Management of Advanced Kidney Cancer: Kidney Cancer Research Network of Canada (KCRNC) consensus update 2019

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The following is a consensus report from the Kidney Cancer Research Network of Canada (KCRNC), with an update from the 10th Canadian Kidney Cancer Forum, held April 11–13, 2019 in Toronto, Ontario.

Introduction

Kidney cancer is the 10th most common cancer among Canadians, with an estimated incidence of 7200 in 2019. In terms of mortality, it ranks 12th among all cancers, and is the most lethal genitourinary malignancy, with an estimated five-year survival of 71%.[1] The estimated number of deaths in Canada due to kidney cancer was reported to be 1900 for 2019.[1] It is more common in men than women (4700 vs. 2500 estimated incidence in 2019).[1]

The most common form of kidney cancer is renal cell carcinoma (RCC), accounting for more than 90% of all renal malignancies.[2] Clear-cell RCC accounts for approximately three-quarters of all cases of RCC.

For more than a decade, targeted systemic therapies have been the standard of care for metastatic RCC (mRCC) and their use was refined over time as clinical experience evolved.[3-8] Since the last updated consensus statement by the Kidney Cancer Research Network of Canada (KCRNC)

in 2017, the treatment landscape has shifted considerably and requires update.

The results of three published phase 3 studies involving immune checkpoint inhibitors have convincingly demonstrated superiority of these agents over upfront targeted therapy alone for certain populations.[9,10] These studies have provided the primary impetus for updating our recommendations. Other international consensus recommendations (e.g., the European Association of Urology [EAU], U.S. National Comprehensive Cancer Network [NCCN]) have also taken these new findings into account. In their updated publications, immune checkpoint inhibitors or immune checkpoint inhibitor/tyrosine kinase inhibitor (TKI) combinations have displaced targeted agents as the frontline treatment of choice for the majority of patients with advanced RCC.[11,12]

This current consensus statement is based on the deliberations and conclusions of a multidisciplinary group of experts who convened during the 10th Canadian Kidney Cancer Forum, April 13, 2019 in Toronto, Ontario. During that session, the authors reviewed the previous advanced disease management consensus statements, published in 2017,[8] discussed the recent relevant evidence, and reached consensus on the revised consensus statements published below. Table 1 shows the major changes that have been made since the 2017 consensus statement. For ease of accessing all informa-

Table 1. Major changes made since the 2017 consensus update

Setting/section	Update for this consensus statement
Adjuvant therapy	Update on data from targeted therapy trials; mention of ongoing studies with immunotherapies
First-line therapy for clear-cell carcinoma	New recommendations and new data on ipilimumab-nivolumab, axitinib-pembrolizumab & avelumab-axitinib
Second-line and later therapy options	New recommendations in the context of revised recommendations for first-line therapy
Role of cytoreductive nephrectomy	New recommendations and data from the CARMENA and SURTIME studies

tion in one place, the sections that have not been updated from the 2017 recommendations and have been left largely unchanged in this document.

As noted in the discussion section of this paper, unanimous consensus was not reached for all treatment options. The published recommendations reflect the majority position for these items.

The authors recognize that the field of systemic therapy for advanced RCC is evolving quickly and remind readers that the recommendations made in this document reflect the available evidence at the time the consensus conference participants reached their conclusions (April 13, 2019). As new data become available, treatment options will invariably change, and members of the KCRNC intend to update these recommendations on a regular basis moving forward.

1. Management of locally advanced kidney cancer

1.1. Neoadjuvant therapy

– **There is no indication for neoadjuvant therapy prior to planned surgical resection outside the context of a clinical trial.**

If patients are felt to be surgically resectable at diagnosis and medically fit, they should proceed immediately to surgery. There is currently insufficient evidence to support a general recommendation for neoadjuvant therapy.

There have been many small studies demonstrating a potential benefit of systemic neoadjuvant approaches (mostly with vascular endothelial growth factor [VEGF] inhibitors), including modest reduction in tumor size and possible facilitation of locally advanced tumor resection and complex partial nephrectomy.[13-26] However, there is no randomized controlled evidence to support a recommendation for widespread adoption of neoadjuvant therapy at this time.

Studies investigating the utility of immune checkpoint inhibitors, VEGF-targeted agents, or their combination in the neoadjuvant setting are currently ongoing.[27-32] There is

also an ongoing study investigating the use of a neoadjuvant vaccine in RCC.[33]

In summary, there is currently insufficient evidence to support a general recommendation for neoadjuvant therapy. However, some patients with advanced localized disease deemed medically or surgically inoperable at diagnosis may have a radiological and/or clinical response to systemic therapy. A multidisciplinary team should re-evaluate them if there is any question that they may have converted to an operable state.[33]

1.2 Adjuvant therapy

– **The use of adjuvant therapy following nephrectomy in non-metastatic RCC patients is not currently recommended outside the context of a clinical trial.**

Adjuvant therapy with cytokines (interferon-alpha) does not improve overall survival (OS) after nephrectomy.[34] Furthermore, our KCRNC consensus statement on the role of adjuvant therapy after nephrectomy for high-risk, non-metastatic RCC published in 2018 recommended that, at this time, adjuvant TKI-based adjuvant therapy is not recommended for routine use after nephrectomy for high-risk nmRCC, but highly motivated patients may benefit from a discussion with their oncologist regarding the risks and benefits of adjuvant TKI.[35]

The statement's wording was due to some conflicting data available with adjuvant VEGF-targeted systemic therapy, some of which suggests a benefit and most of which does not.

