Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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Key messages:
- This ESMO Clinical Practice Guidelines manuscript on renal cell carcinoma was compiled by a multidisciplinary panel of experts
- It provides guidance on the diagnosis, treatment and follow-up of renal cell carcinoma
- Recommendations are accompanied by relevant/available supporting evidence

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Incidence and epidemiology

Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women, respectively, thus representing the seventh most common cancer in men, and the tenth most common cancer in women [1]. However, available statistics include not only renal parenchymal tumours, but also urothelial cancer of the renal pelvis; renal cell carcinoma (RCC) accounts for ~80% of all kidney cancers.

After over two decades of increasing rates, RCC incidence trends worldwide have shown signs of plateauing in recent years. Furthermore, kidney cancer mortality rates overall have levelled. These patterns are consistent with reports of incidental diagnosis and downward shift of tumour stage and size; indeed, the widespread use of non-invasive radiological techniques [e.g. ultrasonography (US), computed tomography (CT)], allows the frequent detection of early and small RCCs, which are potentially curable.

Beyond well-known risk factors for RCC, such as cigarette smoking, obesity and hypertension, evidence is accumulating to suggest an aetiological or, on the contrary, a protective role, for additional factors [2], such as trichloroethylene. In a recently published case control study of 699 RCC patients and 1001 frequency-matched controls, consumption of caffeinated coffee was found to be associated with reduced risk of RCC; interestingly, decaffeinated coffee was associated with an increased risk for aggressive clear cell RCC (ccRCC) [3].

Furthermore, RCC also appears to be more common in patients with end-stage renal failure or acquired renal cystic disease, and in patients on dialysis, those who have had kidney transplantation, or those with tuberous sclerosis syndrome.

Approximately 2%-3% of all RCCs are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being von Hippel-Lindau (VHL) disease. Patients with multiple and bilateral lesions and/or other related affections should be tested for these germline mutations since it is important that they are recognised.

Diagnosis and pathology/molecular biology

As stated above, > 50% of RCCs are currently detected incidentally, making the classical triad of flank pain, gross haematuria and palpable abdominal mass less frequent than in the past. Despite this, RCC remains the 'Internist's cancer' with paraneoplastic syndromes such as hypercalcaemia, unexplained fever, erythrocytosis and Stauffer's syndrome (signs of cholestasis unrelated to tumour infiltration of the liver or intrinsic liver disease, which typically resolve after kidney tumour resection) still being relatively frequent.

Suspicion of RCC should prompt laboratory examinations of serum creatinine, haemoglobin, leukocyte and platelet counts, lymphocyte to neutrophil ratio, lactate dehydrogenase, C-reactive protein (CRP) and serum-corrected calcium [IV, B]. Some of these tests are prognostic for survival and are used for risk assessment within different prognostic score systems (see Staging and risk assessment section).

Most cases of RCC are strongly suspected by imaging. Diagnosis is usually suggested by US and further investigated by CT scan, which allows for assessment of local invasiveness, eventual lymph node involvement or distant metastases. Magnetic resonance imaging (MRI) may provide additional information in investigating local advancement and venous involvement by tumour thrombus.

For accurate staging of RCC, contrast-enhanced chest, abdominal and pelvic CT is mandatory [III, A]; unless indicated by clinical or laboratory signs or symptoms, the use of bone scan or brain CT (or MRI) is not recommended for routine clinical practice [III, A]. In case of an allergy to CT contrast agent or renal insufficiency, adequate staging should include a high-resolution CT scan of the chest without contrast agent, together with an abdominal MRI. Fluorodeoxyglucose positron emission tomography (FDG-PET) is not a standard investigation in the diagnosis and staging of ccRCC and should not be used. The role of new tracers is under investigation.

A renal tumour core biopsy provides histopathological confirmation of malignancy with high sensitivity and specificity; it is especially recommended before treatment with ablative therapies [III, B] as well as in patients with metastatic disease before starting systemic treatment [III, B]. Complications (e.g. bleeding or tumour seeding) are rare or

even exceptional (as in the case of tumour seeding) [4], while diagnostic accuracy remains high [5]. The final histopathological diagnosis, classification, grading and evaluation of prognostic factors are based on the nephrectomy specimen when available.

Pathology assessment

The last edition of the World Health Organization (WHO) histological classification of renal tumours has been reported in 2016 (Table 1), and was based on tumour histology, chromosomal alterations and molecular pathways [6].

ccRCCs represent 80% of malignant renal tumours in adults, with the remaining 20% corresponding to several histological subtypes with different histological, molecular and cytogenetic profiles [7]. Papillary and chromophobe RCCs account for 80% of non-ccRCCs.

Papillary RCCs which represent a heterogeneous disease are characterised by:
- type 1 RCCs more frequently associated to *MET* or epidermal growth factor receptor (EGFR*)* mutations
- type 2 RCCs often unique tumour with an aggressive phenotype that are associated with *SETD2* mutations, *CDKN2A* mutations or *TFE3* fusions [8].

In papillary type 2 with familial history of papillary RCC, a fumarate hydratase (*FH*) mutation should also be investigated.

The main goal in diagnosis of chromophobe RCC, especially in the eosinophilic histological subtype, is the differential diagnosis with oncocytoma. Chromophobe RCCs have diffuse positivity for cytokeratin 7 (CK7), whereas oncocytomas are negative or present focal positivity for CK7. Moreover, chromophobe RCCs display more frequent chromosome loss but fewer somatic mutations. The most frequently mutated gene is tumour suppressor protein 53 (*TP53)* (32%), and the most frequent oncogenic pathways involved in such tumours are mammalian target of rapamycin (mTOR) pathways (23%), including alterations of phosphatase and tensin homologue (*PTEN*) [9].

Microphthalmia associated transcription factor (MiT) family translocation RCCs (t-RCCs) must be ruled out in young patients under the age of 40, if papillary architecture,

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or complex architecture with clear cells and/or epithelioid cells, psammoma bodies are present. The diagnosis is based on the use of both immunohistochemistry and fluorescent *in situ* hybridisation (FISH) analysis to demonstrate the presence of *TFE3*/*TFEB* rearrangement. Recently, Argani et al. reported cases of *TFEB*-amplified RCCs that occur in older patients. These tumours presented high-grade eosinophilic cells with necrosis and papillary or pseudopapillary architecture. The expression of melanocytic markers is variable and FISH analyses revealed high levels of *TFEB* gene amplification. The prognosis of such tumours is poor with usually advanced stage and metastatic outcome [10].

