al. The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy. *J Urol* 2011;185:54-9. https://doi.org/10.1016/j.juro.2010.09.018
52. Choueiri TK, Xie W, Kollmannsberger C, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. *J Urol* 2011;185:60-6. https://doi.org/10.1016/j.juro.2010.09.012
53. Heng DYC, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol* 2014;66:704-10. https://doi.org/10.1016/j.eururo.2014.05.034
54. Fransen van de Putte EE, van den Brink L, Mansour MA, et al. Indications and outcomes for deferred cytoreductive nephrectomy following immune checkpoint inhibitor combination therapy: Can systemic therapy be withdrawn in patients with no evidence of disease? 2023;55:15-22. https://doi.org/10.1016/j.euros.2023.07.002
55. Macleod LC, Odisho AY, Tykodi SS, et al. Comparative effectiveness of initial surgery vs initial systemic therapy for metastatic kidney cancer in the targeted therapy era: Analysis of a population-based cohort. *Urology* 2018;113:146-52. https://doi.org/10.1016/j.urology.2017.11.014
56. Klatte T, Fife K, Welsh SJ, et al. Prognostic effect of cytoreductive nephrectomy in synchronous metastatic renal cell carcinoma: a comparative study using inverse probability of treatment weighting. *World J Urol* 2018;36:417-25. https://doi.org/10.1007/s00345-017-2154-x
57. Song Y, Du CX, Zhang W, et al. Impact of cytoreductive nephrectomy on survival in patients with metastatic renal cell carcinoma treated by targeted therapy. *Chin Med J* 2016;129:530-5. https://doi.org/10.4103/0366-6999.177001
58. Hanna N, Sun M, Meyer CP, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: A national cancer database study. *J Clin Oncol* 2016;34:3267-75. https://doi.org/10.1200/JCO.2016.66.7931
59. de Groot S, Redekop WK, Sleijfer S, et al. Survival in patients with primary metastatic renal cell carcinoma treated with sunitinib with or without previous cytoreductive nephrectomy: Results from a population-based registry. *Urology* 2016;95:121-7. https://doi.org/10.1016/j.urology.2016.04.042
60. Day D, Kanjanapan Y, Kwan E, et al. Benefit from cytoreductive nephrectomy and the prognostic role of neutrophil-to-lymphocyte ratio in patients with metastatic renal cell carcinoma. *Intern Med J* 2016;46:1291-7. https://doi.org/10.1111/imj.13202
61. Xiao WJ, Zhu Y, Dai B, et al. Assessment of survival of patients with metastatic clear cell renal cell carcinoma after radical cytoreductive nephrectomy vs. no surgery: A SEER analysis. *Int Braz J Urol* 2015;41:288-94. https://doi.org/10.1590/S1677-5538.IBJU.2015.02.15
62. Marchioni M, Bandini M, Preisser F, et al. Survival after cytoreductive nephrectomy in metastatic non-clear cell renal cell carcinoma patients: A population-based study. *Eur Urol Focus* 2019;5:488-96. https://doi.org/10.1016/j.euf.2017.11.012
63. Luzzago S, Palumbo C, Rosiello G, et al. Association between systemic therapy and/or cytoreductive nephrectomy and survival in contemporary metastatic non-clear cell renal cell carcinoma patients. *Eur Urol Focus* 2021;7:598-607. https://doi.org/10.1016/j.euf.2020.04.009
64. Kassouf W, Sanchez-Ortiz R, Tamboli P, et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma with non-clear cell histology. *J Urol* 2007;178:1896-1900. https://doi.org/10.1016/j.juro.2007.07.037
65. Riveros C, Ranganathan S, Xu J, et al. Comparative real-world survival outcomes of metastatic papillary and clear cell renal cell carcinoma treated with immunotherapy, targeted therapy, and combination therapy. *Urol Oncol* 2023;41:150.e1-9. https://doi.org/10.1016/j.urolonc.2022.11.022
