The BSMO expert panel recommendations on renal cell carcinoma management: 2025 update

M. Gilon, MD[1], B. Beuselinck, MD, PhD[2], M. Baldewijns, MD, PhD[3], P.R. Debruyne, MD, PhD[4], E. Seront, MD, PhD[5], N. Sundahl, MD, PhD[6], A. Verbiest, MD, PhD[7], S. Rottey MD, PhD[8], C. Gennigens, MD, PhD[1]

SUMMARY

The management of renal cell carcinoma is evolving rapidly. Here, the BSMO expert panel discusses recent advances focusing on systemic therapies, and provides guidelines adapted to the Belgian context.

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INTRODUCTION

The Belgian Society of Medical Oncology (BSMO) renal cancer expert panel first published its recommendations for the management of renal cell carcinoma (RCC) in 2015, followed by regular updates.[1–3] These recommendations are based on international guidelines and phase III trial data, while also considering the specificities of the Belgian health-care system. This updated overview integrates the latest evidence from pivotal trials, with the aim to provide a concise, practical guide to support clinical decision-making in real-world Belgian practice.

EPIDEMIOLOGY

In 2022, 2,076 new cases of RCC were reported in Belgium, including 1,377 men and 699 women (2:1 ratio), with a median age at diagnosis of 68 and 70 years respectively. The majority of patients (63%) were diagnosed with stage I disease, while 9% presented with stage II, 13% with stage III, and 15% with stage IV. Although the incidence of kidney cancer is increasing, mortality rates continue to decline. In 2021, 512 deaths were attributed to RCC, corresponding to a 5-year survival rate of 79.4% after initial diagnosis.[4]

[1]Department of Medical Oncology, CHU de Liège, Liège, Belgium, [2]Department of General Medical Oncology, Leuven Cancer Institute, Leuven University Hospital, Leuven, Belgium, [3]Department of Pathology, University Hospital Leuven, Leuven, Belgium, [4]Department of Medical Oncology, Kortrijk Cancer Centre, General Hospital AZ Groeninge, Kortrijk, Belgium, [5]Department of Medical Oncology, King Albert II Institute, Saint-Luc University Clinics, Brussels, Belgium, [6]Department of Radiation Oncology, General Hospital AZ Groeninge, Kortrijk, Belgium; Department of Human Structure and Repair, Ghent University, Ghent, Belgium, [7]Department of Medical Oncology, University Hospital Antwerp, Edegem, Belgium, [8]Department of Medical Oncology, University Hospital Ghent, Ghent, Belgium

Please send all correspondence to: C. Gennigens, MD, PhD, Department of Medical Oncology, CHU de Liège, Avenue de l'Hôpital 1, 4000 Liège, Belgium, email: Christine.Gennigens@chuliege.be.

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WORK-UP

DIAGNOSIS

RCC is most often diagnosed incidentally on imaging performed for unrelated indications; only about one-third of patients present with symptoms attributable to RCC.[5] When RCC is suspected, contrast-enhanced abdominal CT scan remains the standard imaging modality for diagnosis, tumour characterization, and staging. MRI offers comparable diagnostic accuracy and may be used if CT is contraindicated or inconclusive.[6] In case of cystic renal masses, the 2019 updated Bosniak classification should be used to stratify the risk of malignancy.[7]

STAGING

The metastatic workup should always include a chest CT scan to assess for potential pulmonary metastases, except in cT1a tumours.[8] Brain and bone imaging are recommended in cases of metastatic disease and symptoms suggesting central nervous system or skeletal involvement; when available, MRI is preferred over CT for its superior sensitivity in detecting bone metastases.[9,10] If pembrolizumab is considered in the adjuvant setting, an extended work-up with brain and bone imaging could be considered, as the inclusion criteria of KEYNOTE-564 required complete evaluation to confirm the absence of metastases within 28 days prior to randomization.[11] Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) and bone scintigraphy are not recommended for the diagnosis or follow-up of renal cell carcinoma (RCC). However, novel molecular imaging techniques such as zirconium-labelled girentuximab PET and 99mTc-Sestamibi SPECT/CT have shown efficacy in the diagnostic evaluation of renal masses.[12,13]

RENAL MASS BIOPSY

In case of **metastatic RCC**, histopathological confirmation is mandatory before starting any systemic treatment.[9] On the other hand, for **localised RCC**, percutaneous renal mass biopsy (RMB) before surgery is not a standard of care. However, RMB has an excellent diagnostic accuracy; a recent prospective study from the French kidney cancer database UroCCR showed that RMB were contributive in 92.4% of patients and determined the benign/malignant nature, histological subtype, and grade in respectively 96.9%, 86.4%, and 52.6% of the cases.[14] Performing RMB prior to surgery can help avoid overtreatment, especially in small renal masses (SRM; cT1a, meaning ≤4cm), as up to 30% are benign.[14,15] Furthermore, RMB is a safe procedure, the principal complications being haematomas, haematuria and lumbar pain; seeding is extremely rare.[16] Therefore, RMB is recommended in case of radiologically indeterminate renal masses or whenever it may influence management, particularly for patients with SRM and/or at high risk of severe post-operative renal insufficiency.[9,17–19] RMB is also required in case of ablative treatment and can be considered in patients who are candidates for active surveillance. Still, RMB is not recommended in case of contrast-enhancing renal mass when surgery is planned or cystic renal masses unless a significant solid component is visible at imaging.[17]

PATHOLOGY

Histopathology plays a central role in the diagnosis, prognosis, and therapeutic decisions for RCC. The 2022 WHO classification recognized six RCC entities: clear cell tumours (ccRCC; the most common, accounting for ~ 70% of cases), papillary tumours (pRCC; the former papillary type 1), oncocytic and chromophobe tumours (chRCC), collecting duct tumours, molecular-defined tumours (such as fumarate hydratase-deficient RCC and translocation RCC), and newly recognized entities such as ELOC-mutated RCC. A subset of kidney tumours remain unclassified (NOS); this group includes most cases previously referred to as papillary RCC type 2, now recognised as high-grade RCC with papillary features rather than true papillary RCC.[20]

Unlike previous editions, the latest WHO classification introduces a molecularly defined subset of renal tumours. These neoplasms display highly heterogeneous morphological features that may mimic ccRCC or pRCC and therefore cannot always be reliably diagnosed based on morphology alone. In such cases, molecular testing including FISH, next-generation sequencing (NGS), and RNA sequencing is increasingly used to refine classification and to identify actionable mutations for personalised therapeutic strategies. When molecular testing is unavailable, a detailed morphological description including a comment on possible molecular alterations should be mentioned in the differential diagnosis. Since NGS and RNA sequencing are reimbursed for RCC characterization when performed in institutions accredited under the INAMI convention, complex RCC cases may also be referred to these institutions for further molecular analysis.[20]

