An update on the management of metastatic clear-cell renal cell carcinoma: the BSMO expert panel recommendations

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SUMMARY

The management of recurrent or metastatic renal cell carcinoma is evolving fast, with new therapeutic options becoming available that may improve the outcome of patients. In this paper, recent evolutions are discussed and recommendations are made regarding the management of renal cell carcinoma in a Belgian context.

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INTRODUCTION

In 2015, a paper was published authored by the Belgian Society of Medical Oncology (BSMO) renal cancer task force group, containing specific recommendations for the management of renal cell carcinoma (RCC) in a Belgian context, based on the international guidelines and phase III clinical trials.[1] Since then, the results of several practice-changing clinical trials have been published and international guidelines have been updated. Therefore, an update of these Belgian recommendations is warranted.

In this paper, the authors present a summary of the current guidelines for treatment of metastatic RCC and discuss the consequences of recently published pivotal clinical trials. The treatment of metastatic RCC in the Belgian healthcare environment is discussed.

EPIDEMIOLOGY

Based on data from the Belgian Cancer Registry on the incidence of kidney cancer in Belgium, 1815 persons (1182 males and 633 females) have been diagnosed with kidney cancer in 2016 (the most recent numbers available at present).[2] This corresponds to an age-standardised incidence rate of 11.9 for males and 5.4 for females per 100.000 person years using the world standard population. The mean age at diagnosis was 65.4 years in males and 67.8 years in females.[2]

The 5-year relative survival for the period 2012-2016 is 75.5% for males and 76.9% for females.[2] However, survival is highly dependent on the extent of the disease, ranging from 91% for stage I to around 15% for stage IV disease.[1] In 2016, 13.8% of patients had stage IV disease at diagnosis.[2] In addition, it is estimated that approximately 50% of patients who are treat-

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TABLE 1. Overview of the different prognostic systems for metastatic ccRCC.

	Original MSKCC	Modified MSKCC (Motzer criteria)	Criteria for temsirolimus treatment[1]	IMDC (Heng's criteria)
KPS < 80%	X	X	X	**X**
Hb < LLN	X	X	X	**X**
Elevated corrected Ca	X[2]	X[2]	X[2]	**X**[3]
LDH >1.5 x ULN	X	X	X	
Time between diagnosis and treatment < 1 year		X	X	**X**
No prior nephrectomy	X			
Neutrophil count > ULN				**X**
Platelet count > ULN				**X**
Metastases in > one organ			X	

For each set of criteria, presence of no criteria predicts 'good' prognosis, one or two criteria predicts 'intermediate' prognosis, and presence of three or more criteria predicts 'poor' prognosis.
[1]Patients are considered for treatment with temsirolimus if at least three of the specified criteria are present; [2]corrected Ca > 10 mg/dl ; [3]corrected Ca > ULN ; abbreviations: KPS: Karnofsky performance scale, Hb: haemoglobin, LLN = lower limit of the normal range, LDH: lactate dehydrogenase, ULN: upper limit of the normal range.

ed for localised disease develop metastases later on. Eighty-five percent (85%) of these recurrences occur within three years after initial resection, but relapse can develop even several decades later.[1]

There is a small but clear increase of the incidence in males over the past decade, rising from an age-standardised incidence rate of 10.0 in 2004 to the above-mentioned 11.9 in 2016. The incidence in females remained approximately stable since 2004.[2] As such, the Belgian figures do not show the stabilisation that has been reported elsewhere.[3]

Comparing the Belgian figures internationally, the Belgian age-standardised incidence is approximately equal to the European average. The survival seems better than the European average, which is reported to be 61.3% and 60.8% 5-year relative survival in males and females respectively.[4] However, these European figures also incorporate cancer arising in the renal pelvis, such as transitional cell carcinoma, complicating their interpretation and comparison to the Belgian numbers.

DIAGNOSIS OF RENAL CELL CARCINOMA

Very briefly summarised, a diagnosis of RCC is being considered based on either symptoms (haematuria, flank pain, and a palpable abdominal mass in the classical triad but has become rare), biochemical abnormalities (*e.g.* unexplained hypercalcemia), or an incidental imaging finding. Next, a suspected renal mass can be identified by ultrasound and/or computed tomography (CT). If such a suspicious mass is being discovered, further staging examinations consisting of at least a CT of the thorax, abdomen, and pelvis should be performed. Bone scan and imaging of the brain are not routinely recommended.[3]

It is not in the scope of this paper to discuss into detail the diagnostic features of RCC. Readers who would like to know more about this topic are kindly referred to the various textbooks and guidelines on this subject.

PATHOLOGY REPORT

Before initiation of systemic treatment, a pathological diagnosis of RCC should be obtained. This is important to determine the histological subtype, as well as other parameters such as the international society of urologic pathologists (ISUP) nucleolar grade (only to be applied in case of a clear-cell or papillary RCC), the presence of a sarcomatoid and/or rhabdoid component, and if present the estimated percentage of this

component, the presence of necrosis, the presence of microscopic vascular invasion, and the pTNM stage.[3] The ISUP grade has replaced the previously used Fuhrman grade.[5, 6] Approximately 75 to 80% of RCC are clear-cell, while the remaining cancer types are jointly referred to as non-clear cell RCC. Non-clear cell RCC consists of several distinct disease entities, the most frequent ones being papillary and chromophobe RCC.[3,7] Because non-clear cell RCC is a rare and heterogeneous pathology, a routine second opinion pathology review for these cases should be recommended.

