Management of advanced kidney cancer: Kidney Cancer Research Network of Canada (KCRNC) consensus update 2021

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The following is a consensus report from the Kidney Cancer Research Network of Canada (KCRNC), with an update from the 11th Canadian Kidney Cancer Forum, held virtually on October 16, 2020, and subsequent discussions and updates after the ASCO Genitourinary Cancers Symposium, held in February 2021.

Introduction

For more than a decade, targeted systemic therapies have been the standard of care for metastatic renal cell carcinoma (mRCC) and their use has been refined over time as clinical experience has evolved.[1-6] The 2019 consensus statement by the Kidney Cancer Research Network of Canada (KCRNC) introduced the role of immunotherapy as first-line systemic therapy for mRCC, either as doublet immunotherapy or in combination with a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI), based on phase 3 studies that demonstrated improved survival compared to single-agent VEGFR-TKI (sunitinib).[7-9] Subsequently, there have been updates on two of the important previously reported phase 3 studies (CheckMate 214 and Keynote-426) that have reinforced prior results.[10,11] In addition, there have been two new phase 3 studies published (CLEAR and CheckMate 9ER) of immunotherapy + VEGFR-TKI also demonstrating survival benefit over VEGFR-TKI alone.[12,13] Furthermore, the CLEAR study showed improved progression-free survival (PFS), but not overall survival (OS) benefit, with the use of VEGFR-TKI + mammalian target of rapamycin (mTOR) inhibitor compared to VEGFR-TKI alone. These studies and updates have been included in this report.[13]

The current consensus statement is based on the deliberations and conclusions of key Canadian opinion leaders in the management of advanced renal cell cancer who convened during the 11th Canadian Kidney Cancer Forum, held virtually on October 16, 2020. During that session, the authors reviewed the previous advanced disease management consensus statements, published in 2019,[7] discussed the recent relevant evidence, and reached consensus on the revised statements published below.

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 (October 16, 2020). Two exceptions are the late addition of data from the CLEAR and PAPMET studies, which were presented at the ASCO Genitourinary Cancers Symposium on February 13, 2021 and concurrently published.[13-16] The results of these trials were reviewed by all co-authors and there was agreement to include the findings in this publication to ensure the most contemporary document and recommendations possible. 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 of the primary kidney tumor outside the context of a clinical trial.**

If patients are felt to have surgically resectable disease at diagnosis and are 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 VEGFR-TKIs), including modest reduction in tumor size and possible facilitation of locally advanced tumor resection and complex partial nephrectomy.[17-30] However, there are no randomized controlled trials to support the use of neoadjuvant therapy.

Studies investigating the utility of immune checkpoint inhibitors, VEGFR-TKIs, or their combination in the neoadjuvant setting are currently ongoing.[31-36] There is also a study investigating the use of a neoadjuvant vaccine in RCC.[37]

In summary, there is insufficient evidence to support a specific recommendation for routine use of neoadjuvant therapy outside of clinical trials. 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 these cases if there is any question that they may have converted to an operable state and are likely to benefit from nephrectomy, as discussed in section 2.4 below ("Cytoreductive nephrectomy").

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 OS after nephrectomy[38] and five prospective randomized trials of VEGFR-TKIs have failed to show OS benefit for sunitinib, sorafenib, pazopanib, and axitinib.[39-44]

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 disease-free survival (DFS) with adjuvant sunitinib comparable to the time on therapy.[40] For OS, a secondary endpoint, the most recent published update on S-TRAC 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).[40] 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.[40] In the U.S., sunitinib was approved for use in the adjuvant setting based largely on the findings of this study.[45] Sunitinib is not approved for this indication in Canada.

As is the case in the neoadjuvant space, a number of ongoing studies in the adjuvant setting are seeking to determine the role and duration of therapy of other molecular targeted therapy (everolimus[46]) or immune checkpoint inhibition (atezolizumab,[47] ipilimumab + nivolumab,[48] pembrolizumab,[49] durvalumab ± tremelimumab[50]).

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 not be routinely offered adjuvant systemic therapy and should be encouraged to participate in clinical trials whenever possible.

2. Advanced or metastatic kidney cancer

When recommending systemic therapy for advanced or mRCC, 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 drugs, 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 access to radiation oncology, surgical oncology, 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. Participation in clinical trials is strongly encouraged.