Sarcomatoid and rhabdoid patterns, which are not histologic subtypes in themselves and can occur in any RCC subtype, should be reported if present, as they are associated with a high-grade biological phenotype and poor cancer-specific survival (CSS). Histological evaluation should also include assessment of the International Society of Urological Pathology (ISUP) nuclear grade, vascular invasion, tumour necrosis, invasion of collecting system or peri-renal fat, and pathological staging (pT and, if available, pN categories).[20,21]

TABLE 1. The Leibovich (a), VENUSS (b), IMDC (c) and modified Glasgow (d) prognostic scores.

a. Leibovich score for prediction of recurrence after radical nephrectomy in ccRCC

Primary tumour status (T stage)	Score
pT1a pT1b pT2 pT3 – pT4	0 2 3 4
Regional lymph node status (N stage)	
pNx – pN0 pN1 – pN2	0 2
Tumour size (cm)	
< 10 ≥ 10	0 1
Nuclear grade	
1 – 2 3 4	0 1 3
Histologic tumour necrosis	
Absent Present	0 1
Risk groups: low: 0-2; intermediate: 3-5; high ≥ 6	

b. VENUSS score for prediction of recurrence after radical nephrectomy in pRCC

Primary tumour status (T stage)	Score
pT1 pT2 pT3 – pT4	0 1 2
Regional lymph node status (N stage)	
pNx – pN0 pN1	0 3
Tumour size (cm)	
≤ 4 ≥ 4.1	0 2
Nuclear grade	
1 – 2 3 – 4	0 2
Venous tumour thrombus	
Absent Present	0 2
Risk groups: low: 0-2; intermediate: 3-5; high ≥ 6	

c. IMDC score for prediction of prognosis in metastatic RCC

IMDC risk factors
Less than a year between diagnosis and systemic treatment Karnofsky performance status <80% Anaemia Elevated corrected calcium Neutrophil count above the upper limit of normal Platelet count above the upper limit of normal
Risk groups: favourable: 0 risk factors; intermediate: 1-2; poor: ≥ 3

d. Modified Glasgow Prognostic score for prediction of prognosis in metastatic RCC

CRP	Score
≤ 10 mg/L	0
> 10mg/L	1
Albumin	
< 3.5 g/dl	0
≥ 3.5 g/dl	1

mGPS	1-year relapse-free survival
0	90.9%
1	61.1%
2	10.1%

RISK ASSESSMENT

The 2016 TNM classification system remains the current standard for staging RCC.[22] However, the European Association of Urology (EAU) has recently proposed modifications to improve its prognostic accuracy, including better discrimination within pT1 and pT2 categories, clearer subclassification of venous and adrenal invasion, and more granular nodal staging, but these have not yet been integrated into standard practice.[23]

In addition to TNM staging, the 2003 Leibovich score is frequently used to stratify risk in localised ccRCC, whereas the VENUSS score can be used in localised pRCC (*Table 1*).[24,25] With the approval of adjuvant pembrolizumab for high-risk RCC, the risk stratification used in KEYNOTE-564 has become clinically relevant for selecting patients eligible for this approach. In this trial, intermediate-high risk was defined as pT2, grade 4 or sarcomatoid, N0, M0, or pT3, any grade, N0, M0. High risk was defined as pT4, any grade, N0, M0, or any pT, any grade, with lymph-node positivity, M0.[11]

In metastatic RCC, the International Metastatic RCC Database Consortium (IMDC) score is the most widely used tool to estimate prognosis and guide treatment decisions based on clinical and biochemical parameters (*Table 1*).[26] Although it was developed during the era of vascular endothelial growth factor receptors-tyrosine kinase inhibitors (VEGFR-TKI), its predictive relevance in the current landscape of immune checkpoint inhibitor (ICI)-based therapies has been supported by recent retrospective data.[27] The modified Glasgow Prognostic Score (mGPS), a non-RCC-specific biomarker integrating systemic inflammation and nutritional status (*Table 1*), demonstrated superior prognostic discrimination compared to IMDC score in the IMmotion151 trial (c- index 0.72 *vs.* 0.68) while identifying a larger low-risk population (57.3% *versus* 22.3%).[28,29]

The integration of molecular markers may further enhance the prognostic precision of these models, as RNA sequencing can classify ccRCC into two molecular subtypes that have been validated in several recent pivotal trials.[30,31] The first category comprises approximately half of ccRCC and includes hypervascular, relatively indolent tumours with lower IMDC risk scores that are more sensitive to VEGFR-TKIs. The second category encompasses the other half of ccRCC, which are characterised by low angiogenesis, a more aggressive pattern, and an immune-activated but immunosuppressive tumour microenvironment. These tumours are often associated with systemic inflammation, aggressive clinical behaviour, and sarcomatoid dedifferentiation. They are resistant to VEGFR-TKIs but tend to respond better to ICIs. Since RNA sequencing is not performed routinely, this molecular classification is not used in standard clinical practice. However, some clinical, pathological, and biochemical characteristics can indirectly reflect the underlying molecular subtype.

GENETIC TESTING

Genetic evaluation should be considered in selected patients with clinical features suggestive of a hereditary RCC. According to current EAU guidelines, genetic testing is recommended in individuals diagnosed at ≤ 46 years of age, as well as those with bilateral and/or multifocal tumours, a first- or second-degree relative with RCC, or a close relative carrying a known pathogenic variant. Testing is also advised for certain histological subtypes, such as non–clear cell RCC (nccRCC), or in the presence of extrarenal manifestations suggestive of a hereditary or syndromic form of RCC.[17] Hereditary syndromes associated with RCC are descripted in *Table 2*.[32,33]

LOCALISED RCC

SURGERY

For localised RCC, surgical resection remains the standard of care, offering the best chance for durable oncologic control. **Partial nephrectomy** (PN) is the preferred treatment for T1 tumour over radical nephrectomy (RN), regardless of the surgical technique.[34] PN should also be considered in selected T2 and T3 patients with solitary kidney, bilateral renal tumours or pre-existing renal insufficiency.[9,17] In cases of positive surgical margin, the risk of local recurrence is increased, although CSS appears to remain unaffected; a close monitoring is recommended and immediate totalisation is not mandatory, though it can be discussed in the presence of high-grade tumour and/or large positive margin.[8,19] For renal masses > 7cm, **RN** is considered the gold standard[9]; to date, no randomised controlled trial has directly compared open, laparoscopic and robot-assisted RN, providing clear recommendations on the optimal surgical technique. Routine adrenalectomy or lymph node dissection should not be performed in the absence of radiologic or intraoperative signs of invasion.[17] In cases of cN+, lymph node dissection is indicated mainly for staging, as it has not demonstrated a proven oncologic benefit.[35] In the presence of venous thrombus, aggressive surgical resection should be offered to non-metastatic fit patients, irrespective of the extent of tumour thrombus; these patients warrant referral to a tertiary care centre to ensure comprehensive multidisciplinary assessment and management, particularly in cases involving the inferior vena cava.[17]