Collecting duct carcinoma (CDC) or Bellini duct carcinoma remains a highly aggressive RCC arising from the renal collecting tubules. A recent specific gene expression signature showed that CDC appears to be a unique entity among kidney cancers [11]. Moreover, these tumours are characterised by an immune profile with an average of 22% of tumour-infiltrating lymphocytes [12].

The prognostic factors validated by the International Society of Urological Pathology (ISUP) consensus and the WHO 2016 classification of RCC to be reported in routine practice are [13]:

- The tumour histological subtype
- The ISUP nucleolar grade (instead of the previous Fuhrman grade) that is only applicable to ccRCC and papillary RCC
- A sarcomatoid and/or rhabdoid differentiation that defines a grade 4 tumour
- The presence of necrosis
- The presence of microscopic vascular invasion
- The pathological tumour, node and metastasis (pTNM) staging
- Description of the non-neoplastic renal tissue.

Biology

Beyond the classical one gene–one histology paradigm, a more complex biological classification of RCC (and especially of its clear cell histotype) is emerging [14].

First, RCC proved to be an extremely heterogeneous disease [15]; beyond the seminal genetic alteration (mutation, deletion or hypermethylation) of the *VHL* tumour suppressor gene, which is present in the vast majority of sporadic RCCs, other genetic alterations may occur, especially over time [16], contributing to worsen the prognosis of patients harbouring these tumours. Notably, three of these other genes (*PBRM1*, *BAP1* and *SETD2*) are located on the same short arm of chromosome 3 where the *VHL* gene is also located.

On the contrary, some RCCs are characterised by mutations in the mTOR pathway, and especially in the highly conserved FAT (FRAP, ATM, TTRAP) and kinase domains of the *MTOR* gene; these cancers have been defined as metabolic RCCs [17].

Finally, according to another comprehensive molecular characterisation of papillary RCCs, type 1 and type 2 papillary RCCs were shown to be clinically and biologically distinct. Alterations in the MET pathway were indeed associated with type 1 and activation of the NRF2-ARE pathway was associated with type 2, while CDKN2A loss and a CpG island methylator phenotype in type 2 contributed to convey a poor prognosis [8].

Staging and risk assessment

Staging

The Union for International Cancer Control (UICC) tumour, node and metastasis (TNM) 8 staging system should be used (Table 2).

Risk assessment

The natural clinical course varies in RCC, which has led to the development of different prognostic models for the assessment of the patient's individual risk. Extent of disease, histology, grading and clinical factors have been recognised as having prognostic value in RCC and may be used in localised or in metastatic disease [6].

Localised Disease

Different pre- or postoperative scores have been developed to assess prognosis in RCC, and are used for risk-adapted follow-up strategies. Integrated prognostic scores offer some predictive advantages over single tumour characteristics and are used preferentially. These models are composed of histological and clinical factors. The most recent modifications of the stage, size, grade and necrosis (SSIGN) score [18] (Table 3) and the University of California Los Angeles Integrated Staging System (UISS) (Table 4) [19] score are frequently used.

However, among different prognostic scores a concordance of 0.68-0.89 for cancer-specific survival (CSS), and 0.74-0.82 for recurrence-free survival (RFS) was reported [20], indicating that a plateau has been reached for prognostication with available models. Hence, no clear preference for a specific prognostic model may be given.

Advanced disease

The Memorial Sloan Kettering Cancer Center (MSKCC) system was the gold standard for the risk assessment during cytokine treatment in metastatic RCC (mRCC) [21], and it is still commonly used. Further refinement was introduced with the International Metastatic RCC Database Consortium (IMDC) score, which extended the previous factors to a total number of six in order to increase concordance [22]:

- Karnofsky performance status (PS) < 80%
- Haemoglobin level below the lower limit of normal
- Time from diagnosis to treatment < 1 year
- Corrected calcium above the upper limit of normal
- Platelets greater than the upper limit of normal
- Neutrophils greater than the upper limit of normal

A recent evaluation of this model in second-line treatment underscored its predictive value in previously treated mRCC [23] (Table 5). Interestingly, this model is also applicable in further lines of therapy as well as in non-clear cell histology.

Molecular prognostication and biomarkers

Gene signatures can be used to detect different risk groups in RCC. ClearCode34 is a 34-gene expression panel which proved able to classify ccRCC into two subtypes,

clear cell A (ccA) and clear cell B (ccB), significantly associated with relapse-free survival and CSS, as well as overall survival (OS) [24]. Another gene signature, based on a 16-gene assay, was shown to improve prediction of RFS in localised RCC when compared with the SSIGN score according to the Leibovich score (concordance: 0.81 versus 0.74) [25].

Some gene mutations have also been reported as prognostic. The University of Texas Southwestern group identified distinct clinical outcomes in mutation-defined subtypes of ccRCC : a high-risk *BAP1*-mutant group and a favourable *PBRM1*-mutant group [26]. Notably, 80% of patients from both the development and the validation cohorts had localised (or locoregional) disease.

In the metastatic setting, the immunohistochemical expression of programmed death-ligand 1 (PD-L1) is presently under the spotlight, although the results available so far are still controversial. In 2016, a systematic review and meta-analysis of six studies and 1323 cases clearly demonstrated a negative prognostic role of elevated level of PD-L1 tumour expression in RCC [27], although discrepancies between PDL-1 expression between the primary tumour and the metastases have been reported. A possible predictive value of PD-L1 expression remains controversial, although recently, PD-L1 tumour expression was shown to be able to identify patients benefiting from a combination of two immune-checkpoint inhibitors [28]. In addition, angiogenesis, T-effector/interferon (IFN)-γ response and myeloid inflammatory gene expression signatures have been suggested to predict response to vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) and immunotherapy [29]. As a whole, PD-L1 expression should not be routinely used but is a putative biomarker for future treatment selection because of remaining unanswered issues related to the different tests and cut-offs used, to the cells where PD-L1 expression should be checked and to the role of PD-L1 expression heterogeneity (e.g. between different primary tumour sites, or between primary tumour and its metastases).