2.1. Clear-cell carcinoma (Table 1)

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 favorable-risk patients, a combination of immunotherapy + VEGFR-TKI is the preferred first-line treatment, based on improvements in PFS in this subgroup, when compared to sunitinib monotherapy. Although none of the studies have yet to show statistically significant improvements in OS, events have been few and further followup is needed. Targeted therapy can be considered an alternative active treatment option, primarily for patients who have a contraindication to immunotherapy.**
- **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 or significant comorbidities.**
- **For IMDC intermediate- or poor-risk patients, either ipilimumab + nivolumab OR a combination of immunotherapy + VEGFR-TKI are the preferred first-line therapies. Targeted therapy remains an alternative option, primarily for patients who have a contraindication to immunotherapy or who are felt to be unable to tolerate combination therapy.**

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.[51] Although mRCC has entered 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. These IMDC criteria stratify patients with mRCC into 3 risk groups based on their score: favorable (0), intermediate (1–2), or poor (3–6). It should be emphasized that the IMDC classification is a prognostic classification and not a predictive tool. To date, no reliable or helpful predictive biomarkers exist to inform optimal treatment selection.

Table 1. Therapeutic options for advanced clear-cell RCC
Participation in clinical trials is strongly encouraged in all settings of treatment

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

"Preferred" options originated from studies that have demonstrated overall survival (OS) improvements. "Options" have usually demonstrated a progression-free survival advantage but not necessarily OS survival. *Not yet approved in Canada for this indication. #If not previously used. IMDC: International Metastatic RCC Database Consortium; RCC: renal cell carcinoma; VEGF: vascular endothelial growth factor.

2.1.1.2. IMDC favorable-risk

2.1.1.2.1. Preferred therapies

2.1.1.2.1.1. Pembrolizumab + axitinib

The KEYNOTE-426 study was a randomized, open-label, phase 3 study that assessed the efficacy and safety of pembrolizumab (200 mg IV every three weeks for up to 35 cycles) + axitinib (5 mg orally twice daily) vs. sunitinib (50 mg orally daily, four weeks per six-week cycle) as first-line therapy for mRCC.[9] The 861 patients (30% favorable-, 56% intermediate-, 13% poor-risk) enrolled in this study had clear-cell mRCC and no previous systemic therapy for mRCC. Patients were randomized 1:1 to pembrolizumab + axitinib (n=432) or sunitinib (n=429) with stratification based on IMDC risk group. Dual primary endpoints were OS and PFS in the overall population, while objective response rate (ORR) was the key secondary endpoint.

An update of extended followup results was recently published.[11] For the intention-to-treat (ITT) population, after a median followup of 30.6 months, pembrolizumab + axitinib significantly improved PFS compared to sunitinib, with medians of 15.4 months and 11.1 months, respectively (HR 0.71, 95% CI 0.60–0.84, p<0.0001). OS improvement was confirmed, as median OS had not been reached for pembrolizumab + axitinib, while median survival for sunitinib was 35.7 months (HR 0.68, 95% CI 0.55–0.85, p=0.0003). Pembrolizumab + axitinib demonstrated improved ORR (60% vs. 40%, p<0.0001). Complete response (CR) rate for pembrolizumab + axitinib was 9%.

In a prespecified subgroup analysis, there was a trend for improved PFS and OS with pembrolizumab + axitinib in patients with IMDC favorable-risk (n=269), which was not statistically significant (HR 0.79, 95% CI 0.57–1.09; and HR 1.06, 95% CI 0.60–1.86; respectively). In post-hoc analysis, objective response rate was 70% with pembrolizumab + axitinib vs. 50% with sunitinib. As noted by the authors of this study, the biology of this subgroup is often more indolent and the number of events to date is small. Furthermore, the study was not designed or adequately powered to detect differences between IMDC risk categories.