The phase 3 ASSURE three-arm, randomized, placebo-controlled trial of one year of sorafenib, sunitinib, or placebo showed no significant improvement in disease-free survival (DFS) or OS for patients treated with either of the active intervention arms or placebo.[36] Additionally, more than 40% of patients in the treatment arms had to discontinue their study drugs due to toxicity.[36]

The phase 3 S-TRAC two-arm, randomized, placebo-controlled trial of one year of sunitinib or placebo in patients at high risk of recurrence showed an improvement in the primary endpoint of DFS with adjuvant sunitinib comparable to the time on therapy.[37] For OS, a secondary endpoint, the most recent published update reported that the median had not yet been reached for either arm, with no significant difference between sunitinib and placebo (hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.66–1.28; p=0.6).[38] Quality of life outcomes demonstrate that on most QLQ-C30 subscales, patients in the sunitinib group had lower scores than those in the placebo group.[37] In the U.S., sunitinib was approved for use in the adjuvant setting based largely on the findings of this study.[39] Sunitinib is not approved for this indication in Canada.

Pazopanib has also been evaluated vs. placebo in a phase 3 study in the adjuvant setting (PROTECT).[40] The primary

Table 2. Therapeutic options for advanced clear-cell renal cell carcinoma

Setting	Patients	Preferred	Options
Untreated	Favorable-risk (IMDC)	Axitinib + Pembrolizumab^	Sunitinib Pazopanib Axitinib + Avelumab* High-dose IL-2** Active surveillance
	Intermediate-/poor-risk (IMDC)	Ipilimumab + Nivolumab Axitinib + Pembrolizumab^	Sunitinib Pazopanib Axitinib + Avelumab^^* Cabozantinib Active surveillance
Second-line and beyond#	Prior immune checkpoint inhibitor	Cabozantinib^^^ Axitinib^^^	Sunitinib Pazopanib*** Lenvatinib + Everolimus^^^
	Prior VEGF	Nivolumab Cabozantinib	Lenvatinib + Everolimus Everolimus Axitinib
	Prior VEGF and immune checkpoint inhibitor	Cabozantinib	Sunitinib Pazopanib Axitinib^^ Lenvatinib + Everolimus Everolimus

^Not yet approved in Canada; until approval, sunitinib/pazopanib is preferred for favorable-risk and ipilimumab/nivolumab is preferred for intermediate-/poor-risk. ^^Not yet approved in Canada. ^^^Approved after one prior VEGF therapy only. # If not used prior. *Awaiting mature overall survival data. **Not randomized control trial. ***Need to be monitored closely for first 12 weeks for liver toxicity. IMDC: International Metastatic RCC Database Consortium; VEGF: vascular endothelial growth factor.

endpoint of improved DFS was not met in this study (HR 0.86; 95% CI 0.70–1.06; p=0.165). Mature OS data have not been presented or published.

The ATLAS trial compared axitinib vs. placebo in 724 patients with ≥pT2 and/or N+, any Fuhrman grade RCC.[41] The trial was stopped due to futility at the prespecified interim analysis, with no significant difference in DFS observed at that time (HR 0.87; 95% CI 0.66–1.15; p=0.321).

As is the case in the neoadjuvant space, a number of ongoing studies in the adjuvant setting are seeking to determine the role and longer duration of therapy of other molecular targeted therapy (everolimus,[42] sorafenib[43]) or immune checkpoint inhibition (atezolizumab,[44] ipilimumab-nivolumab,[45] pembrolizumab,[46] durvalumab ± tremelimumab[47]).

To summarize, to date, no clinical trial has demonstrated an OS advantage with adjuvant targeted therapy in patients with RCC after curative resection of the primary tumor. Pending additional data from ongoing adjuvant trials, patients with high-risk tumors who have undergone complete resection should be encouraged to participate in clinical trials whenever possible.

2. Advanced or metastatic kidney cancer

When prescribing systemic therapy for advanced or metastatic RCC, several key factors must be taken into account. Patients are best served if the prescribing physician is an oncology specialist knowledgeable of the disease, the drug, its acute and long-term toxicities, drug interactions, and monitoring of treatment and response. Patients should be managed in a multidisciplinary environment with adequate resources, including nursing care, dietary care, and pharmacy support.

Patients must be evaluated frequently to ensure toxicities are recognized and managed appropriately. Patients and caregivers should be provided with information concerning potential side effects, as well as their prevention and management.