The international guidelines accept that in patients with metachronous metastases the diagnosis made on an earlier nephrectomy or tumourectomy specimen is sufficient, and no additional pathological confirmation is required before the initiation of therapy. In patients with synchronous metastases, a pathological diagnosis based on either the primary tumour or a metastasis must be obtained.[3,5] In this setting, a biopsy will often be necessary, especially since routine cytoreductive nephrectomy is likely to be performed less frequently in the future (see below). A recent meta-analysis concluded renal biopsy to be a safe procedure, resulting in accurate diagnosis. Core biopsies were more accurate than fine-needle aspiration. The agreement observed between the biopsy and the surgical specimen was good (0.683) regarding histologic subtype and fair (0.34) regarding the Furhman grade.[8]

PROGNOSTIC SCORING

Patients who are diagnosed with metastatic RCC can be divided into prognostic categories. This is of particular importance because the category the patient belongs to not only provides information about prognosis, but also results in different treatment recommendations and in different reimbursements. Therefore, while prognostic stratification in the past could be considered an additional tool, it is currently a necessity to determine the patient's treatment options. Several scoring systems exist. All of them divide patients into poor, intermediate, and favourable risk categories based on clinical and laboratory risk factors.

Nowadays, the International Metastatic RCC Database Consortium (IMDC) score developed by *Heng et al.* is used most frequently.[9,10] It was developed for the prediction of survival in patients treated with vascular endothelial growth factor (VEGF)-targeted therapies. In this risk score, six factors are taken into account. If none of these adverse factors are present, the patient has a favourable prognosis, with a median overall survival (OS) of 43.2 months. Patients having one or two adverse factors are classified in an intermediate prognosis group, with a median OS of 22.5 months. Patients with at least three adverse factors are classified in the poor prognosis group, having a median OS of 7.8 months.[10] A related system is used to define patients with poor prognosis who can be considered for treatment with temsirolimus (see below).[11]

An overview of the different scoring systems is provided in *Table 1.*

MANAGEMENT

LOCAL THERAPIES FOR METASTATIC DISEASE

Role of cytoreductive nephrectomy

Contrary to most solid tumours, it used to be common practice in RCC to perform a resection of the primary tumour even when distant metastases were present. This practice is supported by data from prospective, randomised trials showing improvement in OS after treatment with nephrectomy followed by IFNα compared to IFNα alone.[12] Also, in exceptional cases a spontaneous regression of metastases after nephrectomy is observed.[13]

This approach remained standard of care when the systemic treatment progressed to more effective treatment options, such as tyrosine kinase inhibitors (TKI). The results of retrospective studies seemed to confirm this practice.[14-16] However, recently the phase III non-inferiority trial CARMENA was conducted comparing upfront treatment with sunitinib (without prior nephrectomy) to nephrectomy followed by sunitinib in patients with intermediate or poor prognosis according to the modified MSKCC model. The results showed upfront treatment with sunitinib to be non-inferior to nephrectomy followed by sunitinib. Median OS was even numerically longer in the group which did not have a nephrectomy (18.4 months in the non-nephrectomy group compared to 13.9 months in the nephrectomy group) although this difference was not statistically significant.[17] In addition, the SURTIME trial showed patients who were treated with three cycles of sunitinib followed by nephrectomy in the absence of progressive disease, to have a better OS compared to patients who had upfront nephrectomy (median OS of 32.4 *vs.* 15.0 months, HR 0.57, p=0.03).[18] Based on these results, international guidelines were updated and routine cytoreductive nephrectomy in patients with intermediate or poor prognosis is no longer recommended.[3,19] Patients with good prognosis, for whom start of systemic therapy was not immediately needed, were not included in the trial. The European Association of Urology (EAU) maintains that cytoreductive nephrectomy could have a role in patients who do not need urgent medical treatment and in those patients who have sustained benefit on first-line treatment and/or have minimal residual metastatic tumour burden. Nephrectomy also remains an option as a symptomatic treatment for patients with a symptomatic primary

lesion.[19] Both the SURTIME and CARMENA trial showed that delayed cytoreductive nephrectomy is feasible and safe. In addition, while these recent trials examine the use of cytoreductive nephrectomy before first-line sunitinib, it is expected most patients in the future will be treated with immune checkpoint inhibitors in first-line. Clinical trials focusing on the question of nephrectomy in this setting are ongoing.

Role of local therapy of metastases

The rate of single site metastases in renal cell cancer patients is 61% *versus* 39% for metastases at two or more sites. The most common metastatic sites are lung (45.2%), bone (29.5%), lymph nodes (21.8%), liver (20.3%), adrenal (8.9%) and brain (8.1%).[20]

There are no prospective clinical trials evaluating the benefit of metastasectomy in RCC. Retrospective analyses in highly selected patient populations point systematically towards metastasectomy, even of multiple metastases, resulting in benefit for the patient, as illustrated by a prolonged OS, cancer-specific survival, or time without systemic therapy. These results need to be interpreted with caution. If clinicians select patients with oligometastatic spread, slowly progressing disease, and good performance status (PS), it becomes unclear if positive results observed are the consequence of the metastasectomy or rather reflect the overall better prognosis of the selected population.[21,22] Also, depending on the particularities of the case, metastasectomy may be accompanied by a significant risk of complications.[23] Therefore, randomised clinical trials investigating the role of metastasectomy are needed. The current ESMO guidelines advise metastasectomy in selected patients after multidisciplinary review. Factors that may favour metastasectomy are good performance status, a solitary metastasis or oligometastasis, more than two years between diagnosis and development of metastases, no progression on systemic treatment, low or intermediate Fuhrman grade, and the possibility of complete resection of all macroscopic disease.[3] At present, no adjuvant therapy can be advised after complete metastasectomy.[24,25]

Role of radiotherapy

While RCC used to be considered a radio-resistant disease, a role for radiotherapy in the treatment of RCC has emerged. Conventional radiotherapy has a clear role in local symptom control, both for primary and metastatic lesions. However, relative higher doses are needed, *e.g.* 5 x 4 Gy or 10 x 3 Gy rather than a single fraction of 8 Gy.[26]

Furthermore, modern techniques such as *e.g.* stereotactic radiosurgery (SRS) and stereotactic ablative radiotherapy (SABR) have demonstrated to be safe and have excellent local efficacy. They could be used as an alternative to surgical metastasectomy in the above mentioned strategies for oligometastatic disease and/or for the treatment of patients with RCC and brain metastasis.[3,27]