2.1.1.2.1.2. Nivolumab + cabozantinib

The CheckMate 9ER study was a randomized, open-label, phase 3 study that assessed the efficacy and safety of nivolumab + cabozantinib (a dual VEGFR/MET and AXL inhibitor) vs. sunitinib as first-line therapy for mRCC.[12] The 651 patients (22% favorable-, 58% intermediate-, 20% poor-risk) enrolled in this study had clear-cell mRCC (including sarcomatoid features), no previous systemic therapy for mRCC, and any IMDC risk group. Patients were randomized 1:1 to nivolumab (240 mg IV every two weeks for up to two years) + cabozantanib (40 mg orally daily) (n=323) or sunitinib (n=328). Randomization was stratified by IMDC risk group, tumor PD-L1 expression, and geographic region. Primary endpoints were PFS per blinded independent central review (BICR) in the overall population, while OS, ORR per BICR, and safety were the key secondary endpoints. The results of this study were recently published, with a median study followup of 18.1 months for OS. PFS was 16.6 months for nivolumab + cabozantinib and 8.3 months for sunitinib (HR 0.51, 95% CI, 0.41–0.64, p<0.001) in the ITT population. Median OS was not reached for either arm, however, HR was 0.60 (99% CI 0.40–0.89, p=0.001) in the ITT population. ORR by BICR was 55.7% vs. 27.1% favoring the nivolumab + cabozantinib arm (p<0.001). Improvements in PFS, OS, and ORR with nivolumab + cabozantanib were consistent across subgroups, including IMDC risk, tumor PD-L1 expression, and presence of bone metastases. In the favorable-IMDC risk group, HR for PFS by BICR and OS were 0.62 (0.38–1.01) and 0.84 (0.35–1.97), respectively. The CR rate for nivolumab + cabozantinib was 8%.

2.1.1.2.1.3. Lenvatinib + pembrolizumab

The CLEAR study was a randomized, open-label, phase 3 study, that assessed the efficacy and safety of the two drug combinations of lenvatinib + pembrolizumab or lenvatinib + everolimus (mTOR inhibitor) compared to sunitinib as therapy in advanced RCC.[13,14] The 1069 patients (33% favorable-, 55% intermediate-, 10% poor-risk) enrolled in this study had clear-cell mRCC (including sarcomatoid features), no previous systemic therapy for mRCC, and any IMDC risk group. Patients were randomized (1:1:1) to receive either lenvatinib (20 mg orally daily) + pembrolizumab (200 mg IV every three weeks for up to 35 cycles) (n=355), lenvatinib (18 mg orally daily) + everolimus (5 mg orally daily) (n=357) or sunitinib (n=357). The primary endpoint of the study was PFS by independent review committee. OS, ORR as assessed by an independent review committee, safety, and PFS as assessed by investigators were secondary endpoints.

After a median followup of 26.6 months, the PFS by independent review committee was longer with lenvatinib + pembrolizumab (23.9 months) compared to sunitinib (9.2 months) (HR 0.39, 95% CI 0.32–0.49, p<0.001) and also improved with lenvatinib + everolimus (14.7 months) compared to sunitinib (9.2 months) (HR 0.65, 95% CI 0.53–0.80, p<0.001) in the ITT group. PFS by investigator was also longer in the lenvatinib + pembrolizumab arm (22 months vs. 9.5 months, HR 0.47) and lenvatinib + everolimus arm (14.6 months vs. 9.5 months, HR 0.7) vs. sunitinib. Median OS was not reached in any of the three arms, however, the HR of 0.66 was statistically significant for only the lenvatinib + pembrolizumab (95% CI 0.49–0.9, p<0.001) arm compared to sunitinib. ORR and CR rate were 71.0% and 16.1% with lenvatinib + pembrolizumab, 53.5% and 9.8% with lenvatinib + everolimus, and 36.1% and 4.2% with sunitinib, respectfully.

On subgroup analysis, PFS and OS with lenvatinib + pembrolizumab were improved in all IMDC subgroups, with the exception of OS for the favorable group.

2.1.1.2.2. Other options: Sunitinib, pazopanib, or active surveillance

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.[52,53]

The dose and schedule of sunitinib should be individualized for each patient to derive the optimal benefit.[54] It is still recommended to start with the monograph standard of four weeks on at 50 mg per day per six-week cycle. After evaluation of type and timing of toxicities, patients may require adjustments to the schedule and/or dose. Bjarnason and colleagues 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.[54] A prospective clinical trial conducted across Canada examined the same individualized dose titration scheme among 117 patients with metastatic clear-cell RCC.[55] Subjects in this study were started on sunitinib 50 mg/day with the aim to treat for 28 days. Standard treatment breaks of 14 days 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 VEGFR-TKIs 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.[55] In addition, toxicity appeared substantially less than on the traditional 50 mg/day, 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.[56] As first-line therapy, pazopanib (800 mg orally daily) has also been shown to be non-inferior to sunitinib with respect to PFS in the phase 3 COMPARZ clinical trial.[57] Toxicity profiles were different, with sunitinib-treated patients experiencing more fatigue, hand-foot syndrome, and thrombocytopenia, whereas pazopanib-treated patients experiencing more elevations in hepatic transaminases.[57]