66. Carrasco A, Thompson RH, Leibovich BC, et al. The impact of histology on survival for patients with metastatic renal cell carcinoma undergoing cytoreductive nephrectomy. *Indian J Urol* 2014;30:38-42. https://doi.org/10.4103/0970-1591.124204
67. Aizer AA, Urun Y, McKay RR, et al. Cytoreductive nephrectomy in patients with metastatic non-clear cell renal cell carcinoma (RCC). *BJUI* 2014;113:E67-74. https://doi.org/10.1111/bju.12442
68. Graham J, Wells JC, Donskov F, et al. Cytoreductive nephrectomy in metastatic papillary renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol Oncol* 2019;2:643-8. https://doi.org/10.1016/j.euo.2019.03.007
69. Canil C, Kapoor A, Basappa NS, et al. Management of advanced kidney cancer: Kidney Cancer Research Network of Canada (KCRNC) consensus update 2021. *Can Urol Assoc J* 2021;15:84-97. https://doi.org/10.5489/cuaj.7245
70. Mason RJ, Wood L, Kapoor A, et al. Kidney Cancer Research Network of Canada (KCRNC) consensus statement on the role of cytoreductive nephrectomy for patients with metastatic renal cell carcinoma. *Can Urol Assoc J* 2019;13:166-74. https://doi.org/10.5489/cuaj.5786
71. Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: The SURTIME randomized clinical trial. *JAMA Oncol* 2019;5:164-70. https://doi.org/10.1001/jamaoncol.2018.5543
72. Mejean A, Thezenas S, Chevreau C, et al. Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): Update on Carmena trial with focus on intermediate IMDC-risk population. *J Clin Oncol* 2019;37. https://doi.org/10.1200/JCO.2019.37.15_suppl.4508
73. Bhindi B, Graham J, Wells JC, et al. Deferred cytoreductive nephrectomy in patients with newly diagnosed metastatic renal cell carcinoma. *Eur Urol* 2020;78:615-23. https://doi.org/10.1016/j.eururo.2020.04.038

74. Pignot G, Thiery-Vuillemin A, Albigès L, et al. Oncological outcomes of delayed nephrectomy after optimal response to immune checkpoint inhibitors for metastatic renal cell carcinoma. *Eur Urol Oncol* 2022;5:577-84. https://doi.org/10.1016/j.euo.2022.07.002
75. Singla N, Hutchinson RC, Ghandour RA, et al. Improved survival after cytoreductive nephrectomy for metastatic renal cell carcinoma in the contemporary immunotherapy era: An analysis of the National Cancer Database. *Urol Oncol* 2020;38:604.e9-17. https://doi.org/10.1016/j.urolonc.2020.02.029
76. Reimers MA, Figenshau RS, Kim EH, et al. Elective cytoreductive nephrectomy after checkpoint inhibitor immunotherapy in patients with initially unresectable metastatic clear cell renal cell carcinoma. *Clin Genitourin Cancer* 2020;18:361-6. https://doi.org/10.1016/j.clgc.2020.04.002
77. Shirotake S, Miyama Y, Baba Y, et al. Impact of cytoreductive nephrectomy following nivolumab plus ipilimumab therapy for patients with advanced renal cell carcinoma. *Anticancer Res* 2022;42:2727-35. https://doi.org/10.21873/anticanres.15751
78. Dragomir A, Nazha S, Tanguay S, et al. Outcomes of cytoreductive nephrectomy for patients with metastatic renal cell carcinoma: Real-world data from Canadian centers. *Eur Urol Focus* 2022;8:1703-10. https://doi.org/10.1016/j.euf.2021.10.004
79. Singla N, Elias R, Ghandour RA, et al. Pathologic response and surgical outcomes in patients undergoing nephrectomy following receipt of immune checkpoint inhibitors for renal cell carcinoma. *Urol Oncol Semin Orig Investig* 2019;37(:924-31. https://doi.org/10.1016/j.urolonc.2019.08.012