DELAY OF SYSTEMIC TREATMENT

In some cases, it is considered acceptable to delay systemic treatment and initially start with a wait-and-see approach. The rationale for this is that sometimes RCC follows an indolent course. In addition, treatment with TKI's is often toxic and generally not curative, although today immune-checkpoint inhibitors provide a treatment option with a milder safety profile. A wait-and-see strategy is often combined with local treatment: tumourectomy combined with metastasectomy or SRS. It seems to be a reasonable option in patients with ologiometastatic disease, favourable prognosis, or who have limited life expectancy because of other causes. There is some evidence to support such a strategy, but robust data are lacking.[3, 5]

SYSTEMIC TREATMENT

TREATMENT OF CLEAR-CELL RCC

The recommendations for the systemic treatment of metastatic RCC mostly relate to tumours with a clear cell histology, which is the most common subtype.

First-line treatment

Until recently, there were four standard-of-care treatment options in first-line metastatic clear-cell RCC: sunitinib, pazopanib, the combination of IFNα and bevacizumab, and for patients with poor prognostic features temsirolimus.

Both sunitinib and IFNα plus bevacizumab were established as first-line options after demonstrating superiority compared to IFNα alone.[28-33] Pazopanib showed superiority compared to placebo,[34,35] and demonstrated non-inferiority compared to sunitinib.[36] There has been some discussion regarding the interpretation of the results of this non-inferiority trial, since the PFS of pazopanib-treated patients was only narrowly within the pre-defined margin of non-inferiority and the design and statistical methods applied in the trial have been subject to criticism.[37] On the other hand, retrospective data from a real world situation also indicate similar efficacy of sunitinib and pazopanib.[38] Furthermore, it has been shown that pazopanib and sunitinib have different safety profiles,[36] that most patients (70%) being treated in a blinded cross-over study prefer treatment with pazopanib over sunitinib, and that better health-related quality of life was reported during treatment with pazopanib compared to during treatment with sunitinib.[39] Overall, the in-

ternational guidelines consider pazopanib and sunitinib equivalent treatment options.[3,5,40]

Temsirolimus was established as an option in patients with poor prognostic features (*Table 1*) based on a study in which it showed superiority compared to IFNα in this specific population.[11]

Tivozanib is another TKI which was approved by EMA for first line therapy based on a phase III trial in which it demonstrated superior progression-free survival (PFS), but not superior OS, compared to sorafenib. Tivozanib is not marketed in Belgium.[41]

Recently, several clinical trials have been performed, comparing sunitinib to alternative treatments in first-line metastatic ccRCC.

The CheckMate214 trial is a phase III trial in patients with intermediate or poor prognostic features (according to the IMDC prognostic score), comparing the immunotherapy combination of ipilimumab and nivolumab to sunitinib. The treatment schedule consists of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy. The ipilimumab-nivolumab combination resulted in a better OS (median OS not reached *vs.* 26.6 months). Superior OS was observed in each subgroup based on PD-L1 expression. The patients in the immunotherapy arm also reported better health-related quality of life compared to those in the sunitinib arm. Of note, the ipilimumab dose in this schedule is lower compared to the ipilimumab-nivolumab regimen applied in melanoma (ipilimumab 3 mg/kg plus nivolumab 1 mg/kg), contributing to a better safety profile. In this trial, as an exploratory objective, both treatments were also compared in patients with good prognostic features. Here, after 30 months of follow-up, no statistical significant differences were seen for OS, PFS, or objective response rate (ORR), although they were all numerically higher in the sunitinib arm. On the other hand, the CR rate was twice as high in the ipilimumab-nivolumab arm [10 (8%) *vs.* 5 (4%)].[42,43]

Two trials combining an anti-PD1 or anti-PD-L1 checkpoint inhibitor with a TKI have shown superiority compared to sunitinib monotherapy.

In the KEYNOTE-426 trial, the combination of pembrolizumab and axitinib demonstrated a significant survival benefit compared to sunitinib (HR for death 0.53, p <0.0001). Also, ORR (59.3% *vs.* 35.7%) and PFS (15.1 *vs.* 11.1 months) were significantly better in the experimental arm compared to sunitinib monotherapy. The benefit was observed in all subgroups based on prognostic score or PD-L1 expression.[44]

In the JAVELIN Renal 101 trial, the combination of avelumab (anti-PD-L1) and axitinib demonstrated a superior ORR (51.4% *vs.* 25.7%) and PFS (13.8 *vs.* 8.4 months) compared to sunitinib monotherapy. Benefit was consistent among all subgroups based on prognostic group or tumour PD-L1 expression. The trial's primary endpoints were focused on patients with PD-L1 positive tumours, but the results did not differ meaningfully between patients with PD-L1 positive tumours and the overall population.[45] However, as OS data were immature and lacked a signal towards OS benefit, recent international guidelines do not recommend this combination as preferred first-line therapy.[46]

The CABOSUN phase II trial in patients with intermediate or poor prognostic features (according to IMDC criteria) cabozantinib resulted in an improved PFS compared to sunitinib (8.6 *vs.* 5.3 months). Median OS was numerically longer in the cabozantinib group (26.6 *vs.* 21.2 months) but the difference was not statistically significant. Initially, the results of the trial were reported without blinded reading of the imaging, causing the value of these data to be discussed. However, updated data did contain blinded reading of the imaging and confirmed the significant PFS gain. In the subgroup analysis, the most important observation was the difference in PFS between MET positive and MET negative tumours (based on immunohistochemistry). The PFS in the cabozantinib and sunitinib group of patients with MET positive tumours was 13.8 *vs.* 3.0 months respectively, while in patients with MET negative tumours this was 6.9 *vs.* 6.1 months. So the benefit of cabozantinib, which is also a MET inhibitor, compared to sunitinib can be explained at least partly due to its better effects in patients with MET positive tumors.[47,48]

The IMmotion-151 trial is a phase III trial comparing the combination of atezolizumab and bevacizumab to monotherapy with sunitinib. A superior PFS in the experimental arm was shown (11.2 *vs.* 8.4 months), which was consistent among sub-groups. Also, the proportion of patients with a CR was higher in the experimental arm [24 (5%) *vs.* 10 (2%)]. Notably, the subgroup of patients with a tumour with sarcomatoid differentiation had an ORR of 49% in the experimental arm compared to 14% in the control arm. However, no OS benefit was demonstrated after a median follow-up of 24 months (median OS 33.6 *vs.* 34.9 months). The experimental arm did result in a favourable safety profile compared to the control arm, with less side-effects who interfered with the daily functioning of the patients.[49] At present, the atezolizumab-bevacizumab combination is not approved by EMA.