Other putative markers such as circulating DNA (cDNA), microRNA or DNA methylation status were shown to have prognostic relevance in RCC and warrant future investigation. Overall, these data indicate that molecular analysis may provide additional benefit to already established clinical and histo-anatomical parameters,

which may lead to an individual risk assessment in the future. Currently, no specific molecular marker can be recommended for clinical use.

Management of local/locoregional disease

Role of surgery and local therapy
T1 tumours (< 7 cm)

Partial nephrectomy (PN) is recommended as the preferred option in organ confined tumours measuring up to 7 cm (elective indication). This is based on a systematic review including multiple retrospective studies and a prospective, randomised controlled trial (RCT) which compared radical nephrectomy (RN) with PN in solitary T1a-b N0M0 renal tumours < 5 cm with normal contralateral kidney function [I, A] [30].

PN can be carried out via open, laparoscopic or robot-assisted laparoscopic approaches. Laparoscopic RN is recommended if PN is not technically feasible. In patients with compromised renal function, solitary kidney or bilateral tumours, PN is also the standard of care, with no tumour size limitation (imperative indication).

Systematic reviews comparing surgical management of localised RCC (T1-2N0M0) were unable to identify prospective comparative studies reporting on oncological outcomes for minimally invasive ablative procedures compared with PN [30].

Radiofrequency ablation (RFA), microwave ablation (MWA) or cryoablation (CA) treatments are options in patients with small cortical tumours (≤ 3 cm), especially for patients who are frail, present a high surgical risk and those with a solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours. Renal biopsy is recommended to confirm malignancy and subtype in this setting.

Systematic reviews of RFA and PN suggest a long-term CSS for RFA, equal to PN with a low metastasis rate but slightly higher local recurrence rate compared with PN and CA [30]. The quality of the available evidence prevents definitive conclusions regarding morbidity and oncological outcomes for RFA and CA [III].

Active surveillance is an option in elderly patients with significant comorbidities or those with a short life expectancy and solid renal tumours measuring < 40 mm. The growth of renal tumours (mean 3 mm/year) is low in most cases and progression to metastatic disease is reported in 1%-2% [31]. Renal biopsy is recommended to select patients with small masses for active surveillance [III] with high accuracy, especially because of the incidence of non-malignant tumours in this setting [4, 5].

T2 tumours (> 7 cm)
Laparoscopic RN is the preferred option.

Locally advanced RCC (T3 and T4)
Open RN remains the standard of care, even though a laparoscopic approach can be considered.

Systematic adrenalectomy or extensive lymph node dissection is not recommended when abdominal CT shows no evidence of adrenal or lymph node invasion.

The evidence regarding management of venous tumour thrombus is based on retrospective studies with significant risks of bias and confounding. Resection of venous thrombi is challenging and associated with a high risk of complications. Surgical intervention should be considered, but the most effective approach remains unknown and outcome depends on tumour thrombus level [III].

Adjuvant therapy
Several RCTs of adjuvant sunitinib (S-TRAC, ASSURE), sorafenib (ASSURE) and pazopanib (PROTECT) have been reported [32-34]. Only S-TRAC was positive for its primary endpoint, disease-free survival (DFS) by independent review, but without any OS benefit. This result led to approval of sunitinib by the United States Food and Drug Administration (FDA). The European Medicines Agency (EMA) has not approved adjuvant therapy with any of these drugs because of the imbalance between risk and clinical benefit. A recent pooled analysis of S-TRAC, ASSURE and PROTECT did not reveal a statistically significant effect between adjuvant VEGFR-targeted therapy and an improved DFS or OS in patients with intermediate-/high-risk local or regional fully resected RCC [35]. Improvement in DFS may be more likely with the use of full-dose

regimens and in high-risk disease, but adjuvant treatment was associated with high-grade adverse events (AEs).

Neoadjuvant approaches are experimental and should not be proposed outside of clinical trials. Attempting to downsize venous tumour thrombi with systemic targeted therapy cannot be recommended.

Management of metastatic disease

Role of surgery and local therapy

In the cytokine era, cytoreductive nephrectomy (CN) was recommended in patients with good PS [I, A] [36]. Two randomised trials (CARMENA and SURTIME) investigated the role and sequence of CN in the era of VEGFR-targeted therapy [37-38]. While SURTIME was underpowered, CARMENA demonstrated that upfront CN should no longer be considered the standard of care in MSKCC intermediate- and poor-risk patients with asymptomatic primary tumours when medical treatment is required [I, A]. Upfront CN is associated with morbidity and mortality, and there is no subgroup in these studies in which this approach proved to be superior. Secondary CN in patients with local symptoms due to the primary tumour or near complete responses to systemic therapy remains an option.

Results of CARMENA and SURTIME should not be used to abandon CN in patients with low volume metastatic disease, a good PS and favourable and intermediate risk, who are candidates for initial observation. In fact, both trials recruited patients with high median metastatic volumes (42% of total tumour burden for CARMENA) who needed to start sunitinib.

Metastasectomy and other local treatment strategies including whole brain radiotherapy (WBRT), conventional radiotherapy (RT), stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT), CyberKnife® RT and hypofractionated RT can be considered and carried out for selected patients after multidisciplinary review. A systematic review of 16 studies including 2350 patients sought to identify the evidence base for local treatment strategies of metastases from RCC [39]. The results consistently point towards a benefit of complete metastasectomy for OS and CSS, but there is selection bias and the results have to be interpreted with caution. No systemic treatment is recommended after metastasectomy.

No general guidelines can be given to identify cases to refer for local treatment of metastases. Patient selection should be discussed in a multidisciplinary team. Good PS, solitary or oligometastases, metachronous disease with disease-free interval > 2 years, absence of progression on systemic therapy, low or intermediate Fuhrmann grade and complete resection have been associated with favourable outcome after local treatment of metastases from RCC.

Systemic treatment for ccRCC

Recommendations mainly relate to clear cell histology, since most of the pivotal trials have been conducted in this common histological subtype. In addition, recommendations will differ according to risk stratification (see above).

The proper time to start systemic therapy is not well defined. Because of an indolent course of some RCCs a period of observation before starting treatment should be considered, especially in patients with limited tumour burden and few symptoms. Indeed, the outcome of patients who crossed over to an active agent after a brief period of treatment with placebo, within placebo-controlled phase III trials, indirectly supports this option [II, C]. The safety of observation has been suggested by retrospective studies and confirmed by a prospective study [40].