A post-hoc analysis of the COMPARZ trial found that for patients without vs. with adverse event (AE)-related dose reductions, median PFS, median OS, and ORR were 7.3 vs. 12.5 months, 21.7 vs. 36.8 months, and 22% vs. 42% (all p<0.0001) for pazopanib, and 5.5 vs. 13.8 months, 18.1 vs. 38.0 months, and 16% vs. 34% (all p<0.0001) for sunitinib, respectively. The improved outcomes were similar for patients needing dose interruptions for toxicity. Dose modifications or interruptions, when required because of AEs, were associated with improved efficacy, suggesting that AEs might be used as a surrogate marker of adequate dosing for individual patients for both sunitinib and pazopanib.[58]

As outlined above, the results of the CLEAR study showed improved PFS by both independent review and by investigator review for lenvatinib + everolimus compared to sunitinib. However, there is no OS benefit as yet observed at 26.6-month followup, with a HR of 1.15 (95% CI 0.88–1.50, p=0.30). Most participants felt that further maturity of the data was required to potentially recommend this as a first-line treatment and, at this time, lenvatinib + everolimus could not be recommended as a first-line option.[13,14]

In the opinion of the participants at the consensus meeting, an initial period of observation (active surveillance) also remains a reasonable option in select patients, given that all available treatments 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 or in patients with competing risks from other comorbidities. This is supported by prospective, observational data presented by Rini and colleagues.[59] (Refer to section 2.5 regarding management of oligometastases.)

High-dose interleukin (IL) 2 continues to be used in the province of Quebec because of its potential to induce durable, long-term remissions in a small subset of fit patients with advanced RCC.[60] High does IL-2 should only be used by experienced physicians in centers with resources to manage severe acute toxicities. For the most part, this immunotherapy approach has been replaced with the use of newer immune checkpoint inhibitors.

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 ipilimumab (3 mg/kg IV every three weeks for four cycles) + nivolumab (1 mg/kg IV every three weeks for four cycles) followed by nivolumab monotherapy (3 mg/kg IV every two weeks) vs. sunitinib.[8] 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 ipilimumab + nivolumab (n=550) or sunitinib (n=546). As per inclusion criteria, most enrolled patients had IMDC intermediate- (n=425) or poor-risk disease (n=422). The co-primary endpoints were OS, ORR, and PFS in intermediate- and poor-risk patients. The same endpoints were used for the exploratory cohort of favorable-risk patients.[61]

An update of this trial was presented at ESMO 2020 and the ipilimumab + nivolumab arm continues to show

improvement in all three co-primary endpoints at four years of followup.[10,62] In the intermediate- or poor-risk group, median OS was 48.1 months for the ipilimumab + nivolumab compared to 26.6 months for sunitinib (HR 0.65, 95% CI 0.54–0.78). Median PFS was 11.2 months for ipilimumab + nivolumab compared to 8.3 months for sunitinib (HR 0.74, 95% CI 0.62–0.88). PFS curves appear to have plateaued after 30 months, with a PFS rate of approximately 35% at five years following treatment with ipilimumab + nivolumab. CR rate was 10.4% with ipilimumab + nivolumab. Among favorable-risk patients, no significant difference was demonstrated between the treatment arms for OS or PFS (HR 0.93 and 1.84, respectively). Median duration of response has not been reached for ipilimumab + nivolumab responders, and approximately 45% of responding patients remain in remission without any active therapy.

2.1.1.3.1.2. Pembrolizumab + axitinib

The phase 3 study, KEYNOTE-426, evaluated its dual primary endpoints of OS and PFS in the unselected overall population, including patients with favorable-risk (n=269) and intermediate-/poor-risk (n=592).[9,11] The overall data are reported above. With respect to IMDC risk groups, at a median followup of 30.6 months, prespecified subgroup analysis showed that pembrolizumab + axitinib was associated with an OS and PFS improvement in intermediate- or poor-risk disease (HR 0.63, 95% CI 0.50–0.81, p=0.0001; and HR 0.69, 95% CI 0.56–0.84, p=0.0002; respectively). Median duration of response was reached with 23.5 months for pembrolizumab + axitinib vs. 15.9 months in the sunitinib group.