2.1 Clear-cell carcinoma (Table 2)

2.1.1 Untreated patients

– **Choice of initial systemic treatment is based in part on International Metastatic RCC Database Consortium (IMDC) risk status.**
– **For IMDC intermediate- or poor-risk patients, either ipilimumab + nivolumab or pembrolizumab + axitinib is the preferred first-line therapy; avelumab/axitinib and targeted therapy (sunitinib or pazopanib) remain alternative options, the latter especially for patients who have a contraindication to immunotherapy or who are felt to be unable to tolerate combination therapy.**
– **For IMDC favourable-risk patients, pembrolizumab + axitinib is the recommended treatment. Avelumab/axitinib and targeted therapy with sunitinib or pazopanib can be considered as alternative active treatment options.**
– **Active surveillance can also be considered in selected patients with favorable-risk/intermediate-risk with one risk factor, as some patients have slow-growing, low-volume, and/or asymptomatic disease.**

2.1.1.1 Risk-stratification

Risk-stratification is a critical first step in therapeutic decision-making for patients with mRCC. Using data from the targeted-therapy era, Heng and colleagues published a risk-stratification score based on information obtained from the IMDC.[48] Although mRCC has passed into the immune checkpoint inhibitor era, the set of six IMDC criteria (hemoglobin less than the lower limit of normal, corrected calcium greater than the upper limit of normal (ULN), platelets greater than the ULN, neutrophils greater than the ULN, Karnofsky performance status less than 80%, and time from diagnosis to treatment of less than one year) remains the recommended tool for patient counselling, treatment selection (e.g., initial observation, systemic therapy, cytoreductive nephrectomy), and future research studies. It should be emphasized that the IMDC classification is a prognostic classification and not a predictive tool.

2.1.1.2. IMDC favorable-risk

2.1.1.2.1 Preferred therapy: Pembrolizumab + axitinib

The KEYNOTE-426 study was a randomized, open-label, phase 3 study that assessed the efficacy and safety of pembrolizumab + axitinib vs. sunitinib as first-line therapy for mRCC.[10] The 861 patients enrolled in this study had clear-cell mRCC and no previous systemic therapy for mRCC. They were randomized 1:1 to pembrolizumab + axitinib (n=432) or sunitinib (n=429). Randomization was stratified by IMDC risk group. Primary endpoints were OS and progression-free survival (PFS) in the overall population, while objective response rate (ORR) was the key secondary endpoint.

After a median followup of 12.8 months, pembrolizumab + axitinib significantly improved PFS vs. sunitinib, with medians of 15.1 months and 11.1 months, respectively (HR 0.69; 95% CI 0.57–0.84; p=0.0001). Although median OS had not been reached in either arm at the time of the primary data review, pembrolizumab + axitinib was associated with a significant OS improvement (HR 0.53; 95% CI 0.38–0.74; p<0.0001).

Pembrolizumab + axitinib also significantly improved ORR vs. sunitinib (59.3% vs. 35.7%; p<0.0001). With respect to subgroup analysis, all IMDC subgroups benefitted from pembrolizumab + axitinib with respect to OS (favorable risk: HR 0.64; 95% CI 0.24–1.68; intermediate risk: HR 0.53; 95% CI 0.35–0.83; poor risk: HR 0.43; 95% CI 0.23–0.81), as well as PFS.

2.1.1.2.2 Other options: Sunitinib, pazopanib, or initial observation

In a pivotal phase 3 trial, oral sunitinib produced higher response rates, improved quality of life, and resulted in longer PFS and OS than interferon-alfa in patients with metastatic clear-cell RCC.[49,50] In addition, population-based studies from British Columbia and Alberta have shown an almost doubling of OS of mRCC since the introduction of sunitinib and sorafenib.[51,52]

The dose and schedule of sunitinib should be individualized for each patient in order to derive the optimal benefit.[53] It is still recommended to start with the monograph standard of four-week on/two-week off dosing schedule. After evaluation of type and timing of toxicities, patients may require adjustments to the schedule and/or dose. Bjarnason and colleagues have published a single-institution, retrospective review of patients treated with alternate dose and schedule of sunitinib compared to product monograph recommended dosing; they found improved PFS and OS compared to the standard dosing group.[53] A prospective clinical trial conducted across Canada examined the same individualized dose titration scheme among 117 patients with metastatic clear-cell RCC.[54] Subjects in this study were started on sunitinib 50 mg/day with the aim to treat for 28 days. Treatment breaks were reduced to seven days. Sunitinib dose and the number of days on therapy were individualized based on toxicity (aiming for ≤grade II toxicity with dose-escalation in patients with minimal toxicity). Individualized sunitinib therapy proved to be a safe and effective method to manage toxicity, with one of the best efficacies seen for oral VEGF inhibitors in mRCC and no decline in quality of life scores during therapy. The median PFS observed in this study was 12.5 months, which significantly exceeded the expected 8.5 months based on a study with similar eligibility criteria.[54] In addition, toxicity appeared substantially less than on the traditional 50 mg/day for four-week on/two-week off schedule.