First-line treatment

An algorithm for first-line systemic treatment in ccRCC is presented in Figure 1. Three vascular endothelial growth factor (VEGF)-targeted agents have demonstrated efficacy in pivotal phase III trials, mostly focused on good and intermediate patients: bevacizumab (combined with IFN), sunitinib and pazopanib [41-43]. All three drugs have been registered based on improvement of progression-free survival (PFS) over either IFN or placebo. Furthermore, pazopanib has been shown not to be inferior to sunitinib in a large phase III trial [44]. Efficacy of both sunitinib and pazopanib has been confirmed by real-world evidence studies, and these two TKIs are currently the most commonly used treatments in good- and intermediate-risk patients. In addition, tivozanib, a selective VEGF inhibitor, has been shown to improve PFS and response rate versus sorafenib, especially in good-risk patients, and has been recently approved by the EMA [45].

Temsirolimus has been tested in a phase III study in poor-risk patients only versus IFN, demonstrating evidence of improved OS in this patient population [46].

Recently, a large phase III study demonstrated that the combination of nivolumab and ipilimumab was superior to sunitinib in intermediate- and poor-risk patients, but not in good-risk patients [28]. In the intermediate- and poor-risk population, the combination improved OS as well as response rate, with a high complete response rate (9.4%). By contrast, both response rates and PFS were higher with sunitinib in the good-risk group.

In addition to these large phase III trials, some efficacy has been reported with sorafenib, high-dose interleukin-2 (IL2) and low-dose IFN combined with bevacizumab, and such therapies should be considered as possible options when the standard treatments are not available. Similarly, single-agent IFN-alpha, as the inferior arm of three RCTs, should no longer be regarded as a standard option.

Finally, based on a randomised phase II study, cabozantinib appeared to be superior to sunitinib in terms of PFS and response rate and has been approved by the EMA in the first-line setting in intermediate- and poor-risk patients [47].

Based on the recent data, it appears useful to provide recommendations based on risk classification (see level of evidence (LoE) in Figure 1).

In good-risk patients, VEGF-targeted agents should remain the standard of care with sunitinib, pazopanib or bevacizumab combined with IFN. Tivozanib is another standard of care when available.

In intermediate-risk patients, combination of nivolumab and ipilimumab is the new standard of care. If this combination is not available, VEGF-targeted agents should be recommended as in good-risk patients, with cabozantinib being another option in this patient population.

In poor-risk patients, similarly, combination of nivolumab and ipilimumab is the new standard of care. Among targeted agents, cabozantinib is an attractive option when

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available. In this specific patient population, temsirolimus remains an option, as well as TKIs (sunitinib or pazopanib). However, in some poor-risk patients with poor Eastern Cooperative Oncology Group (ECOG) PS, only palliative care should be recommended.

Second-line treatment

An algorithm for second-line systemic treatment in ccRCC is presented in Figure 2.

Evidence that TKIs are active after cytokines has been seen with sorafenib, pazopanib, axitinib and tivozanib. Sunitinib also has activity is this setting. Any of these agents can be used after cytokines. However, since VEGF-targeted therapy is now the first-line standard of care, the number of patients treated with cytokines is decreasing.

After first-line treatment with VEGF-targeted therapy:
• Both axitinib and everolimus are active [48, 49]. Both drugs have shown significant improved PFS over sorafenib (axitinib) or placebo (everolimus).
• Based on recent phase III trials, sorafenib can also be used as an option.

However, second-line treatment has been dramatically modified by the report of two large trials showing improvement in OS with nivolumab and cabozantinib [50-52] over everolimus. Both trials showed very significant improvement in OS and response rate, while PFS was improved only in the cabozantinib trial. In both trials, patients could be treated after either one or two TKIs.

Obviously, availability of these two drugs is still heterogenous, and several situations should be differentiated:
• If only nivolumab is available, it should be recommended
• If both nivolumab and cabozantinib are available, either drug is recommended
• The combination of lenvatinib and everolimus showed PFS and OS benefit over everolimus based on a randomised study of 150 patients [53] and is FDA and EMA-approved. However, based on the size of this study, this combination should be considered as an acceptable option, primarily when nivolumab or cabozantinib cannot be delivered.
• If none of these drugs is available, either everolimus or axitinib can be used.

The optimal duration of treatment, especially for nivolumab, remains unclear, as well as the benefit of treatment beyond progression.

Third-line treatment

An algorithm for third-line systemic treatment in ccRCC is presented in Figure 3. Beyond second-line treatment, enrolment into clinical trials is recommended whenever possible. However, based on recent trials with nivolumab and cabozantinib, different situations should be defined:

- In patients already treated with two TKIs, either nivolumab or cabozantinib is recommended. If neither of these drugs is available, everolimus remains an acceptable option.
- In patients previously treated with one TKI and nivolumab, cabozantinib is recommended, if available. In absence of cabozantinib, either everolimus or axitinib can be used.
- In patients previously treated with one TKI and cabozantinib, nivolumab is recommended, and either everolimus or axitinib remain acceptable options.
- In patients previously treated with VEGF-targeted therapy and an mTOR inhibitor, sorafenib has shown activity [54]. However, nivolumab or cabozantinib can be recommended in this setting. Finally, another TKI or rechallenge with the same TKI is considered as an option.

Medical treatment for non-ccRCC

Clinical data are limited in these rare histological subtypes, which are usually excluded from controlled phase III trials. Therefore, enrolment into specific clinical trials is strongly recommended. The current evidence is mainly based on small prospective studies and subgroup analyses from larger trials, which mainly focus on TKI or mTOR inhibitor testing [55-56]. Although not providing definitive answers, these trials favoured sunitinib over the use of everolimus, indicating a similar pattern as that seen in ccRCC. These results were further supported by data from expanded access programs, retrospective series and from subgroup analysis of the temsirolimus registration trial. Overall, the most robust data exist for the use of sunitinib. These studies also suggest that patients with non-clear cell histology may benefit from treatment with everolimus,

sorafenib, pazopanib or temsirolimus. However, in most of these studies, only patients with papillary and chromophobe tumours were enrolled. More recently, clinical data on checkpoint inhibitors have been reported, which suggest clinical activity in patients with non-ccRCC and support their use in such previously treated patients. An algorithm for first-line systemic treatment in non-ccRCC is presented in Figure 4.