TABLE 2. RCC hereditary syndromes and extrarenal manifestations associated

Syndrome	Gene implicated	RCC histology associated	Extrarenal manifestations associated
Von Hippel-Lindau syndrome	*VHL, ELOC*	Multifocal, bilateral ccRCC and renal cysts	Retinal and central nervous system hemangioblastomas, pheochromocytoma, pancreatic cysts/neuroendocrine tumours
Hereditary pRCC	*c-MET*	Multifocal, bilateral pRCC	None
Birt-Hogg-Dubé syndrome	*BHD (FLCN), PRDM10*	chRCC, hybrid oncocytoma/chRCC, oncocytic tumours, ccRCC, pRCC	Facial fibrofolliculomas, lung cysts, spontaneous pneumothorax
Hereditary leiomyomatosis and RCC syndrome	*FH*	Fumarate hydratase-deficient RCC	Skin leiomyomas, uterine leiomyomas and leiomyosarcomas, adrenal cortical hyperplasia
Tuberous sclerosis	*TSC1, TSC2*	Multiple, bilateral angiomyolipomas, ccRCC, pRCC, chRCC	Cutaneous angiofibroma, lymphangioleiomyomatosis, subungual fibromas, cardiac rhabdomyomas, intestinal polyps, lung cysts, cortical tubers, subependymal giant cell astrocytomas, neurologic manifestation (epilepsy, mental retardation)
Succinate dehydrogenase (SDH)-deficient RCC	*SDHA, SDHB, SDHC or SDHD*	SDH-deficient RCC	Paraganglioma, pheochromocytoma, SDH-deficient gastrointestinal stromal tumour
Hyperparathyroidism - jaw tumour syndrome	*HRTP2 /CDC73*	Mixed epithelial and stromal tumours, Wilms tumours, papillary RCC, renal cysts	Parathyroid tumours, hyperparathyroidism, fibro-osseous mandibular and maxillary tumours, uterine cancer
Cowden syndrome	*PTEN*	ccRCC, pRCC, chRCC	Learning disability, autism, macrocephaly, dermatological manifestations (trichilemmomas, papillomatous papules, and acral and plantar keratosis), intestinal polyps, uterine fibroids, lipomas, hamartomas, arteriovenous malformations; susceptibility to thyroid, breast, endometrial, prostate and colon cancers
MiTF-related melanoma and RCC predisposition syndrome	*MiTF*	MiTF family translocation RCC	Melanoma, pancreatic cancer, pheochromocytoma
Constitutional chromosome 3 translocation	Unknown	*Multiple, bilateral ccRCC*	No consistent extrarenal features
Familial non-syndromic ccRCC	Unknown	Multiple, bilateral ccRCC	No consistent extrarenal features
BAP1-associated RCC	*BAP1*	ccRCC	Uveal and cutaneous melanoma, mesothelioma, and melanocytic BAP1 mutated atypical intradermal tumours
Familial papillary thyroid carcinoma associated renal neoplasms	Unknown	pRCC, oncocytomas	Familial papillary thyroid carcinoma, nodular thyroid disease
Hereditable sickle cell hemoglobinopathy associated renal carcinomas	*SMARCB1* and others	Renal medullary carcinoma	Sickle cell disease/trait

ALTERNATIVES TO SURGERY

Local ablative techniques, such as thermal ablation (TA; cryoablation, radiofrequency, and microwave ablation) and stereotactic ablative radiotherapy (SABR) are effective treatment alternatives to surgery. All methods have shown excellent local control and limited toxicity in T1a tumours, while in larger tumours (≥ T1b) or centrally located tumours, SABR is associated with higher local control rates and lower complication risk.[36,37] Notably, the avoidance of general anaesthesia represents another advantage of SABR. These local ablative treatments can be offered to patients with frailty, high surgical risk, solitary kidney, renal insufficiency, hereditary or bilateral RCC or based on patient preference. RMB is mandatory in case of ablative treatment.[8,9]

Embolization can be proposed to manage symptoms, such as haematuria and flank pain, for patients with locally-advanced unresectable RCC.[17]

ACTIVE SURVEILLANCE

Active surveillance (AS) is defined as initial regular clinical and radiological monitoring of tumour, with treatment deferred unless signs of progression, such as tumour growth or the onset of symptoms. AS should first be distinguished from watchful waiting, which concerns patients with significant comorbidities for whom any active treatment is contra-indicated and who require a follow-up without scheduled imaging, unless clinically indicated.

Approximately 20–30% of SRMs are benign, with a slow local growth rate (0,1– 0,2 cm/year) and a low risk of progression to metastatic disease (< 2%).[38–43] In well-selected patients, *Pierorazio et al.* prospectively demonstrated the non-inferiority of AS compared to other interventions in terms of short- and intermediate-term survival.[41] However, randomised controlled trials are needed to confirm these results and to establish formal recommendations regarding patient selection, surveillance schedules and criteria for initiating active treatment.

Currently, AS is considered a reasonable initial management option for SRMs in patients with significant comorbidities or advanced age.[9,17,18] AS also appears to be a safe strategy for SRM < 2cm, regardless of age or performance status, although further evidence are needed to consider expanding the size cut-off.[44,45] Furthermore, AS may also be discussed for T1b tumours in patients over 75 years of age.[9,46] No strong recommendations exist regarding the surveillance regimen. While the European Society for Medical Oncology (ESMO) and EAU guidelines do not define a specific schedule, the French Association of Urology (AFU) recommends abdominal imaging every 3 to 6 months during the first year, then every 6 to 12 months if the lesion remains stable, with chest imaging at baseline followed by annual monitoring.[19] US guidelines support a similar approach.[18,47] RMB is required to differentiate benign from malignant lesions and to adapt surveillance on tumour histology and grade.[17,48] Active treatment should be considered in case of a growth rate > 0.5 cm/year, tumour size exceeding 3 – 4 cm, symptom onset, improvement in the patient's general condition, or upon patient request.[18,19,47,49]

ADJUVANT TREATMENT

Multiple trials have evaluated **VEGFR-TKI** in the adjuvant setting, consistently failing to demonstrate survival benefits. These negative results include the ASSURE (sunitinib *vs.* sorafenib *vs.* placebo), S-TRAC (sunitinib *vs.* placebo), PROTECT (pazopanib *vs.* placebo), ATLAS (axitinib *vs.* placebo), and SORCE (sorafenib *vs.* placebo) trials.[50–54] Similarly, adjuvant everolimus did not improve disease-free survival (DFS), except in the very high-risk group.[55]

Initial investigations of **ICI** as adjuvant therapies were equally disappointing. The CheckMate 914 trial evaluated the combination of nivolumab and ipilimumab (part A), and nivolumab alone *vs.* placebo (part B) without demonstrating significant clinical benefit.[56,57] The IMmotion010 trial with atezolizumab and the PROSPER trial with perioperative nivolumab similarly failed to meet their primary endpoints.[58,59]

Finally, the KEYNOTE-564 trial has brought the only encouraging results with adjuvant pembrolizumab demonstrating a significant improvement in DFS and overall survival (OS) in patients with localised ccRCC at intermediate-high (grade 4 or sarcomatoid pT2; pT3) or high risk (pT4 or N+), as well as in patients with M1 no evidence of disease (NED) RCC, defined as oligometastases completely resected within one year of nephrectomy.[60] Pembrolizumab (200 mg) or placebo was administered in a 1:1 ratio to a total of 994 patients, every three weeks for up to 17 cycles. With a median follow-up of 69.5 months, KEYNOTE-564 showed 5-year DFS rates of 60.9% in the pembrolizumab arm *vs.* 52.2% in the placebo arm (HR 0.71, 95% CI 0.59-0.86) and 5-year OS rates of 87.7% *vs.* 82.3%, respectively (HR 0.66, 95% CI 0.48–0.90).[61] Grade 3–4 treatment-related adverse events (TRAEs) were more frequent with pembrolizumab (18.6% *vs.* 1.2%), while no significant difference was observed in reported quality of life.