An overview of pivotal clinical trials can be found in *Table 2*.

Of all the above mentioned treatment options, only the combination of pembrolizumab and axitinib demonstrated a survival benefit compared to sunitinib across all prognos-

TABLE 2. An overview of pivotal clinical trials evaluating systemic treatment in ccRCC.

Reference	Population	Treatment arms	ORR	PFS [months]	OS [months]
65	metastatic RCC	Low-dose IL-2 +IFN	9.9%[1]	3.1	13
		High-dose IL-2	23.2%[1]	3.1	17
30, 31	First-line ccRCC	IFNα +bevacizumab	31%*	10.2*	23.3
		IFNα + placebo	13%	5.4	21.3
32, 33	First-line ccRCC	IFNα +bevacizumab	25.5%*	8.5*	18.3
		IFNα	13.1%	5.2	17.4
29, 30	First-line ccRCC	sunitinib	47%*	11*	26.4
		IFNα	12%	5	21.8
34, 35	First-line ccRCC or after cytokine treatment	pazopanib	30%*	9.2*	22.9
		placebo	3%	4.2	20.5
41	First-line ccRCC or after cytokine treatment	tivozanib	33.1%	11.9*	28.8
		sorafenib	23.3%	9.1	29.3
11	First-line RCC with poor prognosis	temsirolimus	8.6%	5.5*[2]	10.9*
		IFNα + temsirolimus	8.1%	4.7	8.4
		IFNα	4.8%	3.1	7.3
36	First-line ccRCC	pazopanib	31%*	8.4 [3]	28.4
		sunitinib	25%	9.5	29.3
42, 43	First-line ccRCC with intermediate or poor prognosis	ipilimumab + nivolumab	42%*	8.2	NR* (30m OS: 60%)
		Sunitinib	29%	8.3	26.6 (30m OS: 47%)
	First-line ccRCC with good prognosis	ipilimumab + nivolumab	39%	13.9	NR (30m OS: 80%)
		sunitinib	50%	19.9	NR (30m OS: 85%)
	First-line ccRCC overall population	ipilimumab + nivolumab	41%	9.7*[4]	NR* (30m OS: 64%)
		sunitinib	34%	9.7	37.9 (30m OS: 56%)
44	First-line ccRCC	pembrolizumab + axitinib	59.3%*	15.1*	NR 18m OS: 82.3%*
		sunitinib	35.7%	11.1	NR 18m OS: 72.1%
46	First-line ccRCC	avelumab + axitinib	51.4%*	13.8*	pending
		sunitinib	25.7%	8.4	pending
49	First-line RCC with cc or sarcomatoid histology	atezolizumab + bevacizumab	37%	11.2*	33.6
		sunitinib	33%	8.4	34.9
47, 48	First-line ccRCC, with intermediate or poor prognosis	cabozantinib	20%	8.6*	26.6
		sunitinib	9%	5.3	21.2
	Sub-analysis: MET+ tumours	cabozantinib	not-rep.	13.8*	not-rep.
		sunitinib	not-rep.	3.0	not-rep.
52	≥2L ccRCC	everolimus	1%	4.0*	NR
		placebo	0%	1.9	8.8
50, 51	2L ccRCC	axitinib	19%	6.7*	20.1
		sorafenib	9%	4.7	19.2
53, 54	≥2L ccRCC	cabozantinib	17%*	7.4*	21.4*
		everolimus	3%	3.9	16.5
55	≥2L ccRCC	nivolumab	25%*	4.6	25.0*
		everolimus	5%	4.4	19.6
63	2L ccRCC	lenvatinib	27%*[5]	7.4*[5]	19.1
		everolimus	6%	5.5	15.4
		lenvatinib + everolimus	43%*[5]	14.6*[5]	25.5*[5]

*statistical significant improvement compared with the comparator arm(s). [1]*Evaluation not according to RECIST,* [2]*compared to IFNα monotherapy only,* [3]*non-inferior compared to the sunitinib arm,* [4]*Despite equal median PFS, PFS was significantly different due to separation of the PFS curves beyond the median,* [5]*compared to everolimus monotherapy only ; abbreviations: ORR: objective response rate, PFS: progression free survival, OS: overall survival, NR: not reached, not-rep.: not reported.*

tic subgroups. The combination of the checkpoint inhibitors ipilimumab and nivolumab also demonstrated an improved OS compared to sunitinib but only in patients with intermediate or poor prognostic features. In patients with good prognostic features no advantage was demonstrated. Although in this group there were more complete responders compared to treatment with sunitinib, OS did not differ significantly and was numerically worse.

Regarding the avelumab and axitinib combination, mature OS data are still awaited and therefore the place of this combination in the treatment of ccRCC is less clear today.

In those patients for whom treatment with an immune checkpoint inhibitor is contra-indicated, treatment with monotherapy sunitinib or pazopanib is still a logical choice for patients with good prognostic features, while for patients with intermediate or poor prognostic features cabozantinib could be considered the first option based on the above mentioned CABOSUN trial.

Today, all the above mentioned treatment options are reimbursed in Belgium, with the exception of axitinib in the pembrolizumab-axitinib and avelumab-axitinib combinations. The checkpoint inhibitor is reimbursement for both combinations. Pending reimbursement, axitinib is provided as samples by the manufacturer upon request.