80. Albiges L, Tannir N, Burotto M, et al. 711P Nivolumab + ipilimumab (N+I) vs sunitinib (S) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214: 4-year followup and subgroup analysis of patients (pts) without nephrectomy. *Ann Oncol* 2020;31:S559-60. https://doi.org/10.1016/j.annonc.2020.08.783
81. All S, Garant A, Hannan R. Stereotactic ablative radiation (SAbR) for oligometastatic RCC. *Semin Radiat Oncol* 2021;31:227-34. https://doi.org/10.1016/j.semradonc.2021.02.002
82. Mikhail M, Chua KJ, Khizir L, et al. Role of metastasectomy in the management of renal cell carcinoma. *Front Surg* 2022;9. https://doi.org/10.3389/fsurg.2022.943604
83. Tang C, Msaouel P, Hara K, et al. Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: A single-arm, single-centre, feasibility, phase 2 trial. *Lancet Oncol* 2021;22:1732-9. https://doi.org/10.1016/S1470-2045(21)00528-3
84. Hannan R, Christensen M, Christie A, et al. Stereotactic ablative radiation for systemic therapy-naïve oligometastatic kidney cancer. *Eur Urol Oncol* 2022;5:695-703. https://doi.org/10.1016/j.euo.2022.06.008
85. Dai J, Hu X, Zhang H, et al. The survival benefit of metastasectomy for metastatic non-clear cell renal cell carcinoma. *J Clin Oncol* 2023;41:686-686. https://doi.org/10.1200/JCO.2023.41.6_suppl.686
86. Dabestani S, Marconi L, Hofmann F, et al. Local treatments for metastases of renal cell carcinoma: A systematic review. *Lancet Oncol* 2014;15:e549-61. https://doi.org/10.1016/S1470-2045(14)70235-9
87. Zhang Y, Schoenhals J, Christie A, et al. Stereotactic ablative radiation therapy (SAbR) used to defer systemic therapy in oligometastatic renal cell cancer. *Int J Radiat Oncol Biol Phys* 2019;105:367-75. https://doi.org/10.1016/j.ijrobp.2019.07.023
88. Wu K, Liu Z, Shao Y, Li X. Nomogram predicting survival to assist decision-making of metastasectomy in patients with metastatic renal cell carcinoma. *Front Oncol* 2020;10. https://doi.org/10.3389/fonc.2020.592243
89. Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: A prospective, phase 2 trial. *Lancet Oncol* 2016;17:1317-24. https://doi.org/10.1016/S1470-2045(16)30196-6
90. Harrison MR, Costello BA, Bhavsar NA, et al. Active surveillance of metastatic renal cell carcinoma: Results from a prospective observational study (MaRCC). *Cancer* 2021;127:2204-12. https://doi.org/10.1002/cncr.33494
91. Kushnir I, Basappa NS, Ghosh S, et al. Active surveillance in metastatic renal cell carcinoma: results from the Canadian Kidney Cancer Information System. *Clin Genitourin Cancer* 2021;19:521-30. https://doi.org/10.1016/j.clgc.2021.05.004
92. Pal SK, Tangen C, Thompson IM, et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: A randomized, open-label, phase 2 trial. *Lancet* 2021;397:695-703. https://doi.org/10.1016/S0140-6736(21)00152-5
93. Atkins MB, Jegede OA, Haas NB, et al. Original research: Phase 2 study of nivolumab and salvage nivolumab/ipilimumab in treatment-naïve patients with advanced non-clear cell renal cell carcinoma (HCRN GU16-260-Cohort B). *J Immunother Cancer* 2023;11:4780. https://doi.org/10.1136/jitc-2022-004780
94. Vogelzang NJ, Olsen MR, McFarlane JJ, et al. Safety and efficacy of nivolumab in patients with advanced non-clear cell renal cell carcinoma: Results from the phase IIIb/IV CheckMate 374 study. *Clin Genitourin Cancer* 2020;18:461-8.e3. https://doi.org/10.1016/j.clgc.2020.05.006