In light of these results, adjuvant pembrolizumab is recommended by both ESMO and EAU for patients with intermediate-high or high-risk localised ccRCC, as defined by the KEYNOTE-564 criteria, and has been approved for reimbursement in Belgium.[9,62] However, some important considerations should be highlighted. First, the interpretation

of these OS data requires caution given that only 48.2% of patients in the placebo arm received ICI-based therapy at relapse, despite this being standard of care.[63] This substantial underutilization of subsequent treatment may have confounded the observed survival benefits. Secondly, adjuvant pembrolizumab inevitably leads to overtreatment of a substantial proportion of patients who would never experience recurrence, unnecessarily exposing them to potential serious and long-term TRAEs. Notably, even in the subgroup of tumours with sarcomatoid dedifferentiation—where adjuvant pembrolizumab provided the greatest improvement in DFS compared to placebo— the OS benefit was comparable to that observed in patients without sarcomatoid dedifferentiation, likely because immunotherapy remains highly effective in the metastatic setting. In this context, patient preference should guide shared decision-making.[62,64] Predictive biomarkers are needed to better identify patients at increased risk of recurrence after surgery, and kidney injury molecule 1 (KIM-1) has emerged as a promising candidate in this context.[65,66] If administered, pembrolizumab should be initiated within 12 weeks of surgery and continued for up to one year.[9]

The use of adjuvant pembrolizumab also raises questions regarding the optimal management of relapse following this treatment. To date, no prospective trials have established clear recommendations for treatment after failure of adjuvant pembrolizumab. Only one retrospective study, involving a cohort of 94 patients, suggested no clear benefit of ICI rechallenge in this setting.[67] However, several limitations hinder the interpretation of these findings. Currently, the EAU recommends that in the event of an early relapse (within 6 months of initiating pembrolizumab) or an intermediate relapse (between 6 months after initiation and 6 months after completion), treatment should favour TKI monotherapy, based on the absence of demonstrated benefit from ICI rechallenge in the CONTACT-03 and TiNivo-2 trials. In contrast, for late relapses (more than 6 months after completion), a benefit from ICI cannot be excluded and rechallenge may be considered, particularly in patients with a longer interval since the end of adjuvant therapy.[62] The Genitourinary Alliance for Research and Development (GUARD) proposed an alternative classification to guide post-relapse treatment, incorporating not only time to recurrence but also tumour burden, histology, molecular features and history of immune-related adverse events. Three clinical profiles were suggested: oligometastatic relapse (especially beyond one year) suitable for local therapy, early polymetastatic relapse (during or within one year of pembrolizumab) indicating immunotherapy resistance and requiring TKI treatment, and intermediate polymetastatic disease (after one year) who should receive individualized treatment, possibly combining anti-PD1 therapy with ipilimumab or VEGFR-TKI based on patient-specific factors.[68]

The first results of the phase III RAMPART trial, comparing durvalumab ± tremelimumab to active surveillance, reported outcomes for arm A (active surveillance) *vs.* arm C (durvalumab every 4 weeks for 1 year plus tremelimumab at day 1 and week 4). Eligible patients had intermediate or high-risk RCC per the Leibovich score, fully resected synchronous ipsilateral adrenal metastases, or a single resected soft-tissue metastasis. A total of 565 patients were randomised. After a median follow-up of 3 years, the primary endpoint was met in the intention-to-treat population, with DFS of 81% in the treatment arm *vs.* 73% with active surveillance (HR 0.65; 95% CI 0.45–0.93; p = 0.0094). Subgroup analyses revealed that the DFS benefit was confined to high-risk patients, with no advantage observed in the intermediate-risk cohort. Notably, only 23% of patients completed treatment as per protocol. Regarding safety, grade ≥3 adverse events occurred in 40% of treated patients *vs.* 8% under active surveillance, though no significant difference in quality of life was reported at 15 months. Results comparing arm A *vs.* arm B (durvalumab monotherapy) are expected in 2026.[69] OS data remain immature at this time.

Looking forward, the ongoing phase III LITESPARK-022 trial is evaluating adjuvant belzutifan + pembrolizumab *vs.* pembrolizumab + placebo in patients at intermediate or high risk of recurrence.[70]

NEO-ADJUVANT THERAPY

Unlike in many other cancers, there is currently no neoadjuvant therapy recommended in RCC. The **PROSPER** trial is the only phase III study to have investigated the use of nivolumab in a perioperative setting; it failed to show a benefit in DFS and was terminated early due to futility.[59] Nevertheless, neoadjuvant therapy could be discussed in selected patients with localised RCC to reduce tumour size in order to allow nephron-sparing surgery, to convert unresectable tumours into resectable ones or to facilitate tumour thrombectomy.[71] Several phase II studies have suggested potential benefits of using TKI, alone or in combination with ICI, with an acceptable safety profile.[72] Notably, in the phase II NeoAvAx trial, which included a cohort of 40 patients with high-risk non-metastatic ccRCC, 3-month neoadjuvant avelumab-axitinib treatment led to partial response in 30% of the patients and a median primary tumour downsizing of 20%; no treatment-related surgical delays and no primary tumour progression were reported, suggesting the feasibility of this approach.[73] However, larger randomised trials are needed to establish the efficacy and safety of neoadjuvant treatment in RCC.

VON HIPPEL-LINDAU SYNDROME ASSOCIATED CCRCC

Belzutifan, an oral hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor, has received conditional marketing authorization from the European Medicines Agency (EMA) as monotherapy for adult patients with von Hippel-Lindau (VHL) disease–associated localised RCC for whom surgery is not considered appropriate. This approval is based on the results of the phase II **LITESPARK-004** trial, a single-arm study that enrolled 61 patients and demonstrated a durable clinical benefit of belzutifan in patients with VHL-associated ccRCC, with an objective response rate (ORR) of 70% after a median follow-up of 61.8 months. In terms of safety, grade 3 TRAEs occurred in 18% of patients, with no grade 4 or 5 events reported. Beyond renal tumours, this agent has also demonstrated activity against other VHL–associated lesions, including hemangioblastomas and pancreatic neuroendocrine tumours, potentially reducing the need for invasive procedures in their management.[74] Therefore, belzutifan should be recommended for patients with VHL-associated ccRCC who do not require immediate surgical interventions.[9] While its reimbursement has not yet been granted in Belgium, belzutifan is available through compassionate use program since April 2025.