2.1.1.3.1.3. Nivolumab + cabozantinib

PFS by BICR was the primary endpoint for the CheckMate 9ER phase 3 clinical trial, while OS was a secondary endpoint.[12] The unselected population included patients with favorable- (n=146), intermediate- (n=376) and poor-risk (n=129) disease. The overall data are reported above. There was improved PFS and OS in the nivolumab + cabozantinib arm for intermediate- (HR 0.54 and 0.70) and poor-risk groups (HR 0.37 and 0.37), respectively. Median duration of response was 20.2 months with nivolumab + cabozantinib vs. 11.5 months with sunitinib.

2.1.1.3.1.4. Pembrolizumab + lenvatinib

The primary endpoint for the phase 3 CLEAR study was PFS by independent review committee. OS was a secondary endpoint. The unselected population included patients with favorable- (n=291), intermediate- (n=682) and poor-risk (n=96) disease. The overall data are reported above.[13,14]

On subgroup analysis, there was improved PFS and OS in the lenvatinib + pembrolizumab arm for IMDC intermediate- (HR 0.44 and 0.72) and poor-risk groups (HR 0.18 and 0.30), respectively, vs. sunitinib.[13]

2.1.1.3.2. Other options

The recommendation that sunitinib or pazopanib are possible but non-preferred options in the upfront setting for intermediate- 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 VEGFR-TKI therapy in pivotal trials as well. The consensus was that sunitinib and pazopanib would still be preferentially used in patients with contraindications for immunotherapy or who are felt to be unable to tolerate combination therapy.

In the CLEAR study,[13] the lenvatinib + everolimus arm showed improved PFS for IMDC intermediate- (HR 0.67) and poor-risk patients (HR 0.73). However, no improvement in OS has been demonstrated for any of the IMDC subgroups. As noted previously, further maturity of data is required and this drug combination is not currently recommended for first-line treatment.

2.1.1.3.2.1. Avelumab + axitinib

JAVELIN Renal 101 was a phase 3, randomized, open-label study comparing avelumab (10 mg/kg IV every two weeks) + axitinib (5 mg orally twice daily) to sunitinib among 886 patients with clear-cell advanced RCC and no prior systemic therapy.[63] All prognostic risk groups were included. The co-primary endpoints were PFS and OS among patients with PD-L1-positive tumors (n=560) as defined by ≥1% of immune cells staining positive within the tumor area of the tested tissue sample using the SP263 assay (Ventana). Secondary endpoints were OS and PFS in the overall population. The updated results after minimum followup of 13 months have been published.[64] In the PD-L1+ group, median PFS was 13.8 months with avelumab + axitinib vs. 7.0 months with sunitinib (HR 0.62, 95% CI 0.490–0.7777, one-sided p<0.001). In the ITT population, the median PFS was 13.3 months with avelumab + axitinib vs. 8.0 months with sunitinib (HR 0.69, 95% CI 0.574–0.825, one-sided 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 (PD-L1 + population: HR 0.828, 95% CI 0.596–1.151, p=0.1301; and overall population: HR 0.796, 95% CI 0.616–1.027, p=0.0392). At this time, the majority of the participants in the 2020 consensus meeting recommended keeping avelumab + axitinib in the "other options" section for first-line therapy pending final analysis for OS. It was noted that other VEGFR-TKI + immunotherapy combinations have demonstrated survival benefit and are, therefore, preferred options.

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

2.1.1.3.2.2. Cabozantinib

The randomized, phase 2 CABOSUN trial compared cabozantinib (60 mg orally daily) to sunitinib first-line.[65] 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.

Health Canada approved the use of cabozantinib as first-line treatment in patients with intermediate- and poor-risk advanced RCC. Although consensus was not reached, some of the participants in the 2020 consensus meeting felt that cabozantinib may be an option for intermediate-/poor-risk patients who are not ideal candidates for immunotherapy.

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 VEGFR-TKIs have activity after immunotherapy.