Based on phase 3 trial data, oral pazopanib produces an improvement in PFS compared to placebo in both cytokine-naive and refractory patients.[55] As first-line therapy, pazopanib has also been shown to be non-inferior to sunitinib with respect to PFS in the phase 3 COMPARZ clinical trial.[56] Toxicity profiles were different, with sunitinib-treated patients experiencing more fatigue, hand-foot syndrome, and thrombocytopenia, whereas pazopanib-treated patients experienced more elevations in hepatic transaminases.[56]

Data from Canadian Kidney Cancer information system (CKCis) database shows that patients treated with sunitinib have a greater OS than pazopanib.[57] Plausible explanations for this include small sample size and potential bias secondary to patient selection. However, another explanation for this difference may be the practice of individualized dose and schedule changes that Canadian medical oncologists employ with sunitinib, in accordance with data from Bjarnason.[54,58] Publications from other retrospective patient cohorts show similar outcomes with either sunitinib or pazopanib in concordance with COMPARZ data.[59]

In the opinion of the participants at the consensus meeting, an initial period of observation also remains a reasonable option in select patients, given that all available treat-

ments can be associated with side effects and that some patients may experience an indolent clinical course with stable or slow-growing, low-volume, and/or asymptomatic metastases. This is supported by prospective observational data presented by Rini and colleagues.[60]

2.1.1.3. IMDC intermediate- or poor-risk

2.1.1.3.1 Preferred therapies

2.1.1.3.1.1 Ipilimumab + nivolumab

The CheckMate 214 study was a randomized, open-label, phase 3 trial of nivolumab + ipilimumab followed by niv-olumab monotherapy vs. sunitinib monotherapy.[9] The 1096 subjects enrolled in the trial were ≥18 years of age with previously untreated advanced RCC with a clear-cell component. They were randomized to either nivolumab + ipilimumab (n=550) or sunitinib (n=546). As per inclusion criteria, the majority of enrolled patients had IMDC inter-mediate- (n=425) or poor-risk (n=422). The co-primary end-points were OS, ORR, and PFS in intermediate- and poor-risk patients. The same endpoints were used for the exploratory cohort of favorable-risk patients.

After a median followup of 25.2 months, among inter-mediate-/poor-risk patients, the ipilimumab-nivolumab arm was associated with improvements in all three co-primary endpoints. ORR was 42% vs. 27% (p<0.001), including complete responses in 9% vs. 1% for ipilimumab + niv-olumab vs. sunitinib, respectively. Median PFS at the time of the primary data report was 11.6 for ipilimumab + niv-olumab and 8.4 months for sunitinib (HR 0.82; p=0.03, not statistically significant), and median OS was not reached for ipilimumab + nivolumab and 26 months for sunitinib (HR 0.63; p<0.001). A data update presented at GU-ASCO 2019 and recently published showed that these trends continued out to 30 months' followup.[61] Numerically, the proportions of patients achieving a complete response (CR) seems to be increasing and has reached 11% with the longer followup. Among favorable-risk patients, there has not been any sig-nificant difference demonstrated between the treatment arms for PFS or OS.

2.1.1.3.1.2 Pembrolizumab + axitinib

The clinical trial informing this recommendation is KEYNOTE-426, described above.[10] The primary endpoint of the study was in the unselected overall population, including patients with intermediate-/poor-risk (n=592) and with favor-able-risk (n=269).[10] The overall data are reported above. With respect to IMDC risk groups, subgroup analysis showed that pembrolizumab + axitinib was associated with an OS improvement in intermediate- (HR 0.53; 95% CI 0.35–0.82) and poor-risk (HR 0.43; 95% CI 0.23–0.81) groups.

2.1.1.3.2 Other options

The recommendation for sunitinib or pazopanib as possible, non-preferred options in the upfront setting for intermedi-ate- or poor-risk come from the same data sets as described above in the favorable-risk setting; intermediate- and poor-risk patients were treated with VEGF-targeted TKI therapy in pivotal trials as well. The consensus was that these agents would still be preferentially used in patients with contrain-dications for immunotherapy, in patients with poor clinical condition due to extensive RCC, and in those who needed a more rapid response to therapy. It should also be noted that in sunitinib-intolerant, poor-risk patients, pazopanib remains an option for treatment.

2.1.1.3.2.1 Avelumab + axitinib

JAVELIN Renal 101 was a phase 3, randomized, open-label study comparing avelumab + axitinib with sunitinib among 886 patients with clear-cell advanced RCC and no prior systemic therapy.[62] All prognostic risk groups were included. The co-primary endpoints were PFS and OS among patients with PD-L1-positive tumors (n=560). In this group, medi-an PFS was 13.8 months with avelumab plus axitinib vs. 7.2 months with sunitinib (HR 0.61; 95% CI 0.47–0.79; p<0.001). In the overall population, the median PFS was 13.8 months vs. 8.4 months (HR 0.69; 95% CI 0.56–0.84; p<0.001). OS data for this study were immature at the data cutoff, with a suggestion of benefit for avelumab + axitinib, but no statistical significance to date (HR 0.78; 95% CI 0.55–1.08; p=0.0679).

Axitinib is currently only approved in Canada as mono-therapy after failure of prior systemic therapy with either a cytokine or sunitinib. Avelumab is not currently approved in Canada for mRCC (although it has indications for other malignancies).