METASTATIC RCC MANAGEMENT

For carefully selected patients with a favourable IMDC score and low tumour burden, active surveillance should be considered.[75,76]

LOCAL MANAGEMENT IN METASTATIC RCC

Cytoreductive nephrectomy

Upfront cytoreductive nephrectomy (CN) may be considered in highly selected patients amenable for radical oligometastatic treatment (primary tumour and either a solitary metastasis or limited oligometastatic disease), particularly in those with good performance status, favourable or intermediate IMDC risk, and no immediate need for systemic therapy.[8] The CARMENA and SURTIME trials demonstrated that patients requiring systemic treatment derive greater benefit from initiating systemic therapy rather than immediate CN, although these studies predate the use of modern ICI-based combinations. [77,78] Moreover, these studies included only patients who required systemic therapy shortly after CN. Patients with indolent tumours and limited metastatic burden, in whom CN could be performed followed by observation of the metastases, were not included.[79] Following CN with complete resection of metastases within one year after CN, adjuvant pembrolizumab may be proposed; however, it remains uncertain whether metastasectomy followed by adjuvant immunotherapy is superior to observation and deferred ICI-based therapy at progression in oligometastatic patients.

Alternatively, **deferred CN** may be considered in cases of durable response to initial systemic treatment. While high-level evidence is currently lacking, this approach appears to be safe and may lead to sustained disease control.[80,81] The ongoing NORDIC-SUN trial is expected to provide further insights on this strategy.[82]

In cases of locally symptomatic metastatic RCC (such as bleeding or pain), **palliative nephrectomy** may be considered, as it provides symptom resolution in approximately 91% of patients. However, this approach carries a non-negligible risk of complications and perioperative mortality, and should therefore be reserved for carefully selected patients in whom symptoms are unlikely to be adequately managed through less invasive measures.[83]

Local treatment of metastases

Local treatment of metastases may be considered in selected patients with metastatic RCC for various reasons, including symptom relief, prevention of local complications, deferral of systemic therapy, or achieving complete remission in oligometastatic disease.[19] Oligometastatic RCC, typically defined as fewer than five metastatic lesions, should be discussed within a multidisciplinary team to determine the most appropriate strategy—whether local treatment, systemic therapy, or active surveillance. **SBRT**, particularly in cases of brain or bone metastases, is an effective local option for symptoms control. In selected patients with favourable or intermediate-risk oligometastatic disease, SBRT to all active sites may offer excellent local control and delay systemic therapy, with a more favourable tolerance profile compared to systemic treatments.[84] Further evidence is awaited from ongoing trials such as SOAR-trial, which compares SABR to all metastatic sites followed by standard-of-care systemic therapy *versus* systemic therapy alone in patients with oligometastatic RCC.[85] Although randomised prospective data are lacking, retrospective studies suggest that complete **metastasectomy** with negative margins may improve OS and CSS and delay the initiation of systemic therapy; however, no clear consensus exists regarding patient selection, which should be based on a comprehensive assessment of patient characteristics, disease burden and dynamic, tumour biology, and surgical considerations.[86]

FIRST-LINE FOR METASTATIC CCRCC MANAGEMENT

In first-line treatment of metastatic ccRCC, four ICI-based combinations have proven an OS benefit over sunitinib

and are currently reimbursed in Belgium. These include three PD-1 inhibitor plus VEGFR-TKI combinations (pembrolizumab-axitinib, nivolumab-cabozantinib, pembrolizumab-lenvatinib*) and one dual ICI regimen (nivolumab-ipilimumab*), which currently has the longest follow-up (9 years) among all approved doublets. [87–91] In contrast, PD-L1 inhibitors have not shown a significant OS benefit; however, the avelumab-axitinib combination remains reimbursed in Belgium.[92,93]

TKI alone may be considered as first-line treatment for patients with IMDC favourable-risk ccRCC (sunitinib or pazopanib), or in cases of contraindication to ICI therapy (sunitinib, pazopanib, or cabozantinib in intermediate- or poor-risk patients).[8]

The triplet combination of cabozantinib, nivolumab, and ipilimumab was evaluated in the **COSMIC-313 trial** and demonstrated a progression-free survival (PFS) benefit compared to the nivolumab–ipilimumab doublet after a median follow-up of 14.9 months. However, this benefit came at the cost of increased grade 3–4 TRAEs (79% in the triplet arm *vs.* 56% in the control arm). To date, this combination is not recommended, pending mature OS data.[94] Finally, the combination of axitinib and the PD-1 inhibitor toripalimab has emerged as another promising option for the first-line treatment of intermediate- or poor-risk metastatic ccRCC.[95]

Among the four main combinations mentioned above, no specific regimen is currently preferred, and indirect cross-trial comparisons are not recommended. Treatment selection should be based on informed shared decision-making between clinician and patient, taking into account trial outcomes, toxicity profiles, and several individualising factors including IMDC risk category, need for rapid response, disease characteristics, comorbidities, and contraindications.

IMDC category – Although the use of IMDC risk categories has become secondary in the latest ESMO and EAU guidelines, in Belgium, only pembrolizumab–axitinib and nivolumab-cabozantinib doublets are reimbursed for patients with favourable-risk metastatic ccRCC. These two combinations, while they have not demonstrated a clear OS benefit over sunitinib in this subgroup, are recommended due to improved response rates, response duration and PFS.[9] Following the most recent update of the CheckMate 214 trial, nivolumab–ipilimumab improved OS in favourable-risk patients, with a median OS of 77.9 months *versus* 66.7 months in the sunitinib group (HR = 0.80, 95% CI 0.59-1.09); however, this combination is not reimbursed for this patient category in Belgium.[90] For intermediate- and poor-risk patients, both ICI–TKI combinations and dual ICI therapy are considered equivalent in terms of efficacy, though they differ in toxicity profiles and practical considerations, as outlined below.