95. Albiges L, Pouessel D, Beylot-Barry M, et al. Nivolumab in metastatic non-clear cell renal cell carcinoma: First results of the AcSe prospective study. *J Clin Oncol* 2020;38(6_suppl):699-699. https://doi.org/10.1200/JCO.2020.38.6_suppl.699
96. McDermott DF, Lee JL, Ziobro M, et al. Open-label, single-arm, phase 2 study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. *J Clin Oncol* 2021;39:1029. https://doi.org/10.1200/JCO.20.02365
97. Fitzgerald KN, Lee CH, Voss MH, et al. Cabozantinib Plus nivolumab in patients with non-clear cell renal cell carcinoma: Updated results from a phase 2 trial. *Eur Urol* 2024; Epub ahead of print. https://doi.org/10.1016/j.eururo.2024.04.025
98. Albiges L, Gurney H, Atduev V, et al. Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): A single-arm, multicenter, phase 2 trial. *Lancet Oncol* 2023;24:881-91. https://doi.org/10.1016/S1470-2045(23)00276-0
99. Pal SK, Agarwal N, Singh P, et al. Cabozantinib (C) in combination with atezolizumab (A) in urothelial carcinoma (UC): Results from cohorts 3, 4, 5 of the COSMIC-021 study. *J Clin Oncol* 2022;40(16_suppl):4504-4504. https://doi.org/10.1200/JCO.2022.40.16_suppl.4504
100. Suárez C, Larkin JMG, Patel P, et al. Phase 2 study investigating the safety and efficacy of savolitinib and durvalumab in metastatic papillary renal cancer (CALYPSO). *J Clin Oncol* 2023;41:2493-2502. https://doi.org/10.1200/JCO.22.01414
101. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus vs. sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): A multicenter, open-label, randomized, phase 2 trial. *Lancet Oncol* 2016;17:378. https://doi.org/10.1016/S1470-2045(15)00515-X
102. Tykodi SS, Gordan LN, Alter RS, 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:e003844. https://doi.org/10.1136/jitc-2021-003844
103. Choueiri TK, Heng DYC, Lee JL, et al. Efficacy of savolitinib vs sunitinib in patients with met-driven papillary renal cell carcinoma: The SAVOIR phase 3 randomized clinical trial. *JAMA Oncol* 2020;6:1247-55. https://doi.org/10.1001/jamaoncol.2020.2218
104. Bergmann L, Al E. LBA75 - Prospective randomised phase 2 trial of ipilimumab/nivolumab vs. standard of care in non-clear cell renal cell cancer: Results of the SUNNIFORECAST trial. ESMO 2024. Published online 2024. https://doi.org/10.1016/j.annonc.2024.08.2318
105. Hutson TE, Michaelson MD, Kuzel TM, et al. A single-arm, multicenter, phase 2 study of lenvatinib plus everolimus in patients with advanced non-clear cell renal cell carcinoma. *Eur Urol* 2021;80:162-70. https://doi.org/10.1016/j.eururo.2021.03.015
106. Sawaya GBN, Dragomir A, Wood LA, et al. Real-world assessment of clinical outcomes in patients with metastatic renal cell carcinoma with or without sarcomatoid features treated with first-line systemic therapies. *Eur Urol Oncol* 2024;7:570-80. https://doi.org/10.1016/j.euo.2023.11.016
107. Tannir NM, Signoretti S, Choueiri TK, et al. Efficacy and safety of nivolumab plus ipilimumab vs. sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. *Clin Cancer Res* 2021;27:78-86. https://doi.org/10.1158/1078-0432.CCR-20-2063
108. Schvartsman G, Carneiro APCD, Filippi RZ, et al. Rapid deep responses with nivolumab plus ipilimumab in papillary renal cell carcinoma with sarcomatoid dedifferentiation. *Clin Genitourin Cancer* 2019;17:315-8. https://doi.org/10.1016/j.clgc.2019.05.023