2.1.1.3.2.2 Bevacizumab + atezolizumab

IMmotion151 was a phase 3, randomized, open-label study comparing bevacizumab + atezolizumab with sunitinib in 915 patients with mRCC and a component of clear-cell or sarcomatoid RCC.[63] The median OS in the intention-to-treat population was 33.6 months vs. 34.9 months (HR 0.93; p=0.4751), indicating there is no statistically significant ben-efit over suntinib. The median PFS in the intention-to-treat population was 11.2 vs 8.4 months (HR 0.83; p=0.02190). At interim analysis, the median OS in the PD-L1-positive population was 34.0 months vs. 32.7 months (HR 0.84; p=0.2857) and in the PD-L1-positive population, the medi-an PFS was 11.2 months in the atezolizumab/bevacizum-ab group vs. 7.7 months in the sunitinib group (HR 0.74; p=0.0217). Neither drug is approved in Canada for the treat-ment of mRCC.

2.1.1.3.2.3 Cabozantinib

The randomized, phase 2 CABOSUN trial compared oral cabo-zantinib (a dual VEGFr/MET and AXL inhibitor) to oral sunitinib first-line.[64] This small, investigator-initiated trial (n=157) had 81% intermediate- and 19% poor-risk patients and demonstrated a significant improvement in PFS in favor of cabozantinib. In unplanned analyses, it showed particularly promising activity in patients with bone metastases, although this was a very small subset of patients. It should be noted that the sunitinib arm median PFS was significantly shorter than expected partly because 23% of the patients in the sunitinib arm were not evaluable for response vs. 8% in the cabozantinib arm.

Cabozantinib is approved for use in RCC in Canada, but only for patients who have progressed on previous VEGF-targeted therapy. Despite this restriction, some participants at the 2019 consensus meeting were in favor of including this therapy in the "other options" section for first-line use in patients with intermediate-/poor-risk given the CABOSUN results.

2.1.2 Second-line and later therapy options

2.1.2.1 Progression on or intolerance to first-line immune checkpoint inhibitor-based regimen

– **For patients who progress on, or who are intolerant of first-line immune checkpoint inhibitors, there is no prospective, randomized, phase 3 evidence available to select a preferred treatment option; options for patients in this situation include sunitinib, pazopanib, axitinib, cabozantinib, or lenvatinib/everolimus.**

For those individuals who progress on a regimen that includes an immune checkpoint inhibitor, there are no data yet available to guide the selection of subsequent therapy. Several retrospective reviews show that TKIs have activity after immunotherapy. The only prospective study in this setting has demonstrated the activity of axitinib after immunotherapy, therefore, axitinib is a preferred option post-immunotherapy progression. Seventy-four percent of patients had received two or more therapies prior to axitinib. In this study, axitinib was given on an individualized schedule, with significant inter-individual variation in the optimal dose and schedule, as has been shown for sunitinib.

Based upon the METEOR study, cabozantinib is also a preferred option post-immunotherapy progression.

We await the results of more prospective studies in the post-immunotherapy setting to provide information about best practices in this space.

Currently, the selection of a VEGF-targeted therapy that is among the recommended first-line options (i.e., sunitinib, pazopanib) is a reasonable choice. Based on their evidence of activity in the first- or second-line setting, other options include axitinib, cabozantinib, and lenvatinib/everolimus.

2.1.2.2 Progression on or intolerance to first-line sunitinib or pazopanib

– **For patients who are intolerant to sunitinib or pazopanib, switching to the other VEGF inhibitor is a reasonable choice.**
– **For patients who progress on first-line sunitinib or pazopanib, preferred options are nivolumab, axitinib, or cabozantinib.**
– **Other evidence-based options are lenvatinib/everolimus (based on a small phase 2 study demonstrating a PFS advantage over everolimus monotherapy) or everolimus monotherapy (although found to be inferior to alternatives such as nivolumab and cabozantinib).**

2.1.2.2.1 Intolerance to first-line VEGF-targeted therapy

If patients stop first-line therapy due to toxicity and not progression, another first-line therapy is very reasonable to try. Data from the IMDC suggest the outcomes when therapies are switched due to toxicity, and not progression, are better than would be seen as second-line therapy after progression.[65]

2.1.2.2.2 Progression on first-line VEGF-targeted therapy — preferred options

2.1.2.2.2.1 Nivolumab

In the phase 3 CHECKMATE 025 trial, intravenous nivolumab produced better response rates and a significantly longer OS compared to oral everolimus in patients who had failed one or two previous lines of systemic therapy regardless of the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score or number of previous antiangiogenic therapies.[66] Benefit was observed irrespective of PD-L1 expression. In addition, grade 3 or 4 treatment-related adverse events and treatment-related adverse events leading to discontinuation were less frequent with nivolumab than with everolimus. Quality of life outcomes increased over time in the nivolumab group and were significantly better than the everolimus group at each assessment point.

There is also data to support the use of nivolumab in the third-line setting. In the CHECKMATE 025 trial, 28% of randomized subjects had received two prior VEGF-targeted therapies.[66] OS results suggest a benefit of nivolumab over everolimus in this setting.

The phenomena of pseudoprogression and delayed responses on immuno-oncology agents may make monitoring of efficacy challenging, but it should be noted this occurs in a small minority of patients.[67,68] Thus, treatment beyond progression should be restricted to patients showing clinical benefit or stability.