Need for response – In patients with locally threatening metastases (*e.g.*, nerve or spinal cord compression, extensive lung metastases with lymphangitic carcinomatosis) in whom rapid tumour reduction is needed and pseudo progression should be avoided, ICI–TKI combinations should be favoured, as they lead to faster response and lower rates of primary resistance. However, for most patients, dual ICI therapy may be more appropriate, offering the potential for more durable outcomes and a higher likelihood of achieving complete response.[96] Notably, long-term data from CheckMate 214 demonstrated a tail in the overall survival curve, with approximately 30% of patients maintaining survival beyond 9 years.[90]

Sarcomatoid features – All PD-1 targeted combinations demonstrated particular benefit over sunitinib.[97–99] This likely reflects the greater immunogenicity and lower angiogenic dependency of sarcomatoid tumours, which may explain their substantial sensitivity to ICI.[100,101] Therefore, ICI-based combination are strongly recommended in patients with sarcomatoid features.[9]

Location of metastases – Patients with brain metastases (BM) are often excluded from clinical trials, making treatment selection more challenging in this population. Cabozantinib has demonstrated intracranial activity in retrospective cohort studies and in the phase II CABRAMET trial, where 61.5% of patients with non-locally pretreated BM achieved a partial intracranial response.[102,103] This effect may be related to the elevated expression of c-MET in BM compared to primary renal tumours.[104] Therefore, in case of brain metastases, cabozantinib-nivolumab is the preferred first-line option. As the presence of brain metastases can now impact first-line choice, screening for brain metastases, even in absence of neurologic symptoms, is warranted. The nivolumab–ipilimumab combination has also shown encouraging global antitumour activity in patients with BM, with a global ORR of 32% and intracranial progression reported in only 25% of the 28 patients included in the CheckMate 920 cohort. However, data on intracranial response are lacking.[105] Nivolumab in monotherapy is only associated with poor intracranial response.[106] Patients with glandular metastasis, including those to the pancreas, thyroid, contralateral adrenal gland, breast and parotid, display more angiogenic features and might be good candidates for first-line VEGFR-TKI.[107]

Toxicities and contraindications – Treatment selection should also be guided by contraindications and toxicity profile of each regimen. ICI are generally contraindicated in patients with a history of organ transplantation or severe active autoimmune disease, due to the risk of immune-related complications or graft rejection. Dual ICI therapy should be avoided in patients for whom corticosteroid use would be

* Only available for intermediate- and poor-risk patients according to IMDC risk score.

TABLE 3. Summary of clinical trials evaluating the four ICI- and VEGFR-based combination as first-line therapy in ccRCC
ITT : intention-to-treat population, I/P : intermediate or poor risk patients based on IMDC categories

Study	Treatment	Control arm	Median follow-up (months)	OS HR	PFS HR	ORR (%)
CheckMate 9ER[91]	Nivolumab – cabozantinib	Sunitinib	68	ITT : 0.79 I : 0.86 P : 0.49	ITT : 0.58 I : 0.63 P : 0.36	ITT : 56 I : 56 P : 41
KEYNOTE-426[87]	Pembrolizumab - axitinib	Sunitinib	43	ITT : 0.73 I/P : 0.64	ITT : 0.68 I/P : 0.67	ITT : 60 I/P : 56
CLEAR[88]	Pembrolizumab – lenvatinib	Sunitinib	49	ITT : 0.79 I/P : 0.74	ITT : 0.47 I/P : 0.43	ITT : 71.3
Checkmate 214[90]	Nivolumab - ipilimumab	Sunitinib	108	ITT : 0.71 I/P : 0.69	/	ITT : 39 I/P : 42

problematic, such as those with severe osteoporosis or poorly controlled diabetes. VEGFR-TKI, on the other hand, should be used with caution in cases of impaired wound healing or significant vascular comorbidities such as coronary artery disease, recent cerebrovascular accidents, thromboembolism or uncontrolled hypertension. The chronic toxicity profile of VEGFR-TKIs, including fatigue, cytopenia, hepatotoxicity, hypothyroidism, gastrointestinal intolerance, and renal dysfunction, should be discussed with patients, as these may impact quality of life and require long-term management.[108]

The optimal **treatment duration** is not clearly defined.[9] ICI-TKI combination trials typically limited immunotherapy to two years while recommending TKI until progression, though fewer than 40% of progression-free patients remained on treatment at data cut-off.[87,88,109] By contrast, in the CheckMate 214 trial, nivolumab was administered until progression.[89] However, the clinical benefit of extending PD-1 blockade beyond two years remains uncertain. A recent retrospective Belgian study suggested that elective ICI discontinuation after 21 to 25 months in responders did not adversely affect outcomes.[110] In clinical practice, therapy is frequently discontinued after two years in patients achieving complete responses.

BEYOND FIRST LINE

Following first-line ICI–TKI or dual ICI therapy, any VEGFR-TKI not previously administered may be considered, including cabozantinib, axitinib, pazopanib, and sunitinib—all of which are reimbursed in Belgium. Among these options, cabozantinib is generally preferred in patients with Karnofsky performance status ≥ 70% if not used upfront, as it is the only TKI to have demonstrated an OS benefit over everolimus in the **METEOR** trial.[111] Cabozantinib was also used as control arm in the phase III **CONTACT-03** study, hence delivering phase III data in second line.[112] Moreover, several retrospective studies have also shown its benefit in the second line.[113] Axitinib may be considered as a second-line option, having shown a PFS advantage in the **AXIS** trial following first-line cytokines or VEGFR-TKI.[114] In contrast, upon progression on first-line ICI-combinations, ICI rechallenge/continuation has not demonstrated efficacy, as evidenced by the negative results of the **CONTACT-03** (cabozantinib *vs.* cabozantinib–atezolizumab) and **TiNivo-2** (tivozanib *vs.* tivozanib-nivolumab) trials.[112,115] In the third-line setting, a VEGFR-targeted therapy not previously administered or everolimus can be considered, as everolimus demonstrated a PFS benefit over placebo in patients who progressed on sunitinib or sorafenib in the **RECORD-1** trial.[9,116] Although not currently available in Belgium, belzutifan has shown promising results in this setting in the **LITESPARK-005** trial. After a median follow-up of 35.8 months, belzutifan significantly improved PFS compared to everolimus, with a median PFS of 5.6 months in both arms (HR 0.75, 95% CI 0.63–0.88) and a 24-month PFS rate of 17.5% *vs.* 4.1%, respectively. However, no OS benefit was observed (median OS of 21.4 *vs.* 18.2 months; HR 0.92, 95% CI 0.77–1.10, p = 0.18). The safety profile was more favourable in the belzutifan arm, with TRAEs–related discontinuation occurring in 6.2% of patients, compared to 15.3% with everolimus.[117] The ongoing phase III **LITESPARK-011** is evaluating the efficacy of belzufitan in combination with lenvatinib *vs.* cabozantinib in patients with advanced RCC progressing after anti-PD-1/PD-L1 therapy.[118] A recent press release reported positive PFS data.[119]