Second- and further lines of treatment

Several drugs have been evaluated in second-line treatment. In the AXIS trial axitinib was compared to sorafenib. Approximately half of the patients included in this trial were previously treated with sunitinib, while the other first-line treatments were mainly cytokines and in few patients bevacizumab plus IFNα, or temsirolimus. While the ORR and PFS in the axitinib arm were superior to the sorafenib arm, no significant OS difference was demonstrated.[50,51]

In the RECORD-1 trial, everolimus was compared to placebo in patients who had received at least one line of therapy. All patients had already been treated with sunitinib, sorafenib, or both, and in addition could have been treated with other treatments such as cytokines or chemotherapy. Everolimus resulted in only 1% objective responses, but also in an increased number of patients with SD (63% *vs.* 32%). Median PFS was 4.0 months, a significant increase compared to placebo. Since 26% of patients had a PFS of more than 6 months, it seems that a subpopulation had a prolonged stabilisation of the disease upon treatment with everolimus.[52]

The METEOR trial compared cabozantinib to everolimus in patients who had received at least one line of therapy, including at least one VEGFR-targeted TKI. Cabozantinib was shown to significantly improve OS (median OS 21.4 *vs.* 16.5 months).[53,54]

Finally, the CheckMate 025 trial compared nivolumab to everolimus. It included patients who had received maximum three lines of previous therapy, including one or two lines of anti-angiogenic therapies. The trial demonstrated that nivolumab results in a significantly improved OS compared to everolimus (median OS 25.0 *vs.* 19.6 months).[55]

Another treatment that has been approved by EMA for second-line metastatic RCC is the combination of lenvatinib and everolimus. This is based on a phase II trial which showed both the combination lenvatinib – everolimus and monotherapy lenvatinib to result in a better OS compared to everolimus monotherapy. In addition, the combination arm showed longer OS than monotherapy lenvatinib but the difference was not statistically significant.[56] Both ESMO and EAU guidelines consider this phase II trial insufficient to recommend the use of lenvatinib for the treatment of RCC.[3,5] In Belgium this treatment is not reimbursed so far.

Which second-line therapy could be considered most appropriate? The arguments for everolimus seem to be the poorest, since it has been shown to be inferior both to nivolumab and to cabozantinib. It may result in disease stabilisation in few patients, and is generally considered an option as a later treatment line.

Since sorafenib proved inferior to axitinib in terms of ORR and PFS, it is generally considered not the best option for second-line, but does remain an option for later therapy.

There is no head-to-head comparison between axitinib, cabozantinib, and nivolumab. In terms of ORR and OS, the results seem comparable between the trials.

Second-line choices are also influenced by the first-line therapy the patient received. In particular, the appearance of immune checkpoint-inhibitors in first-line, and also the combinations including axitinib, will influence second-line choices.

Emerging evidence is supporting the benefit of TKIs after previous immune checkpoint-inhibitors. Several prospective trials and retrospective series have reported response rates of 18 to 47% and progression-free survival of 6 to 9 months on TKI after previous immune checkpoint-inhibitor or immune checkpoint-inhibitor combinations.[57-63]

Therefore, it seems that patients who were treated with pembrolizumab or avelumab in combination with axitinib in first-line should be treated with cabozantinib in second-line. Patients who were treated with nivolumab-ipilimumab in first-line could be treated with either cabozantinib or axitinib. For patients with good prognosis, who have been treated with a tyrosine-kinase inhibitor in monotherapy in first-line, second-line therapy could consist either of nivolumab, cabozantinib, or axitinib. In this setting it seems reasonable to choose nivolumab in order to switch

the mechanism of action rather than to treat subsequently with two TKI's, especially if the first-line TKI did not result in a long period of disease control.

With regard to reimbursements, the RIZIV/INAMI has recently revised its criteria for most drugs that are used in RCC. This was triggered by the approval of nivolumab-ipilimumab for first-line therapy, making a lot of the reimbursement criteria of other drugs inapplicable. With regard to second-line therapy, only nivolumab and cabozantinib are reimbursed, while axitinib is no longer reimbursed in second-line (except for patients for whom second-line therapy with an immune-checkpoint inhibitor or a VEGF-targeted therapy other than axitinib is not recommendable, applicable, or reimbursable). This is based on the ESMO guidelines, which also recommend only nivolumab and cabozantinib as preferred second-line therapies.[3] From third-line on axitinib, sunitinib, pazopanib, sorafenib, and everolimus are all reimbursed in Belgium.

The role of interleukin-2 (IL-2)

High-dose IV IL-2 is FDA approved as a treatment option for metastatic RCC since 1992. It has the ability to induce durable responses in a subset of patients.[64] A phase III trial showed an ORR of 23.2% and a median OS of 17.5 months.[65] However, its use is limited to selected patients because of the frequent and potentially dangerous side effects, in particular capillary leak syndrome. Because of these, the treatment requires prolonged hospitalisation for observation.[66] While the ESMO guidelines still consider high-dose IV IL-2 a treatment option, it is no longer available in Belgium since the manufacturer decided to discontinue its marketing.[3]

Of note, several IL-2 based drugs that are expected to result in less side effects are currently in clinical development for the treatment of solid tumours, for example NKTR-214 and RO6874281.

(Neo)adjuvant treatment

The advantage of (neo)adjuvant treatments in RCC has been evaluated in several trials.