2.1.2.2.2.2 Cabozantinib

The randomized, phase 3 METEOR trial compared oral cabozantinib to everolimus among patients previously treated with one or more prior VEGF-targeted TKIs.[69] A small minority of patients had also received a checkpoint inhibitor

in addition to one or two TKIs. Cabozantinib demonstrated a significant improvement in PFS (primary endpoint), ORR, and OS in the overall population.[69] Approximately 30% of patients had received at least two prior VEGF-targeted TKI therapies; even in this subset, notable benefit in PFS and OS were observed in patients receiving cabozantinib compared to those receiving everolimus. Additional prior checkpoint blockade therapy did not appear to impact benefit and significant improvements in outcome were maintained in this small patient population.

2.1.2.2.2.3 Axitinib

The participants in the expert consensus meeting at the 2019 Kidney Cancer Forum did not reach consensus on the placement of axitinib in the VEGF-pretreated population.[70] A sizable minority of participants recommended that it be placed in the "other options" rather than the "preferred" section, as the evidence was not considered to be very strong. The data in question are from the phase 3 AXIS trial, in which oral axitinib demonstrated improved PFS compared to oral sorafenib as second-line therapy in patients progressing after first-line therapy with sunitinib.[70] Data on axitinib in the third-line setting are more limited. However, there are patients who went on to receive axitinib post-nivolumab or cabozantinib in CHECKMATE 025 and METEOR studies, respectively. Retrospective analyses suggest patients demonstrate benefit to VEGF-targeted TKIs in the third-line setting, with axitinib falling in that category.[71,72]

2.1.2.2.3 Progression on first-line VEGF-targeted therapy — other options

2.1.2.2.3.1 Lenvatinib + everolimus

A small, three-arm, randomized, phase 2 trial of oral lenvatinib, oral everolimus, and the combination of both demonstrated improved PFS for the combination arm over everolimus alone (median 14.6 months vs 5.5 months; HR 0.40; 95% CI 0.24–0.68; p=0·0005).[73] The subjects were 153 patients who had progressed on VEGF-targeted therapy and were randomized 1:1:1 to lenvatinib alone, everolimus alone, or the combination of lenvatinib and everolimus.

2.1.2.2.3.2 Everolimus

In the phase 3 RECORD-1 trial, oral everolimus (mTOR inhibitor) produced a significantly longer PFS than placebo, with an acceptable toxicity profile in patients who had failed sunitinib or sorafenib or both.[74] In that trial, 25% of subjects randomized had received two prior VEGF-targeted TKI therapies and a significant improvement in PFS was seen in the everolimus arm vs. the placebo arm. It should be noted, however, that everolimus has been found to be inferior to several other therapies in randomized trials, including the phase 3 CHECKMATE 025 (nivolumab) and METEOR (cabozantinib), and the phase 2 study compared to lenvatinib + everolimus.[66,69,73]

2.1.2.3 Progression on or intolerance to prior VEGF inhibitor AND prior immune checkpoint inhibitor

- **For patients who progress on, or who are intolerant of, both prior VEGF inhibitor and prior immune checkpoint inhibitor, there is no evidence base available to select a preferred treatment option; options for patients in this situation include any of the options that have not previously been tried among: sunitinib, pazopanib, axitinib, cabozantinib, or lenvatinib/everolimus.**

There is a paucity of data on which to base treatment decisions in this space. In the absence of evidence-based recommendations, therapeutic options include any of the therapies mentioned in the above section with evidence in first- or subsequent-line therapy that have not yet been used for a particular patient. Cabozantinib is a preferred option in this space based upon the METEOR study.

2.2 Non-clear-cell histology

- **There is no standard therapy for non-clear-cell RCC and enrollment in clinical trial is the preferred option. It is generally accepted that non-clear-cell histology patients should be treated similarly to clear-cell histology patients. Clinical trials support the use of immunotherapy in this setting (ipilimumab + nivolumab; pembrolizumab + axitinib) or sunitinib if immunotherapy is not felt to be an option.**

Table 3. Options for patients with advanced metastatic sarcomatoid or poorly differentiated RCC in the absence of clinical trials

Therapy	Rationale
Ipilimumab + Nivolumab[81] (preferred)	Based on subgroup analysis of sarcomatoid RCC patients in CheckMate 214 showing a complete response rate of 18% and a mOS of 31 months compared to sunitinib (CR: 0% and mOS 13.6)
Axitinib + Pembrolizumab[103] (preferred)	Based on subgroup analysis of sarcomatoid RCC patients in KEYNOTE 426 showing a complete response rate of 12% and improved mOS (not reached) compared to sunitinib (CR: 0%)
Sunitinib	Based on prospective, non-randomized data from the Expanded Access Program
Sorafenib	Based on prospective, non-randomized data from the ARCCS Expanded Access trial
Temsirolimus	Based on subgroup analysis from the pivotal phase 3 trial in which these patients were eligible
Chemotherapy	Based on phase 2 data using agents such as 5-fluorouracil, gemcitabine, doxorubicin, and combinations of these showing activity
Sunitinib + gemcitabine	Single-arm, phase 2 trial

ARCCS: Advanced Renal Cell Carcinoma Sorafenib; CR: complete response; OS: overall survival; RCC: renal cell carcinoma.