After first-line therapy, there is no recommendation possible based on available data. However, at least for papillary tumours, which are the most common non-ccRCCs, the use of the ccRCC algorithm is an acceptable option.

In addition to these general recommendations, some specific situations should be considered:

- cMET inhibitors have shown activity in papillary RCC with *cMET* mutation or amplification [57]. Crizotinib or other cMET inhibitors such as cabozantinib appear as acceptable option instead of usual VEGF TKIs.
- Some patients with chromophobe RCC may benefit from mTOR inhibitors since mutation on chromosome 7 was shown to lead to a loss of the folliculin gene with upregulation of mTOR [9].
- Some data suggest that sarcomatoid tumours are very inflamed tumours, usually with poor-risk features, and are sensitive to immune checkpoint inhibitors. Thus, the use of nivolumab/ipilimumab combination should be considered as a good option for these patients.
- Finally, CDCs (and also medullary carcinomas) were reported to behave more like aggressive urothelial tumours rather than RCCs and may therefore be considered for chemotherapy, although expected results are still poor.
- None of these 'genetic' recommendations can be graded, as data are limited and no clear treatment recommendation can be made for these subgroups with distinct biology.

Role of radiotherapy and bisphosphonates

Although radiosensitivity of RCC is not perfect, this is not a radioresistant disease. RT has been shown to provide good symptom palliation and local control in RCC depending on the dose that can be delivered [58]. There is a developing rationale with emerging data suggesting that the apparent radioresistance of RCC can be overcome

through the ceramide pathway with the use of higher dose-per-fraction treatments usually delivered by new high-precision RT methods such as SBRT [IV, B] [59]. This can be exploited and used in many different clinical situations, particularly for unresectable local recurrences or oligometastatic disease.

There is no current evidence for the use of RT in the neoadjuvant or adjuvant setting. This is on the basis of four negative 'old' trials with two pre-operative and two adjuvant studies. Despite being randomised trials, there are several major limitations in trial design and methodology that included inappropriate case selection, sub-therapeutic RT regimes and inadequate patient numbers. Furthermore, treatment morbidity was substantially increased and the RT techniques used then have now been superseded by improved modern irradiation methods such as intensity-modulated radiotherapy (IMRT) or SBRT [II, D].

RT can be used to treat unresectable local or recurrent disease with the aim of improving local control. For patients in whom surgery cannot be carried out due to poor PS or unsuitable clinical condition, RT can be an alternative if other local therapies such as radio frequency ablation are not appropriate. Modern image-guided RT techniques are needed to enable a high biological dose to be delivered, such as volumetric-modulated arc therapy (VMAT) or SBRT [IV, B]. As discussed earlier, there is an emerging role for its use in the synchronous or metachronous development of oligometastatic mRCC disease, oligoprogression or in mixed response scenarios with immunotherapy or targeted therapies, although none of these techniques can be graded [IV, B].

RT is an effective treatment for palliation of local and symptomatic mRCC disease or to prevent the progression of metastatic disease in critical sites such as the bones or brain [I, A]. For symptomatic bone metastasis, local RT (either as a single fraction or fractionated course) can provide good symptom relief in up to two-thirds of cases with complete symptomatic responses in up to 20%-25% [I, A].

For the management of spinal cord compression, an ambulatory status at diagnosis and limited metastatic disease are favourable prognostic factors in those patients able to undergo surgery. The use of initial surgery and postoperative RT was reported in a randomised trial to improve survival and maintenance of ambulation compared with irradiation alone [I, A] [60].

In the management of mRCC patients with brain metastases, the use of corticosteroids can provide effective temporary relief of cerebral symptoms. WBRT between 20 and 30 Gy in 4-10 fractions respectively is effective for symptom control [II, B]. Most trials in brain metastasis include only a small proportion of RCC cases [61-63]. With the use of SRS delivering larger doses per fraction, the mRCC response outcomes are not thought to differ from other solid tumours. For the subset of good-prognosis patients with a single unresectable brain metastasis, SRS with or without WBRT should be considered [II, A]. There is less reported late cognitive dysfunction using SRS alone compared with the combination therapy [II, A]. Adequate control of brain metastases prior to initiation of anti-VEGF therapy is recommended (expert opinion).

Finally, randomised data from two trials support the use of postoperative SRS following resection of one to three brain metastases, although these data should be interpreted with caution.

Multidisciplinary management is needed to optimise care for mRCC patients suffering from bone metastasis. The approach will need to be individualised to the extent of bone metastasis, its location and potential consequences (see sections above on RT palliation and spinal cord compression). In widespread mRCC bone metastasis, bisphosphonate therapy with zoledronic acid has been shown to significantly reduce skeletal related events (SREs) in patients and increase time to first SRE [64]. The receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor denosumab has been shown in a randomised trial to extend the time to first SRE by 4.3 months and was non-inferior to zoledronic acid [65]. In addition, denosumab has the convenience of subcutaneous administration with no requirement for renal monitoring or dose adjustment [I, A]. Bone-targeted therapy with either zoledronic acid or denosumab should be considered in mRCC patients with reasonable life expectancy and widespread bony metastasis, weighing the potential benefits of the treatment with the potential harms (risk of osteonecrosis of the jaw) [II, A]. Further trials are ongoing to explore its other applications.

Personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine. However, there is growing evidence that some biomarkers will have clinical implications in the near future, as suggested above for papillary RCC with *cMET* mutation.

Follow-up, long-term implications and survivorship

So far, there is no evidence that early treatment of metastasis results in better outcome of metastatic disease when compared with delayed treatment. Overall, there is no evidence that any particular follow-up protocol influences the outcome in early RCC as well as in advanced RCC.

The follow up scheme for localised RCC following surgery should depend on the therapeutic possibilities upon recurrence. CT scans of thorax and abdomen are routinely carried out, with time intervals depending on risk factors. It is recommended to perform CT scans every 3-6 months in high-risk patients for the first two years, while a yearly CT scan is probably sufficient in low-risk patients (expert opinion).

Long-term follow-up is proposed in some institutions, due to the possibility of late relapse, but its benefit has never been demonstrated [66].