Trials evaluating classical immunotherapy such as high-dose IL-2, IFN-α, or IFN-α combined with low-dose IL-2 could not demonstrate any benefit. An increase in PFS was observed after treatment with an autologous tumour vaccine, but the study's methodology was criticised and the drug did not proceed to the clinic. A trial with a carbonic anhydrase inhibitor could not demonstrate benefit, although in the subgroup with the highest carbonic anhydrase expression an increase in disease free survival (DFS) was reported. Again, this product did not proceed to the clinic.[67,68]

A lot of trials have been performed to evaluate the potential of TKI's in the adjuvant setting. Four phase III trials have been performed, evaluating axitinib *vs.* placebo (ATLAS), pazopanib *vs.* placebo (PROTECT), sunitinib *vs.* placebo (S-TRAC), and sunitinib *vs.* sorafenib *vs.* placebo (ASSURE). Of these trials, only S-TRAC was positive for the primary endpoint, showing increased DFS (mean DFS 6.8 *vs.* 5.6 years). S-TRAC included patients with local disease with high risk of recurrence, defined as a T3 or T4 tumour and/or the presence of lymph node involvement. While DFS (the primary end-point) was increased, no OS benefit could be demonstrated.[69] It has been shown that DFS only moderately correlates to OS in RCC.[70] Based on the results of S-TRAC, adjuvant sunitinib was approved by the FDA. However, EMA did not approve sunitinib in this setting, and both the ESMO and EAU guidelines do not consider the evidence sufficient to recommend adjuvant sunitinib in RCC.[3,5]

Adjuvant and neo-adjuvant immunotherapy trials are currently ongoing.

Finally, a pooled analysis of studies indicates that adjuvant radiotherapy after radical nephrectomy results in less local recurrences, but does not influence DFS or OS.[71]

In conclusion, no (neo)adjuvant therapies can be recommended at present. Inclusion of patients in (neo)adjuvant immunotherapy trials could be of interest.

TREATMENT OF NON-CLEAR CELL RENAL CELL CARCINOMA

Approximately 75% of RCC have a clear-cell histology, the other histologies are collectively referred to as non-clear cell RCC (non-ccRCC). Non-ccRCC consists in itself of several entities who all have their distinct pathologic, clinical, and genetic features. As such, clear-cell RCC and the different non-clear cell subtypes should all be considered separate diseases.[72] Therefore, there is little scientific rationale to extrapolate results obtained in clear-cell RCC to non-clear cell types or to consider the the complete RCC population as one disease entity that should be treated the same way.

The available clinical data to guide treatment in non-ccRCC are scarce and often involves non-controlled trials or heterogeneous populations.

Sunitinib was compared to everolimus in non-ccRCC patients in three randomised trials. In the ASPEN trial, sunitinib was shown to be superior to everolimus with regard to PFS, while a non-significant trend was observed in the ESPN trial and in a subgroup analysis of the RECORD3 trial including the non-cc RCC patients. In all these trials a heterogeneous population of different non-ccRCC subtypes were included, with the numbers of each specific subgroup being small. Therefore, it is difficult to draw conclusions

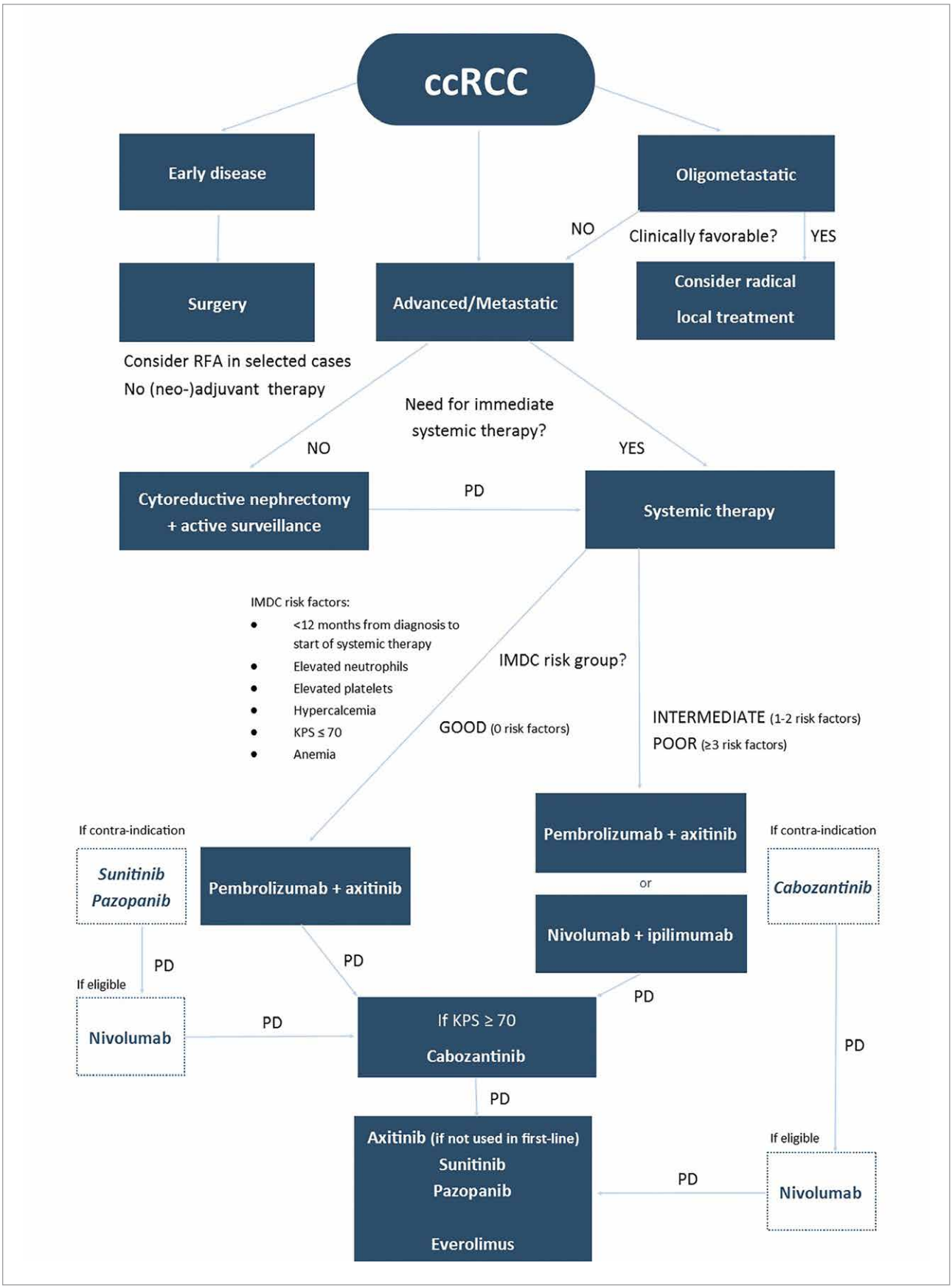

FIGURE 1. Proposed treatment algorithm for ccRCC based on current evidence and Belgian reimbursement criteria.
PD: progressive disease; KPS : Karnofsky performance status; IMDC: International Metastatic ccRCC Database Consortium.