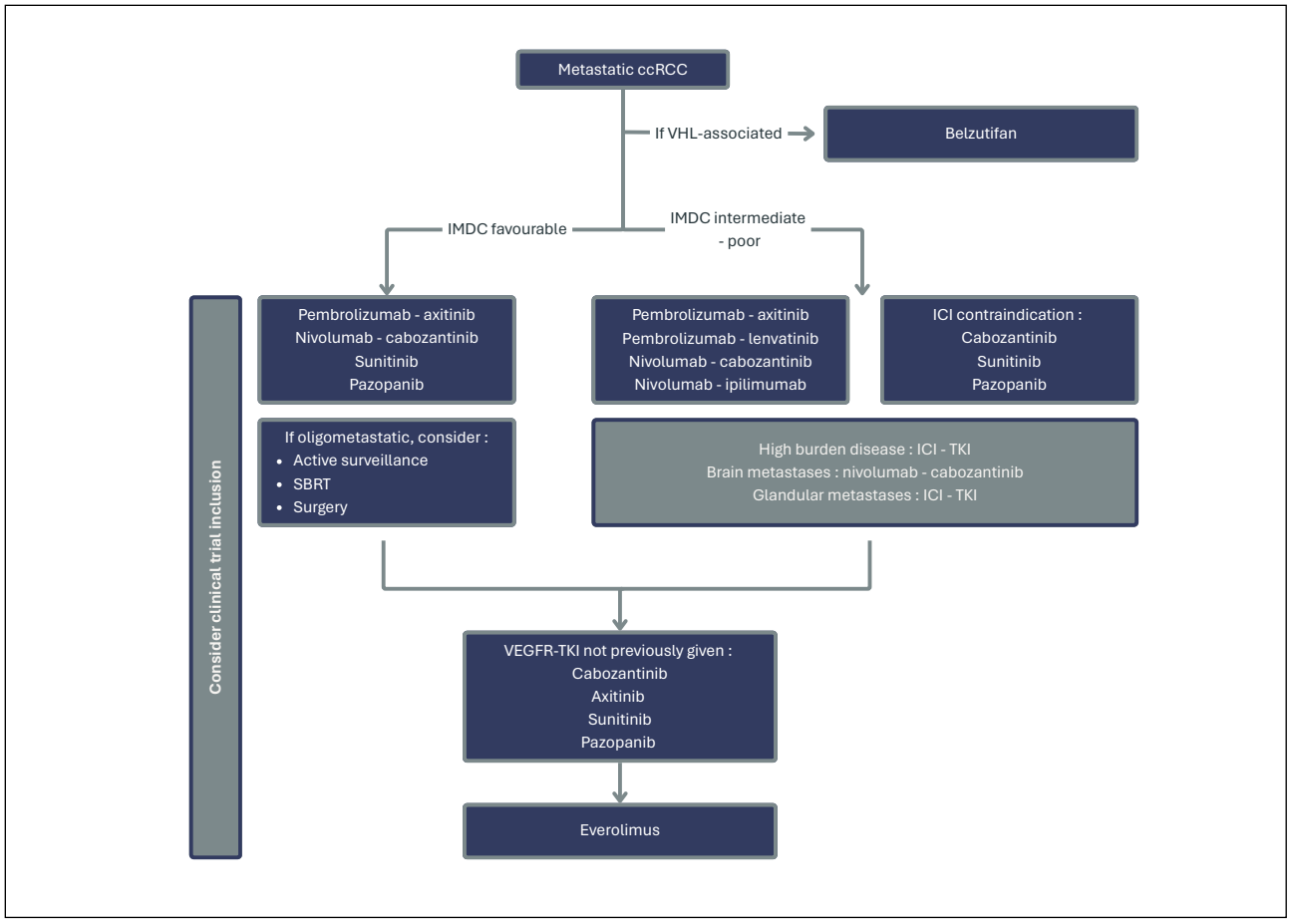

FIGURE 1. Flow chart for the treatment of metastatic ccRCC in the Belgian context.

NON CCRCC MANAGEMENT

Non-clear cell renal cell carcinomas (nccRCCs) are rare tumours that have been either excluded from or underrepresented in large clinical trials. Recently, however, several larger phase II studies have been published on nccRCC cohorts, including one randomising patients between sunitinib and ipilimumab-nivolumab arms, and two single-arm studies evaluating cabozantinib-nivolumab and lenvatinib-pembrolizumab.[120–122] Nevertheless, these studies were conducted before the 2022 WHO histological classification and do not reflect recent changes in histological categorisation, such as the distinction between papillary type 1 and type 2 RCC, now considered separate entities.

In localised stages, the diagnostic approach and management recommendations (surgery, ablative treatments, active surveillance) are broadly similar to those for ccRCC, exception made for adjuvant pembrolizumab indication. However, robust data are lacking to establish strong guidelines for metastatic nccRCC. In Belgium, as reimbursement conditions do not specify histology, these tumours can be treated similarly to ccRCC. Inclusion in clinical trials is highly encouraged.

Among nccRCC, **pRCC** is the most common subtype. Data regarding pRCC management are limited and primarily derived from phase II studies. Cabozantinib demonstrated improved PFS and ORR compared to sunitinib, although no OS advantage was observed.[123] Pembrolizumab also showed activity in the first-line setting, whereas nivolumab results were less encouraging, albeit based on substantially smaller cohorts.[124–126] Additionally, both ICI-TKI combinations (pembrolizumab-lenvatinib, cabozantinib-nivolumab) and dual ICI (nivolumab-ipilimumab) yielded promising outcomes, with ORR reaching up to 54% and 47% for the pembrolizumab–lenvatinib and cabozantinib-nivolumab combinations, respectively. Ipilimumab-nivolumab yielded an ORR of 28% in the CheckMate 920 study and 29% (with 10% complete response) in the SUNNIFORECAST study. Among these studies, the pembrolizumab–lenvatinib trial included 93 patients, making it the largest and most robust series to date.[120–122,127] In contrast, everolimus, either alone or combined with lenvatinib, demonstrated inferior efficacy compared to TKI- or ICI-based regimens.[128,129] Given the absence of direct comparative evidence, no strong therapeutic

TABLE 4. Drugs approved for use in renal cell carcinoma, with a summary of their reimbursement criteria as stated by the RIZIV/INAMI.