During systemic therapy in mRCC patients, 2-4-month follow-up schemes with CT scan should be advised to determine response and resistance. Although not perfect, Response Evaluation Criteria in Solid Tumours (RECIST) remains the most frequently used method to assess drug efficacy. However, in the case of RECIST-defined disease progression, there is no clinical evidence that this quantity of progression is a clinically valid endpoint that should require treatment interruption or modification.

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. A summary of recommendations is shown in Table 6. The relevant literature has been selected by

the expert authors. An MCBS table with ESMO-MCBS scores is included in Table 7. ESMO-MCBS v1.1 [67] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016. LoEs and grades of recommendation (GoRs) have been applied using the system shown in Table 8. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

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Disclosure

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Table 1. WHO 2016 classification of renal cell tumours

Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal cell carcinoma
Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
MiT family translocation renal cell carcinomas
Succinate dehydrogenase-deficient renal cell carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Renal cell carcinoma, unclassified
Papillary adenoma
Oncocytoma

WHO, World Health Organization.

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Table 2. UICC TNM 8 staging of RCC

T – Primary Tumour

TX   Primary tumour cannot be assessed

T0   No evidence of primary tumour

T1   Tumour 7 cm or less in greatest dimension, limited to the kidney

     T1a   Tumour 4 cm or less

     T1b   Tumour more than 4 cm but not more than 7 cm

T2   Tumour more than 7 cm in greatest dimension, limited to the kidney

     T2a   Tumour more than 7 cm but not more than 10 cm

     T2b   Tumour more than 10 cm, limited to the kidney

T3   Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia

     T3a   Tumour extends into the renal vein or its segmental branches, or tumour invades the pelvicalyceal system or tumour invades perirenal and/or renal sinus fat (peripelvic) fat but not beyond Gerota fascia

     T3b   Tumour extends into vena cava below diaphragm

     T3c   Tumour extends into vena cava above the diaphragm or invades the wall of the vena cava

T4   Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

N – Regional Lymph Nodes

NX   Regional lymph nodes cannot be assessed

N0   No regional lymph node metastasis

N1   Metastasis in regional lymph node(s)

M – Distant Metastasis

M0   No distant metastasis

M1   Distant metastasis

pTNM Pathological Classification[a]

Stage

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

[a]The pT and pN categories correspond to the T and N categories.

RCC, renal cell carcinoma; TNM, tumour, node, metastasis; UICC, Union for International Cancer Control.

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Table 3. SSIGN score for localised RCC

Feature		Score
Pathological T category of primary tumour (as per 2002 TNM staging)	pT1a	0
	pT1b	2
	pT2	3
	pT3a-pT3c	4
	pT4	4
Regional lymph node status (as per 2002 TNM staging)	pNx or pN0	0
	pN1 or pN2	2
Tumour size	< 10 cm	0
	10 cm or more	1
Nuclear grade	1 or 2	0
	3	1
	4	3
Histological tumour necrosis	No	0
	Yes	1

Scores	Group	5-year metastasis-free survival rate (%)
0-2	Low risk	97.1
3-5	Intermediate risk	73.8
6 or more	High risk	31.2

RCC, renal cell carcinoma; SSIGN, size, stage, grade and necrosis; TNM, tumour, node, metastasis

Adapted from [18], with permission from John Wiley & Sons, Inc.

Table 4. UISS risk groups and 5-year disease-specific survival [19]

Patient Group		Prognostic Group			
		T stage	Fuhrman's grade	ECOG status	5-year disease-specific survival (%)
Localised disease (N0, M0)	Low risk	1	1–2	0	91.1
	Intermediate risk	1	1–2	1 or more	80.4
		1	3–4	Any	
		2	Any	Any	
		3	1	Any	
		3	2–4	Any	
	High	3	2–4	1 or more	54.7
		4	Any	Any	
Metastatic Disease	Low risk	N_1M_0	Any	Any	32
		N_2M_0/M_1	1–2	0	
	Intermediate risk	N_2M_0/M_1	1–2	1 or more	19.5
			3	0, 1 or more	
			4	0	
	High	N_2M_0/M_1	4	1 or more	0

ECOG, Eastern Cooperative Oncology Group; UISS, University of California Los Angeles Integrated Staging System.

Table 5. Median OS estimates in first and second line RCC according to IMDC risk groups

Number of risk factors	Risk category	Median OS (months)	
		First line [23]	Second line [22]
0	Favourable	43.2	35.3
1–2	Intermediate	22.5	16.6
3–6	Unfavourable	7.8	5.4

IMDC, International Metastatic RCC Database Consortium; OS, overall survival; RCC, renal cell carcinoma.

Table 6. Summary of recommendations

Diagnosis and pathology/molecular biology

- Laboratory examinations of serum creatinine, haemoglobin, leukocyte and platelet counts, lymphocyte to neutrophil ratio, lactate dehydrogenase, C-reactive protein (CRP) and serum-corrected calcium tests should be carried out to confirm suspicion of RCC [IV, B]
- For accurate staging, US and contrast-enhanced chest, abdominal and pelvic CT are recommended [III, A]
- A renal tumour core biopsy is recommended before treatment with ablative therapies and in patients with metastatic disease before starting systemic treatment [III, B]
- Pathology should be assessed using the 2016 WHO histological classification of renal tumours and ISUP grading

Staging and risk assessment

- The UICC TNM 8 staging system should be used

Management of local/locoregional disease

- For organ confined T1 tumours < 7 cm PN is recommended. Laparoscopic RN is recommended if PN is not feasible [I, A]
- In patients with compromised renal function, solitary or bilateral tumours, PN is also recommended with no tumour size limitation
- RFA, MWA or CA are options in patients with small cortical tumours ≤ 3 cm, frail patients, high surgical risk, solitary kidney, compromised renal function and hereditary RCC or bilateral tumours [III]
- Renal biopsy is recommended to confirm malignancy and subtype for these patients
- Active surveillance for elderly patients with significant comorbidities or those with short life expectancy and solid renal tumours < 40 mm; renal biopsy is recommended to select these patients [III]
- For T2 tumours > 7 cm laparoscopic RN is preferred option
- For T3 and T4 tumours (locally advanced), open RN is the standard of care, although a laparoscopic approach can be considered

Management of advanced/metastatic disease

- CN is recommended in patients with good PS [I, A] except in intermediate- and poor-risk patients with asymptomatic primary tumours when medical treatment is required [I, A]
- RT can be used to treat unresectable local or recurrent disease and in patients unsuitable for surgery due to poor PS or unsuitable clinical condition. RT is an alternative if radioablation is not appropriate
- Image-guided RT techniques such as VMAT or SBRT are needed to enable a high dose to be delivered [IV, B]