In patients with metastatic or advanced RCC with non-clear-cell histologies, enrolment in clinical trials should be encouraged whenever possible. Other options include sunitinib, sorafenib, temsirolimus, and pazopanib (Table 3).[75-79]

Two phase 2 trials randomized patients to everolimus vs. sunitinib as first-line therapy for non-clear-cell pathologies with crossover allowed at progression. The ESPN trial futility analysis resulted in early termination of the trial due to inferior PFS and OS for everolimus.[80] The ASPEN trial demonstrated sunitinib was superior to everolimus for PFS.[81] Thus, sunitinib is the preferred first-line targeted treatment for non-clear-cell RCC.

In patients with advanced or metastatic sarcomatoid or poorly differentiated RCC, options show modest responses and include sunitinib, sorafenib, temsirolimus, and chemotherapy (Table 3).[75-77,82] In a phase 2 study, the combination of sunitinib and gemcitabine has been shown to be tolerable and the combination may be more effective than either therapy alone.[83] A recently presented post-hoc analysis of patients with sarcomatoid mRCC randomized to immunotherapy or sunitinib in the CheckMate 214 study suggests significant efficacy of immunotherapy compared to sunitinib.[84] The ORR was 56.7% for immunotherapy compared to 19.2% for sunitinib, with CR proportions of 18.3% vs. 0%. Median OS was 31.2 months compared to 13.6, again favoring immunotherapy (HR 0.55; 95% CI 0.33–0.90; p<0.0155). Rini and colleagues also presented a post-hoc analysis of similar patients, which showed an ORR rate of 59% compared to 31.5% with pembrolizumab + axitinib compared to sunitinib.[85] CR rate was 12% for the combination and 0% for sunitinib. PFS and OS were also improved.

2.3 Role of cytoreductive nephrectomy

– **Cytoreductive nephrectomy can be considered in appropriately selected patients presenting with de novo mRCC, ideally after a multidisciplinary discussion. This is based on expert consensus of this authorship group.**
  - o **Patients with a good performance status (Eastern Cooperative Oncology Group [ECOG] ≤1 or Karnofsky Performance Status [KPS] ≥80%), minimal symptoms related to metastases, a resectable primary tumor, and a limited burden of metastatic disease should be offered upfront cytoreductive nephrectomy followed by metastases-directed therapy, a period of surveillance, or systemic therapy.**
  - o **Patients with significant systemic symptoms from metastatic disease, active central nervous system metastases, a limited burden of disease within the kidney relative to the cumulative extra-renal volume of metastases, rapidly progressing disease, a poor performance status (ECOG >1 or KPS <80%), and/or limited life expectancy should not undergo cytoreductive nephrectomy.**

– **Patients with mRCC who don't fall within the two above categories should be offered initial treatment with systemic therapy, with consideration of cytoreductive nephrectomy given to those with a significant clinical response.**

The recommendations for cytoreductive nephrectomy come from a recent KCRNC consensus statement by Mason and colleagues.[86] These recommendations were based largely on two randomized, controlled studies published in 2018: CARMENA and SURTIME.[87,88] It should be noted that these key pieces of evidence regarding cytoreductive nephrectomy and systemic therapy are both from the VEGF-targeted era. To what extent these are applicable in the era of immune checkpoint inhibition has yet to be investigated.

2.4 Role of local therapy in oligometastases

– **In select patients with a limited number of sites of metastatic disease and stable clinical condition, local therapy, such as resection and/or stereotactic body radiotherapy, to treat of all sites of metastatic disease may be a reasonable option.**

2.4.1 Metastatectomy

There are no randomized trials showing the benefit of metastasectomy in RCC with oligometastatic disease. However, among patients with metachronous metastases after nephrectomy, about one-third are eligible for metastasectomy and several large cohorts report 50% five-year survival following complete resection of metastases.[89,90] Based on available observational data, patients most likely to benefit from metastasectomy are those diagnosed with metastases after at least a two-year disease-free interval, those with isolated metastases, and those with surgically favorable metastatic locations (e.g., lung, thyroid, and adrenal).[91] A period of observation is reasonable to confirm that the metastatic disease is not rapidly progressing. In addition, patients on systemic therapy should be re-evaluated during their course of disease for the option of metastasectomy to render no evidence of disease (NED) either due to favorable response or oligoprogression (see section 2.5). There is no defined role for adjuvant systemic therapy after metastasectomy if a patient is rendered NED.2.4.2 Stereotactic body radiotherapy (SBRT)

SBRT is another option for oligometastases. Unlike conventional radiotherapy, SBRT involves delivery of very conformal, ultra-hypofractionated radiation over 1–5 fractions, where the goal is to eradicate or provide long-term local control of the treated tumor(s). In patients with medically inoperable, early-stage RCC, SBRT to the primary tumou results in very high local control rates.[92,93] Similar high local control rates of approximately 90% are observed when using SBRT to treat RCC metastases in various body sites (thoracic,

abdominal, soft tissue, bone, brain).[94,95] Such data refutes the previously held notion that RCC is radio-resistant.

Thus, SBRT can be an alternative to surgical metastasectomy in patients who are inoperable or whose tumor(s) are not easily resectable without morbidity. It can also be complimentary to surgical resection when there are multiple metastases where a combined approach can be considered to spare patients multiple surgical procedures.