The only prospective study in this setting has demonstrated the activity of axitinib after immunotherapy; therefore, axitinib may be a preferred option post-immunotherapy progression.[66] Seventy-four percent of patients had received two or more therapies prior to axitinib. In this study, axitinib (initial starting dose 5 mg orally twice daily) was given on an individualized schedule, with significant inter-individual variation in the optimal dose and schedule, as has been shown for sunitinib. The authors suggested that individualized dosing of axitinib should be considered, given in combination with immunotherapy.

Based a subgroup analysis of the METEOR study, cabozantinib is also a preferred option post-immunotherapy progression, particularly after VEGFR-TKI + immunotherapy combination.[67]

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 VEGFR-TKI-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 VEGFR-TKI is a reasonable choice.**
– **For patients who progress on first-line sunitinib or pazopanib, preferred options are nivolumab 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 VEGFR-TKI-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.[68]

2.1.2.2.2. Progression on first-line VEGFR-TKI-targeted therapy: Preferred options

2.1.2.2.2.1. Nivolumab

In the phase 3 CheckMate 025 trial, intravenous nivolumab (3 mg/kg IV every two weeks) produced better response rates and a significantly longer OS compared to oral everolimus (10 mg orally daily) 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.[69] Benefit was observed irrespective of PD-L1 expression. In addition, grade 3 or 4 treatment-related AEs and treatment-related AEs 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 VEGFR-TKI-targeted therapies.[69] 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.[70,71] Thus, treatment beyond progression should be restricted to patients showing clinical benefit, stability, or a mixed response.

2.1.2.2.2.2. Cabozantinib

The randomized, phase 3 METEOR trial compared cabozantinib to everolimus among patients previously treated with one or more prior VEGFR-TKIs.[67] 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.[67] Approximately 30% of patients had received at least two prior VEGFR-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.

2.1.2.2.3. Progression on first-line VEGFR-TKI-targeted therapy: Other options

2.1.2.2.3.1. Axitinib

Axitinib is listed as "other options" in VEGF-pretreated populations largely based on data from the phase 3 AXIS trial, in which axitinib demonstrated improved PFS, but no OS benefit compared to sorafenib as second-line therapy in patients progressing after first-line sunitinib.[72] However, in this study, axitinib was compared to a more arguably active agent, sorafenib, as opposed to the CheckMate 025 and METEOR studies, which were compared to less active everolimus. Further, there are patients in the CheckMate 025 and METEOR trials who went on to receive axitinib post-nivolumab or cabozantinib, respectively. Retrospective analyses suggest patients demonstrate benefit to VEGFR-TKIs in the third-line setting, inclusive of axitinib.[73,74]

2.1.2.2.3.2. 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).[75] The subjects were 153 patients who had progressed on VEGFR-TKI-targeted therapy and were randomized 1:1:1 to lenvatinib alone (24 mg daily), everolimus alone (10 mg daily), or the combination of lenvatinib (18 mg daily) and everolimus (5 mg daily).

2.1.2.2.3.3. 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.[76] In that trial, 25% of subjects randomized had received two prior VEGFR-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 subsequent randomized trials, including the phase 3 CHECKMATE 025 (nivolumab) and METEOR (cabozantinib), and the phase 2 study compared to lenvatinib + everolimus.[67,69,75]

2.1.2.3. Progression on or intolerance to prior VEGFR-TKI AND prior immune checkpoint inhibitor

– **For patients who progress on, or who are intolerant of, both prior VEGFR-TKI and prior immune checkpoint inhibitor, there is little evidence 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 may be a preferred option in this space based upon the METEOR study.

2.2. Non-clear-cell histology

– **There is no standard therapy for advanced non-clear-cell RCC and enrollment in clinical trial is the preferred option. It is generally accepted that patients with non-clear-cell histology should be treated similarly to patients with clear-cell histology. Clinical trials support the use of immunotherapy in this setting (ipilimumab + nivolumab; pembrolizumab + axitinib; pembrolizumab monotherapy), cabozantinib, or sunitinib**

In patients with metastatic or advanced RCC with non-clear-cell histology, enrollment in clinical trials should be encouraged whenever possible.