- RT is an effective treatment for palliation of local and symptomatic mRCC disease or to prevent the progression of metastatic disease in critical sites such as bones or brain [I, A]
- For mRCC patients with brain metastases, the use of corticosteroids can provide temporary relief of cerebral symptoms. WBRT between 20 and 30 Gy in 4-10 fractions is recommended for effective symptom control [II, B]
- For good-prognosis mRCC patients with a single unresectable brain metastasis, SRS with or without WBRT should be considered [II, A]

Follow-up, long-term implications and survivorship
- Follow-up for high-risk patients includes CT scans of thorax and abdomen every 3-6 months for the first two years; an annual CT scan is recommended for low-risk patients
- For mRCC patients during systemic therapy, 2-4-month follow-up with CT scan is advised
- RECIST is the most frequent used method to assess drug efficacy

CA, cryoablation; CT, computed tomography; ISUP, International Society of Urological Pathology; MWA, microwave ablation; PN, partial nephrectomy; PS, performance status; RCC, renal cell carcinoma; RECIST, response evaluation criteria in solid tumours; RFA, radio frequency ablation; RN, radical nephrectomy; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SRS, stereotactic radiosurgery; TNM, tumour, node and metastasis; UICC, Union for International Cancer Control; US, ultrasound; VMAT, volumetric-modulated arc therapy; WBRT, whole brain radiotherapy; WHO, World Health Organization.

Table 7. ESMO-Magnitude of Clinical Benefit Scale (MCBS) table for new therapies/indications in renal cell carcinoma[a]

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/Toxicity	MCBS Score[b]
Nivolumab, a PD-1 checkpoint inhibitor	Advanced clear-cell renal cell carcinoma previously treated with one or two regimens of anti-angiogenic therapy	Study of nivolumab vs. everolimus in pre-treated advanced or metastatic clear-cell renal cell carcinoma (CheckMate 025) [50] Phase III NCT01668784	Everolimus Median OS: 19.6 months	OS gain: 5.4 months	OS HR: 0.73 (0.57-0.93)	Improved toxicity profile and QoL	5 (Form 2a)
Cabozantinib	Advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors	A study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma (METEOR) [52] Phase III NCT01865747	Everolimus Median OS: 16.5 months	OS gain: 4.9 months	OS HR: 0.66 (0.53–0.83)	__	3 (Form 2a)

| Lenvatinib in combination with everolimus | Advanced or metastatic renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy | Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial [53]

Phase II

NCT01136733 | Everolimus

Median OS: 15.4 months | OS gain: 10.1 months | OS HR: 0.51 (0.30–0.88) | __ | 4 (Form 2a; secondary endpoint of OS in a small phase II randomised study) |

[a]EMA approvals from January 2016 to end December 2018.

[b]ESMO-MCBS version 1.1 [67].

CI, confidence interval; EMA, European Medicines Agency; HR, hazard ratio; OS, overall survival; PD-1, programmed death 1; QoL, quality of life.

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

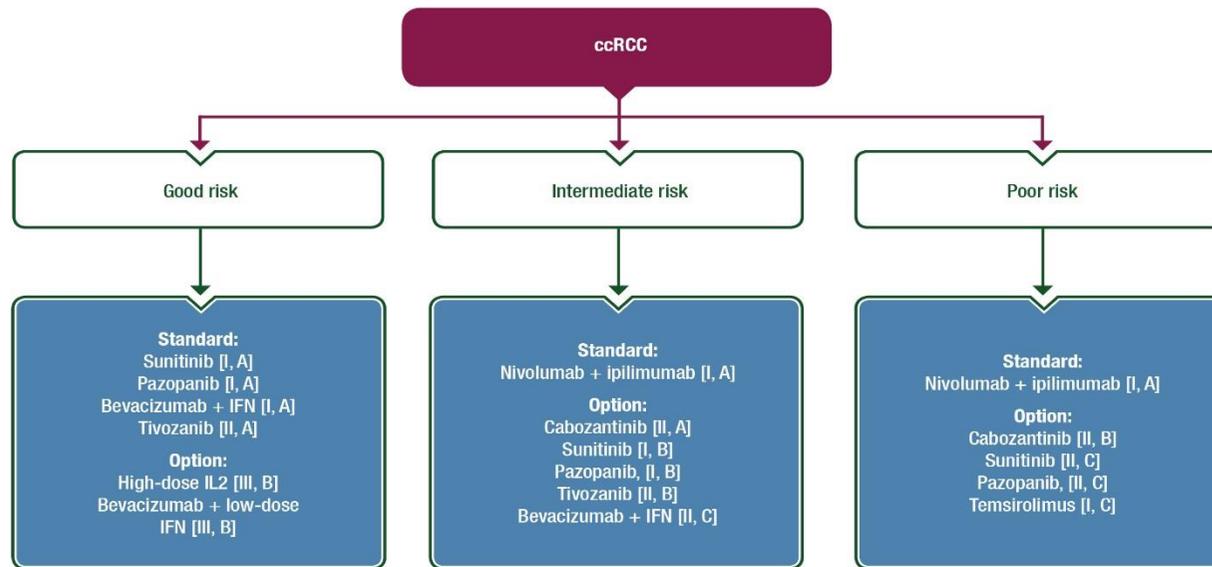[a]By permission of the Infectious Diseases Society of America [69].