Drug	Therapeutic class	Indication for first line	Indication after first line	INAMI Reimbursement Conditions
Sunitinib	VEGFR-TKI	Yes (NCT00098657)[135]	Yes (INMOSUN-SOGUG)[136]	Patients with advanced or metastatic RCC: - In first line for IMDC-favourable risk. - In first or second line for IMDC intermediate/poor-risk patients ineligible for cabozantinib or ICI. - From third line on.
Pazopanib	VEGFR-TKI	Yes (VEG105192)[137]	Yes (NCT03200717)[138]	Patients with advanced or metastatic RCC: - In first line for IMDC-favourable risk. - In first or second line for IMDC intermediate/poor-risk patients ineligible for cabozantinib or ICI. - From third line on.
Cabozantinib	VEGFR/ MET/AXL-TKI	Yes -Alone (CABOSUN)[139] - With nivolumab (CheckMate 9ER)[91]	Yes (METEOR)[111]	Patients with advanced RCC: - In first line in IMDC, intermediate/poor risk. - From second line on, if the patient has KPS ≥70 and failed treatment with an immune-checkpoint inhibitor and/or a VEGF-targeted therapy other than cabozantinib.
Axitinib	VEGFR-TKI	Yes, with pembrolizumab (KEYNOTE-426)[87]	Yes (AXIS)[114]	Patients with advanced RCC: - In first line, combined with pembrolizumab or avelumab (no risk group specified) - Who failed at least two prior therapies with an immune-checkpoint inhibitor and/or a VEGF-targeted therapy, other than axitinib. - In second line if treatment with an immune-checkpoint inhibitor or a VEGF-targeted therapy, other than axitinib, is not recommendable, applicable, or reimbursable.
Lenvatinib	Multi-target TKI	Yes, with pembrolizumab (CLEAR)[88]	Yes, with everolimub (Study 205)[140]	Patients with advanced RCC in first line for IMDC intermediate/poor risk, in combination with pembrolizumab.
Sorafenib	VEGFR-TKI	No (less active VEGFR-TKI)	No (less active VEGFR-TKI)	Patients with advanced RCC in whom at least two therapies (INF-α, IL-2, immune-checkpoint inhibitor, or a VEGF-targeted therapy other than sorafenib) failed, or if these therapies are not recommendable, applicable, or reimbursable.
Everolimus	mTOR inhibitor	No	Yes (RECORD-1)[116]	Reimbursed after failure of ≥2 prior therapies or when VEGF/ ICI options are not appropriate. Only for clear cell RCC.
Belzutifan	HIF-2α inhibitor	No	Yes (LITESPARK-005)[141]	Approved by EMA; not currently reimbursed in Belgium, only available through compassionate use program in case of VHL syndrome.
Tivozanib	VEGFR-TKI	No	Yes (TiNivo-3)[115]	Approved by EMA; not currently reimbursed in Belgium.
Nivolumab	Anti–PD-1 inhibitor	Yes, in combination: - With ipilimumab (CheckMate 214)[89] -With cabozantinib (CheckMate 9ER)[91]	Yes, in monotherapy (CheckMate 025)[142]	Patients with advanced RCC: - In first line, combined with cabozantinib. - In first line, combined with ipilimumab, for IMDC intermediate/poor risk. - From second line on (monotherapy) after VEGFR-TKI.
Ipilimumab	Anti–CTLA-4 inhibitor	Yes, with nivolumab (CheckMate 214)[89]	No	- In first line, combined with nivolumab, for IMDC intermediate/poor risk (limited to 4 doses per patient)
Pembrolizumab	Anti–PD-1 inhibitor	Yes - With lenvatinib (CLEAR)[88] - With axitinib (KEYNOTE-426)[87]	No	- Adjuvant in patients with high risk of relapse after nephrectomy with or without metastasectomy. - In first line for advanced RCC, combined with axitinib (all risk groups) or with lenvatinib (intermediate/poor risk only)
Avelumab	Anti–PD-L1 inhibitor	No, because no OS advantage was shown (JAVELIN Renal 101)[92]	No	-In first line, combined with axitinib, for advanced RCC.

recommendations can currently be made. However, based on the available data, cabozantinib monotherapy and ICI-based combinations (cabozantinib–nivolumab or pembrolizumab–lenvatinib) are considered preferred options. Since ICI-based combinations are only available in first line, it seems reasonable to initiate treatment with one of these regimens. In second-line settings, any systemic therapy, including VEGFR-TKIs, mTOR inhibitors or ICI, can be considered.[9,17] Although some pRCCs harbour cMET alterations, routine molecular testing is unnecessary as specific cMET inhibitors are unavailable, and cabozantinib (which targets cMET) is effective regardless of cMET status.

In **fumarate hydratase-deficient RCC**, ICI-TKI combinations showed activity, with an ORR of 56% in a phase II study including 41 patients treated with the anti-PD1 sintilimab plus axitinib.[130] Similarly, in a retrospective series of 48 patients, ICI-TKI regimen yielded an ORR of 33%.[131] ICIs without VEGFR-TKIs appear to be less active.

Although previously considered refractory to VEGFR-TKIs and ICIs, recent data show **chRCC** responses to lenvatinib-pembrolizumab (28% ORR in KEYNOTE-B61, n=29) and ipilimumab-nivolumab (26% ORR in SUNNIFORECAST, n=28).[120,122] Small studies reported activity with lenvatinib-everolimus and bevacizumab-everolimus, but everolimus and bevacizumab are not available in Belgium.[129,132]

For **translocation carcinoma**, limited data exist. In the KEYNOTE-B61 trial, only 6 patients with translocation carcinoma were included, with an ORR of 67%.

Collecting duct carcinomas and SMARCB1-deficient renal medullary carcinomas are mainly treated with platinum-based chemotherapy but cabozantinib monotherapy may be an alternative for collecting duct carcinoma.[9]

Finally, for **NOS RCC**, therapeutic approaches are similar to other nccRCC subtypes.

METASTATIC RCC WITH BONE METASTASES

Approximately 35% of patients with metastatic RCC present with bone metastases, which are typically osteolytic and associated with significant morbidity due to high incidence of skeletal-related events (SREs). Bone resorption inhibitors (BRIs), such as denosumab, may be considered to reduce SRE risk. However, concomitant use of VEGFR-TKIs and BRIs is associated with an increased risk of medication-related osteonecrosis of the jaw (MRONJ).[133] Careful patient selection and risk stratification can help minimise its incidence. In patients with limited bone metastases, localised radiation therapy may be preferred, potentially avoiding the need for BRIs. Known risk factors for MRONJ include poor dental health and smoking. During BRI therapy, dental extractions should be avoided whenever possible. When extractions are unavoidable, preventive strategies—including prophylactic antibiotics, use of leukocyte- and platelet-rich fibrin (L-PRF) membranes, and temporary discontinuation of BRIs three months prior to the procedure until complete healing—can reduce MRONJ risk.[134]

CONCLUSION

Over the past years, RCC management has been significantly reshaped by the emergence of non-surgical strategies for localised disease, along with the establishment of new standards in adjuvant therapy and the development of novel systemic treatments. Looking ahead, research will not only introduce new therapeutic options but also refine the use of existing ones through improved patient selection. Finally, more robust data are needed to support stronger recommendations for the management of nccRCC subtypes, which remain underrepresented in clinical research.

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KEY MESSAGES FOR CLINICAL PRACTICE

1. **In localised RCC, surgery remains the standard of care. However, thermal ablation, stereotactic ablative radiotherapy, and active surveillance represent effective alternatives for patients with T1 tumours and significant comorbidities.**

2. **Adjuvant pembrolizumab is recommended for patients with intermediate-high or high-risk localised ccRCC, but treatment initiation should rely on shared decision-making given the benefit–risk balance.**

3. **In metastatic RCC, active surveillance or local treatments should be considered for patients with a favourable IMDC score, low tumour burden, and no immediate need for systemic therapy.**

4. **In the first-line setting, no ICI-based combination has demonstrated superiority over another; treatment choice should therefore be individualised according to patient and tumour characteristics.**

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