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.[77] The ASPEN trial demonstrated sunitinib was superior to everolimus for PFS.[78]

The results phase 2 KEYNOTE 427 study of first-line pembrolizumab monotherapy (200 mg IV every three weeks) in non-clear-cell RCC (cohort B) have been presented in abstract form.[79] (At 18 months, PFS rate was 18.9 months [range 9.9–26.0 months] and OS 67%. Overall response rate was 26% [95% CI 19.5–33.5]; 10 CRs, 33 partial responses [PRs]).

The PAPMET phase 2, open-label study was designed to assess the role of MET kinase inhibitors compared to standard of care sunitinib in patients with advanced papillary RCC. This data was presented at the 2021 ASCO Genitourinary Cancers Symposium and concurrently published.[15,16] PFS was the primary endpoint. Initially, patients were randomized to one of four arms: cabozantinib, crizotinib, savolitinib, or

Table 2. Options for patients with advanced metastatic sarcomatoid or poorly differentiated RCC
Participation in clinical trials is strongly encouraged

Therapy	Rationale
Ipilimumab + Nivolumab[80] (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[81] (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%)
Nivolumab + cabozantinib[82] (preferred)	Based on subgroup analysis of sarcomatoid RCC in Checkmate 9ER showing improved PFS (10.9 m and mOS not reached compared to sunitinib (PFS 4.2 and mOS 19.7 m)
Sunitinib	Based on prospective, non-randomized data from the Expanded Access Program

CR: complete response; mOS: median overall survival; PFS: progression-free survival; RCC: renal cell carcinoma.

sunitinib. The savolitinib (n=29) and crizotinib (n=28) arms were stopped to accrual after a prespecificied futility analysis, while planned accrual for both the cabozantinib (n=44) and sunitinib (n=46) arms were completed. PFS was longer in the cabozantinib arm (9.0 months) compared to the sunitinib arm (5.6 months), with HR 0.60 (0.37–0.97, one-sided p=0.019). There was no improvement in PFS with savolitinib or crizotinib compared to sunitinib. There were no differences in OS between all four treatment arms. Response rate for cabozantinib was 23% vs. 4% for sunitinib (two-sided p=0.010).[16]

2.3. Sarcomatoid variant or poorly differentiated RCC (Table 2)

In patients with advanced or metastatic sarcomatoid or poorly differentiated RCC, strong preference is to use immunotherapy-based therapies. In patients who are not candidates for immunotherapy, sunitinib can be considered.

A post-hoc analysis of patients with sarcomatoid mRCC randomized to ipilimumab + nivolumab or sunitinib in the CheckMate 214 study suggests significant efficacy of ipilimumab + nivolumab compared to sunitinib.[80] The ORR was 56.7% for ipilimumab + nivolumab compared to 19.2% for sunitinib, with CR proportions of 18.3% vs. 0%. Median OS was 31.2 months compared to 13.6 months, again favoring ipilimumab + nivolumab (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.[81] CR rate was 12% for the combination and 0% for sunitinib. PFS and OS were also improved.

The CheckMate 9ER phase 3 study of first-line treatment of advanced RCC included 75 (11.5%) patients with sarcomatoid features treated with either nivolumab + cabozantinib (n=34) vs. sunitinib (n=41). Results of 18.1-month followup, presented at the ASCO Genitourinary Symposium 2021, demonstrated an improved PFS and OS with nivolumab + cabozantinib compared to sunitinib (10.9 months vs. 4.2 months, HR 0.39 [95% CI 0.22–0.70]; and not reached vs. 19.7 months, HR 0.36 [95% CI 0.16–0.82]). ORR for nivolumab + cabozantinib was 55.9% vs. 22.0% with sunitinib.[82] Further data will be reported with additional followup.

Patients with sarcomatoid features were eligible for the CLEAR study (n=73, 7%), however, no separate analysis of this group has been presented.[13,14]

2.4. 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.**
  - **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.**
  - **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 upfront 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 deferred cytoreductive nephrectomy given to those with a significant and stable clinical response.**

The recommendations for cytoreductive nephrectomy come from a recent KCRNC consensus statement by Mason and colleagues.[83] These recommendations were based largely on two randomized, controlled studies published in 2018: CARMENA and SURTIME.[84,85] 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.