Figure 1. Systemic first-line treatment of ccRCC.
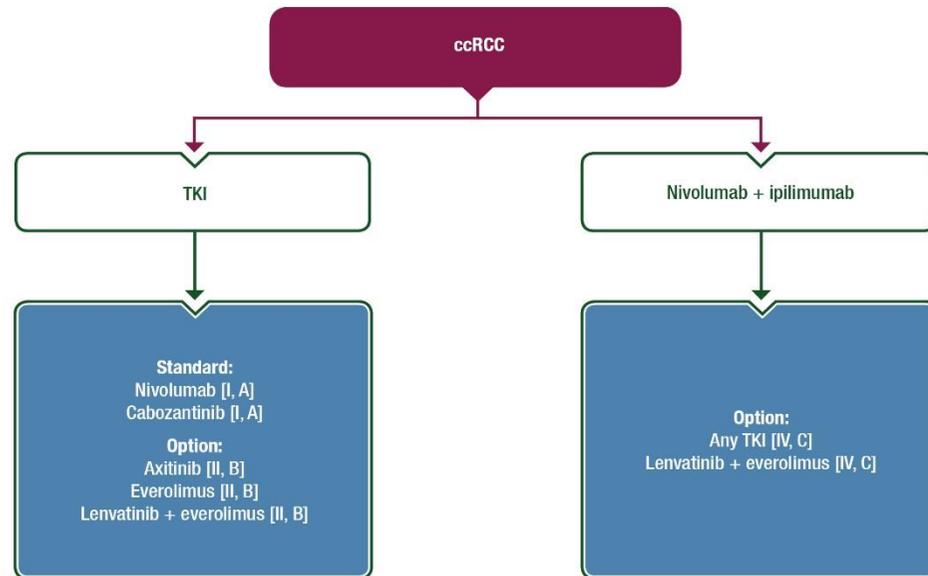ccRCC, clear cell renal cell carcinoma; IFN, interferon; IL2, interleukin 2.

Figure 2. Second-line treatment of ccRCC.
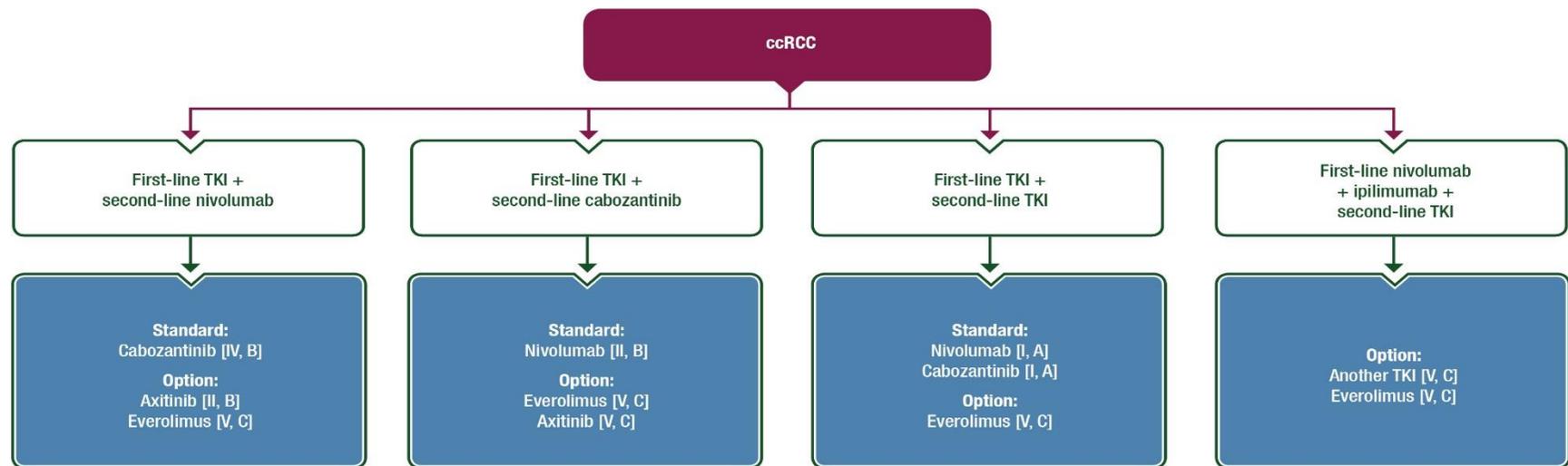ccRCC, clear cell renal cell carcinoma; TKI, tyrosine inhibitor.

Figure 3. Third-line treatment of ccRCC.
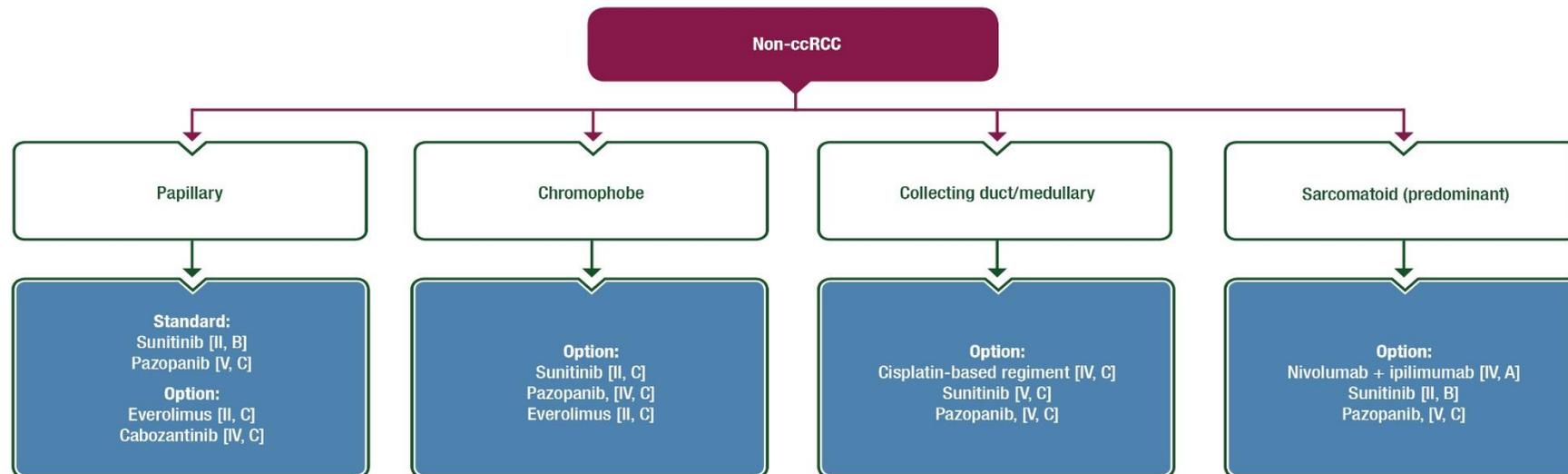ccRCC, clear cell renal cell carcinoma; TKI, tyrosine inhibitor.

Figure 4. Systemic first-line treatment of non-ccRCC.
Non-ccRCC, non-clear cell renal cell carcinoma.