that are applicable to each patient based on these data.[73] Nevertheless, sunitinib is considered the standard of care for non-clear cell RCC by the ESMO guidelines.[3]

In some subtypes, specific approaches can be considered. For example, papillary renal cell carcinoma is known to harbour frequent mutations or amplifications of MET. Therefore, the treatment of this tumour type with MET-inhibitors, such as forentinib, savolitinib, crizotinib (which targets both ALK and MET), and also cabozantinib is being explored. Randomised data are awaited.[73] Cabozantinib is the only one available and reimbursed in Belgium.[74]

Recently, single-arm prospective data on the use of pembrolizumab have been reported.[75] The objective response rate was 25.4% for papillary RCC, 9.5% for chromophobe RCC, and 34.6% for unclassified RCC. Another phase II trial has evaluated the combination of atezolizumab and bevacizumab and the ORR was 26% in non-ccRCC.[76]

In summary, current data point towards an increased benefit of immunotherapy combination strategies in first-line, followed by a TKI in second-line (with a preference for the MET-inhibitor cabozantinib in papillary RCC). If available, enrolment in specific clinical trials is recommended for patients with non-ccRCC.[3]

In practice, not all the above mentioned options are reimbursed in Belgium. In fact, with the exception of everolimus, all drugs available for clear-cell RCC are also reimbursed for non-clear cell RCC, because reimbursement is for RCC as a whole (*Table 3*).

SOME PRACTICAL ASPECTS IN THE TREATMENT OF ADVANCED RCC

Dose reductions and management of toxicities during TKI therapy

Unfortunately, treatment with TKI's is associated with frequent adverse events, which are often dose-dependent. Nevertheless, dose-reductions in these patients have a drawback because a clear relationship between plasma concentrations of the drug and efficacy has been observed.[77,78] Therefore, it is generally recommended to try to control side-effects from TKI's by maximal supportive measures, before considering dose-reduction.

The other way around, patients who tolerate treatment well may benefit from dose escalation, as has been demonstrated in a trial in which patients treated with axitinib were randomised between a fixed dose regimen and a regimen in which dose-escalation was allowed. A significant higher response rate was seen in the dose-escalation arm compared to the fixed dose regimen (54% *vs.* 34%). PFS and OS were numerically increased in the dose-escalation arm, but those differences were not significant.[79]

Supportive care

While this paper focusses on the treatment of metastatic RCC, obviously these patients also require additional care such as palliation of cancer-related symptoms, supportive measurements for the management of side-effects, prevention of complications, *etc.*

For example, patients with symptomatic lesions (*e.g.* bone metastasis) or with brain metastasis can be treated with radiotherapy.[3] Also, in patients with bone metastasis additional treatment with zoledronic acid or denosumab should be considered.[80]

Some questions remain regarding the concomitant treatment with a bone resorption inhibitor and a VEGF-R targeted TKI. A retrospective analysis has shown this combination to carry an increased risk of osteonecrosis of the jaw. However, in the opinion of the authors of that study, the increased risk did not alter the favourable risk-benefit ratio in patients with multiple bone metastases and a risk for skeletal-related events.[81]

CONCLUSIONS AND PROSPECTS

The treatment of metastatic RCC has evolved rapidly over the past decade. This paper attempts to provide the reader with an accessible overview of the current treatment options in metastatic RCC, including the most recently published clinical trial results. Little over a decade ago, treatment options were essentially limited to cytokines such as IL-2 and IFNα, while today TKI's and checkpoint inhibitors are at the forefront. Ipilimumab combined with nivolumab and checkpoint inhibitors combined with a TKI are new standard options in first-line patients. In second-line, trials have been focusing on a post-TKI situation. Therefore, some uncertainty exists regarding recommendations for a post-checkpoint inhibition second-line treatment. Several options exist, and the previous therapy plays a major role in selecting the optimal second-line therapy. Beyond second-line, exact recommendations on treatment sequence cannot be provided.

It seems highly unlikely that the scheme outlined in this paper will remain valid for a long time, since the field continues to evolve rapidly.

Despite these evolutions, some gaps in the evidence remain. For example, the best way to integrate metastasectomy or other local treatment modalities in the management of patients with metastatic RCC remains unclear, and clinical trials evaluating this question are lacking. Also, while the role of cytoreductive nephrectomy in the era of TKI treatment has only recently been evaluated in prospective clinical trials, the role of this procedure in the era of immune checkpoint inhibitors is not yet investigated. With regard

TABLE 3A. Drugs approved for use in advanced or metastatic RCC, with their approved indications as mentioned in the SPC and a summary of their reimbursement criteria as stated by the RIZIV/INAMI.