Based on the ESMO 2020 update of the Checkmate 214 study of ipilimumab + nivolumab vs. sunitinib, in a small subgroup of patients with renal tumor in situ (53 patients), ORR to ipilimumab + nivolumab was 35% in the primary

tumor. However, the median OS was inferior in this subgroup for both the ipilimumab + nivolumab (26.1 months) and sunitinib (14.3 months) arms. No CRs were observed in patients with the primary renal lesion in situ.[62]

Exploratory subgroup analysis of patients from Keynote-426 by prior nephrectomy was presented at the International Kidney Cancer Symposium 2020. Pembrolizumab + axitinb showed OS, PFS, and ORR benefit relative to sunitinib as first-line therapy in mRCC patients who underwent prior nephrectomy (n=718) and those who did not undergo prior nephrectomy (n=143).[86]

In terms of alternate forms of cytoreduction, the ongoing, randomized, phase 2 CYTOSHRINK trial (n=78) is evaluating the role of cytoreductive stereotactic body radiation therapy (SBRT) to the renal primary plus ipilimumab + nivolumab vs. ipilimumab + nivolumab alone for patients with de novo mRCC and IMDC intermediate- or poor-risk disease.[87]

2.5 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 SBRT, to treat all sites of metastatic disease may be a reasonable option.**

2.5.1. Metastasectomy

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.[88,89] Based on available observational data, patients most likely to benefit from metastasectomy are those diagnosed with metastases after at least a two-year DFS, those with isolated metastases, and those with surgically favorable metastatic locations (e.g., lung, thyroid, and adrenal).[90] 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 them no evidence of disease (NED) either due to favorable response or oligoprogression (see section 2.6). There is no defined role for "pseudoadjuvant" systemic therapy after metastasectomy if a patient is rendered NED.

2.5.2. 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 tumor results in very high local control rates.[91,92] 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).[93,94] 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.

2.6. 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 37 mRCC patients with oligoprogression while on sunitinib or pazopanib has been reported in abstract form.[95] At a median followup of 11.6 (1.8–53.5) months, the median PFS from study entry was 9.6 months (95% CI 7.4–20.5), with the vast majority of progression occurring outside of the irradiated areas. The two-year local control of the irradiated tumors was 96%. The two-year OS from study entry was 77%. The cumulative incidence of changing systemic therapy was 47% at one year and 75% at two years, with a median time to a change in systemic therapy of 12.6 months, thus essentially prolonging the PFS for the TKI.

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 previously been studied primarily in metastatic non-small-cell lung cancer patients who developed oligoprogression while on TKIs.[95]

2.7. Role of radiation therapy in symptom control

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

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.

2.8. 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 an SRE as part of their disease.[97] 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 mRCC patients showed that administration of ZA compared to placebo resulted in a significant decrease in SREs in the ZA group.[98,99] 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 in this trial had mRCC.[100] 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, particularly those with impaired renal function obviating bisphosphonate use.

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 (ONJ). Patients should also be monitored for this throughout the course of their therapy, as there a higher incidence (10%) for ONJ in combination with VEGFR-TKIs.[101]

2.9. 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. Patients and caregivers 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 the Canadian guideline on genetic screening for hereditary renal cell cancers.**
- **Patient enrolment in the Canadian Kidney Cancer information system (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[102] and the Canadian Cancer Society.[103] 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 have hereditary RCC, every patient should be screened for hereditary RCC risk using the Canadian guideline that includes 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.[104]

To facilitate clinical and basic research in kidney cancer in Canada, the web-based CKCis national registry was developed in 2009. To date, this registry includes 13 000 patients diagnosed with kidney cancer from 14 academic centers across Canada. Voluntary patient enrollment is strongly encouraged.

Summary

Advanced RCC has seen many treatment advances in the past several years, with the introduction of many novel therapies. Recent evidence from the KEYNOTE 426 and CheckMate 214 studies, and now the addition of the CheckMate 9ER and CLEAR studies, has mandated a rearrangement of treatment algorithms for advanced clear-cell RCC with the use of doublet immunotherapy or immunotherapy in combination VEGFR-TKI. We now await both clinical experience, prospective clinical trials, and development of predictive biomarkers to help inform the optimal choice and sequence of currently available treatment options.

In absence of head-to-head comparison between combination approaches at this time, therapy should be individualized based on patient profiles and disease characteristics, and each agent chosen should be optimized to obtain the best results, with multidisciplinary care being paramount in achieving maximal benefit for patients.

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.

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