There is no role for "adjuvant" therapy in a NED situation after complete resection of metastases (pazopanib trial randomized).

2.5 Role of local therapy in oligoprogression

– **Local therapy may be considered in the setting of oligoprogression**

There are no randomized trials for the management of metastatic RCC patients with sites of oligoprogression. A Canadian phase 2 trial of using SBRT in metastatic RCC patients with oligoprogression while on sunitinib is currently accruing (NCT02019576).[96] Treatment with local therapy (surgery, SBRT, cryotherapy, and/or radiofrequency ablation [RFA]) can be considered, with the goal of delaying the need to start or change systemic therapy. Such an approach has been studied primarily in metastatic non-small-cell lung cancer patients who developed oligoprogression while on TKIs.[97]

2.6 Role of radiation therapy in symptom control

– **Radiation therapy may be considered to palliate symptoms from the primary tumor and metastases.**

RCC is not a radio-resistant tumor and many patients can achieve palliation of symptoms related to their cancer through radiation therapy (RT). New radiation techniques, such as stereotactic RT, may improve outcomes compared to traditional external beam RT; several ongoing trials are in progress.[96] Clinical trials involving RT should be supported.

2.7 Role of bone-modifying agents for patients with skeletal metastases

– **Bone-modifying agents can be considered for patients with bone metastases to decrease skeletal-related events (SRE).**

About one-third of patients with metastatic RCC will develop bone metastases, which can lead to SRE as part of their disease.[98] Currently available bone-modifying agents have been shown to reduce SREs in this population.

In a phase 3 trial of zoledronic acid (ZA) vs. placebo, a subset analysis of 74 RCC patients showed that administration of ZA compared to placebo resulted in a significant decrease in SREs in the ZA group.[99,100] Thus, monthly administration of ZA is a reasonable option. Careful monitoring of renal function is required.

Denosumab is an inhibitor of the receptor activator of nuclear factor kappa-B (RANK) ligand. In a phase 3 trial of denosumab vs. ZA for treatment of malignancy with bone metastases (excluding breast or prostate cancer patients), a subset of patients enrolled on this trial had metastatic RCC.[101] This trial demonstrated non-inferiority for denosumab compared to ZA in terms of SRE reduction for the group overall, although no subgroup analysis for RCC patients was done. Thus, denosumab could also be considered a reasonable option for this population of patients.

Patients receiving bone-modifying agents are at risk of hypocalcemia, therefore, calcium and vitamin D supplements are recommended. However, paraneoplastic hypercalcemia can also occur in RCC, so monitoring of serum calcium levels is important regardless. Patients starting on any bone-targeted therapy should ensure they have had a thorough dental history and recent dental examination prior to starting therapy, given the risk for developing osteonecrosis of the jaw. Patients should also be monitored for this throughout the course of their therapy.

2.7 Patient and caregiver issues

– **Patients should be provided access to multidisciplinary care, including kidney cancer specialists and health professionals with expertise in supportive care.**
– **Information should be provided to patients and caregivers on community resources. Canadian (and other) patients should be encouraged to contact and/or join Cancer du rein Canada/Kidney Cancer Canada (*www.kidneycancercanada.ca*).**
– **Screening of patients for hereditary kidney cancer risk, including appropriate genetic testing, should be the standard of care, as outlined in our Canadian guideline on genetic screening for hereditary renal cell cancers.**
– **Patient enrolment in the CKCis database is strongly encouraged.**

Patient care should involve a multidisciplinary team with expertise in the management of RCC, which may involve communication with and/or referral to another center.

All patients and caregivers should be referred to a reputable patient group for information and support, such as Kidney Cancer Canada[7] and the Canadian Cancer Society.[102] These groups provide accurate information that has been expertly reviewed and presented in a format that is easy for patients to understand. They also provide support to help patients and caregivers cope with a cancer diagnosis. Patients and caregivers should be asked at visits if they are connected to a patient group and have the information and support they need.

While a minority of patients has hereditary RCC, every patient should be screened for hereditary RCC risk using the Canadian consensus guidelines that include risk factors such as first- or second-degree relative with renal tumor, young

age (<45 years old), bilateral disease, uncommon histology, and associated hereditary conditions.[103]

In order to improve the ability of Canadian researchers to study kidney cancer, the CKCis was developed to facilitate population-based research. Voluntary patient enrolment is strongly encouraged.

Summary

Advanced RCC has seen many treatment advances in the last several years, with the introduction of many novel therapies. Recent evidence from the KEYNOTE 426 and CheckMate 214 studies has mandated a rearrangement of treatment algorithms for advanced clear-cell RCC. We now await both clinical experience and prospective clinical trials to help inform the optimal sequence of therapy with these newer therapies, VEGF-targeted therapies and other evidence-based options. Ongoing participation in research and clinical trials to further our knowledge in this field continues to be an essential priority for healthcare professionals with an interest in advanced RCC.

Therapy should be individualized based on patient profiles and disease characteristics, and each agent chosen should be optimized to obtain best results, with multidisciplinary care being paramount in achieving maximal benefit for patients.

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