Active substance	Brand name	Indication based on the SPC.	Reimbursement in Belgium based on RIZIV/INAMI criteria
sunitinib	Sutent	Patients with advanced or metastatic RCC.	Patients with advanced or metastatic RCC: - In first-line for patients with good prognosis according to IMDC criteria. - In patients in whom at least two therapies (INF-α, IL-2, immune-checkpoint inhibitor, or a VEGF-targeted therapy other than sunitinib) failed - In all patients in first- or second-line if treatment with an immune-checkpoint inhibitor and/or cabozantinib are not recommendable, applicable, or reimbursable.
pazopanib	Votrient	Patients with advanced RCC, in first-line or after a treatment with cytokines.	Patients with advanced or metastatic RCC: - In first-line for patients with good prognosis according to IMDC criteria. - In patients in whom at least two therapies (INF-α, IL-2, immune-checkpoint inhibitor, or a VEGF-targeted therapy other than pazopanib) failed - In all patients in first- or second-line if treatment with an immune-checkpoint inhibitor and/or cabozantinib are not recommendable, applicable, or reimbursable.
sorafenib	Nexavar	Patients with advanced RCC that failed treatment with IFNα or IL-2, or who are considered inappropriate candidates for those therapies.	Patients with advanced RCC: - In patients 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.
axitinib	Inlyta	Patients with advanced or metastatic RCC that have failed prior therapy with sunitinib or a cytokine.	Patients with advanced RCC: - 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
cabozantinib	Cabometyx	Patients with advanced RCC, which is either: - treatment-naive and of intermediate or poor risk[1] - or which has already been treated with VEGF-targeted therapy.	Patients with advanced RCC: - In first-line in patients with intermediate or poor risk. - in all patients from second-line on, if patient failed treatment with an immune-checkpoint inhibitor and/or a VEGF-targeted therapy, other than cabozantinib.
lenvatinib	Kisplyx	In combination with everolimus: Patients with advanced RCC following one prior VEGF-targeted therapy.	Not marketed in Belgium[2]
everolimus	Afinitor	Patients with advanced RCC, that has progressed during or after VEGF-targeted therapy.	Patients with advanced clear-cell RCC: - who failed at least two prior therapies with an immune-checkpoint inhibitor and/or a VEGF-targeted therapy. - in second-line, if treatment with an immune-checkpoint inhibitor and/or a VEGF-targeted therapy is not recommendable, applicable, or reimbursable
temsirolimus	Torisel	First-line treatment of patients with metastatic RCC who have at least three out of six prognostic risk factors.[3]	First-line treatment of patients with advanced RCC who have at least three out of six prognostic risk factors[3] if treatment with an immune-checkpoint inhibitor and/or cabozantinib is not recommendable, applicable, or reimbursable
nivolumab	Opdivo	Patients with advanced RCC who have received previous treatment. In combination with ipilimumab: First-line treatment of patients with intermediate / poor risk advanced RCC.[1]	Patients with advanced RCC who have received previous treatment. (patients cannot have progressed on another anti-PD1/anti-PD-L1 inhibitor) In combination with ipilimumab for the first-line treatment of patients with advanced RCC with an intermediate or poor prognosis.

TABLE 3B. Drugs approved for use in advanced or metastatic RCC, with their approved indications as mentioned in the SPC and a summary of their reimbursement criteria as stated by the RIZIV/INAMI.

Active substance	Brand name	Indication based on the SPC.	Reimbursement in Belgium based on RIZIV/INAMI criteria
ipilimumab	Yervoy	In combination with nivolumab: First-line treatment of patients with intermediate / poor risk advanced RCC.[1]	In combination with nivolumab for the first-line treatment of patients with advanced RCC with an intermediate or poor prognosis[1].
pembrolizumab	Keytruda	In combination with axitinib for the first-line treatment of advanced RCC.	In combination with axitinib for the first-line treatment of advanced RCC. (Axitinib is not reimbursed in this setting[4])
avelumab	Bavencio	In combination with axitinib for the first-line treatment of advanced RCC.	In combination with axitinib for the first-line treatment of advanced RCC. (Axitinib is not reimbursed in this setting[4])
IFNα-2a	Roferon A	Advanced RCC	In combination with bevacizumab for patients with advanced RCC (primary tumour extending beyond renal fascia, local recurrence, or metastatic): - who failed at least two prior therapies with an immune-checkpoint inhibitor and/or a VEGF-targeted therapy other than bevacizumab. - in first-line, if treatment with an immune-checkpoint inhibitor either in monotherapy or in combination with cabozantinib, sunitinib, or pazopanib is not recommendable, applicable, or reimbursable.
bevacizumab	Avastin	In combination with IFNα-2a: First-line treatment of advanced and/or metastatic RCC.	For patients with advanced or metastatic RCC: - Treatment of patients with a good prognosis[1] who did not tolerate treatment with first-line sunitinib or pazopanib (grade 3 or 4 adverse events within the first 4 weeks of treatment). - First-line treatment of patients with an intermediate prognosis[1] for whom treatment with an immune-check-point inhibitor either in monotherapy or in combination with cabozantinib, sunitinib, or pazopanib is not recommendable, applicable, or reimbursable
interleukin 2	Proleukin	Patients with metastatic RCC. Patients positive for all three risk factors below should not be treated with IL-2. Risk factors associated with decreased response rates and median survival are: - ECOG ≥ 1 - metastases to more than 1 organ. - Less than 24 months between initial diagnosis and the date the patient is evaluated for IL-2 treatment.	Not marketed in Belgium anymore since December 2019.

[1]according to IMDC criteria, [2]in Belgium lenvatinib is only marketed as Lenvima, which has no indication of RCC listed in the SPC, [3]see Table 1, [4]Pending reimbursement, axitinib is provided as samples by the manufacturer upon request ; abbreviations: SPC: summary of product characteristics, RIZIV/INAMI: Rijksinstituut voor ziekte- en invaliditeitsverzekering/ Institut national d'assurance maladie-invalidité , The Belgian national health insurance.

to the medical treatment, the preferred treatment sequence after first-line immune checkpoint inhibition is not well defined. Also, personalised treatment approaches remain limited to broad prognostic categories. Lastly, we should not overlook non-clear cell RCC. After all, approximately 25% of all RCC patients have non-clear cell variants. Here we are confronted with a striking lack of knowledge, clinical trials, and treatment guidelines. More research on these topics is urgently needed.

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