109. Tang C, Zhou Y, Ge S, et al. Incidence, clinical characteristics, and survival of collecting duct carcinoma of the kidney: A population-based study. *Front Oncol* 2021;11. https://doi.org/10.3389/fonc.2021.727222
110. Pécuchet N, Bigot F, Gachet J, et al. Triple combination of bevacizumab, gemcitabine and platinum salt in metastatic collecting duct carcinoma. *Ann Oncol* 2013;24:2963-7. https://doi.org/10.1093/annonc/mdt423
111. Yin M, Wang W, Rosenberg J, et al. Targeted therapy in collecting duct carcinoma of the kidney: A case report and literature review. *Clin Genitourin Cancer* 2016;14:e203-6. https://doi.org/10.1016/j.clgc.2015.11.008
112. Miyake H, Haraguchi T, Takenaka A, et al. Metastatic collecting duct carcinoma of the kidney responded to sunitinib. *Int J Clin Oncol* 2011;16:153-5. https://doi.org/10.1007/s10147-010-0116-z
113. Procopio G, Sepe P, Claps M, et al. Cabozantinib as First-line treatment in patients with metastatic collecting duct renal cell carcinoma: Results of the BONSAI trial for the Italian Network for Research in Urologic-Oncology (Meet-URO 2 Study). *JAMA Oncol* 2022;8:910-13. https://doi.org/10.1001/jamaoncol.2022.0238
114. Study Details | Pembrolizumab Plus Enfortumab Vedotin in Collecting Duct and Renal Medullary Carcinoma | ClinicalTrials.gov. Available at: Accessed June 19, 2024. https://www.clinicaltrials.gov/study/NCT06302569?cond=Collecting Duct Renal Cell Carcinoma&limit=100&rank=6. Accessed June 19, 2024.

115. Holland P, Merrimen J, Pringle C, et al. Renal medullary carcinoma and its association with sickle cell trait: A case report and literature review. *Curr Oncol* 2020;27:e53. https://doi.org/10.3747/co.27.5043
116. Shah AY, Karam JA, Malouf GG, et al. Management and outcomes of patients with renal medullary carcinoma: A multicenter collaborative study. *BJU Int* 2017;120:782-92. https://doi.org/10.1111/bju.13705
117. Lebenthal JM, Kontoyiannis PD, Hahn AW, et al. Clinical characteristics, management, and outcomes of patients with renal medullary carcinoma: A single-center, retrospective analysis of 135 patients. *Eur Urol Oncol* 2024; Epub ahead of print. https://doi.org/10.1016/j.euo.2024.07.002
118. Wilson NR, Wiele AJ, Surasi DS, et al. Efficacy and safety of gemcitabine plus doxorubicin in patients with renal medullary carcinoma. *Clin Genitourin Cancer* 2021;19:e401-8. https://doi.org/10.1016/j.clgc.2021.08.007
119. Wiele AJ, Surasi DS, Rao P, et al. Efficacy and safety of bevacizumab plus erlotinib in patients with renal medullary carcinoma. *Cancers* 2021;13. https://doi.org/10.3390/cancers13092170
120. Study Details | Phase II Trial of Nivolumab Plus Ipilimumab in Patients With Renal Medullary Carcinoma | ClinicalTrials.gov. Available at: https://clinicaltrials.gov/study/NCT03274258. Accessed June 19, 2024.
121. Nze C, Msaouel P, Derbala MH, et al. A phase 2 clinical trial of pembrolizumab efficacy and safety in advanced renal medullary carcinoma. *Cancers* 2023;15. https://doi.org/10.3390/cancers15153806
122. Msaouel P, Hong AL, Mullen EA, et al. Updated recommendations on the diagnosis, management, and clinical trial eligibility criteria for patients with renal medullary carcinoma. *Clin Genitourin Cancer* 2019;17:1-6. https://doi.org/10.1016/j.clgc.2018.09.005
123. Search for: Renal Medullary Carcinoma | Card Results | ClinicalTrials.gov. Available at: Accessed June 19, 2024. https://www.clinicaltrials.gov/search?cond=RenalMedullary Carcinoma. Accessed June 19, 2024.

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