Management of advanced kidney cancer: Canadian Kidney Cancer Forum consensus update

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This is the most recent report from the Kidney Cancer Research Network of Canada (KCRNC), with an update from the 6th Canadian Kidney Cancer Forum held in February 2015 in Toronto, Ontario.[1-4]

Kidney cancer, predominantly renal cell carcinoma (RCC), is the most lethal genitourinary malignancy and kills more than 1750 Canadians a year.[5] The overall incidence is increasing by 2% per year for unknown reasons, with most new cases being small renal masses. For almost a decade, targeted systemic therapies have been available and have been integrated into clinical practice with evolving experience. Preservation of kidney function with widespread adoption of partial nephrectomy is a focus of treatment of early stage disease. These and other advances have revolutionized care and stimulated research and discovery. There are several guidelines in Canada that address various aspects of RCC patient care.[1-4,6,7]

Five previous forums were held in 2008, 2009, 2011, 2013, and 2014. As before, the 2015 meeting was small, by invitation and attended by survivors, caregivers, expert clinicians and researchers in fields relevant to kidney cancer care. The attendees included representatives of Kidney Cancer Canada (www.kidneycancercanada.org).[8]

During the conference, prior management consensus statements were reviewed and updated using the same process. This report is an update of the advanced disease management component of the consensus published in 2013.[4] The Forum again addressed strategies for kidney cancer control in Canada, which included updates from the now operational Canadian Kidney Cancer Information System (CKCis), as well as reports back from the KCRNC main working groups. These KCRNC groups are working on initiatives in four major domains to improve kidney cancer patient care: (1) personalized medicine; (2) quality care initiatives; (3) survivorship, and (4) genetics. Prior to the start of the Forum, satellite meetings of various working groups also took place, including a new initiative known as the James Lind Alliance (JLA) working group. The JLA is a non-profit organization founded in 2004 that brings together patients, clinicians, and caregivers and through a rigorous process identifies the top 10 uncertainties, or unanswered questions, about a given medical problem.[9] The working group established the top 10 uncertainties for kidney cancer management in Canada and we believe this is the first time such an undertaking for kidney cancer has ever happened worldwide and will help inform the working groups on research priorities. This consensus statement pertains to the management of advanced disease.

Management of locally advanced kidney cancer

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, they should proceed immediately to surgery. Routine use

of neoadjuvant therapies is not indicated at this time. The final results of clinical trials with neoadjuvant anti-angiogenic agents (vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFr TKI), VEGF antibodies or mammalian target of rapamycin (mTOR) inhibitors) will not be available for several more years. Some patients deemed inoperable at diagnosis may have a dramatic response to targeted therapy and if there is any question that they may have converted to an operable state, they should be re-evaluated by a urologist.

Adjuvant therapy

- There is no indication for adjuvant therapy after surgical resection, unless in the context of a clinical trial.

Adjuvant therapy with cytokines does not improve overall survival after nephrectomy.[10] Several clinical trials with adjuvant anti-angiogenic agents (VEGFr TKI, VEGF antibodies or mTOR inhibitors) have been completed with patients in follow-up. At the 2015 GU Cancers Symposium in Orlando, Florida, preliminary results of the ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) trial were presented.[11] This was a three-arm randomized, placebo-controlled trial of 1 year of either sorafenib, sunitinib, or placebo. The authors reported that there was no significant improvement in progression-free (PFS) or overall survival (OS) for patients treated with either the active intervention arm or placebo. Thus, at the present time there is no clinical trial data in support of adjuvant therapy in this population after curative resection of the primary tumour. Further updates are anticipated, as well as results from other adjuvant trials. Patients with high-risk tumours who have undergone complete resection should be encouraged to participate in clinical trials whenever possible.

Advanced (metastatic) kidney cancer

Enrolling patients in well-designed clinical trials should always be considered the first option for patients with advanced or metastatic RCC.

First-line therapy

- Targeted therapy is the preferred treatment (Table 1)
- In select patients, observation can also be considered, as some patients have slow growing asymptomatic disease
- High-dose interleukin-2 can be considered in highly selected patients

The field of systemic therapy is evolving quickly and the recommendations made in this document reflect the available evidence at the time the consensus conference participants reached their conclusions. As new data become available, treatment options will invariably change.

RCC is a heterogeneous disease and there are several prognostic factors that may help clinicians risk stratify their patients. These include clinical factors, such as patient performance status and laboratory parameters. The first of these prognostic scores was published by Motzer and colleagues and was used to define entry criteria or stratify for patient enrolment in clinical trials.[12] It is for this reason that treatment recommendations differ based on patient risk (Table 1). This prognostication system was developed in the cytokine era. In the targeted therapy era, Heng and colleagues have published a similar, but not identical, risk stratification score based on information obtained from the International Metastatic Renal Cell Database Consortium (IMDC), which is applicable to patients receiving targeted therapy today.[13]

Based on phase III clinical trial data, **sunitinib** produces higher response rates, improved quality of life, and a longer PFS than interferon-alfa in patients with metastatic clear cell RCC.[14] Subsequent survival analysis showed that patients treated with sunitinib had a longer overall survival than patients treated with interferon.[15] In addition, population-based studies from British Columbia and Alberta have shown an almost doubling of overall survival of metastatic RCC since the introduction of sunitinib and sorafenib.[16,17] The dose and schedule of sunitinib should be optimized for each patient in order to derive most benefit. This may require adjustments from the standard 4-week on/2-week off dosing schedule. Bjarnason and colleagues have published a single institution retrospective review of patients treated with

Table 1. Targeted therapy in various settings

Setting	Patients	Therapy (level 1 evidence)	Other options (<level 1 evidence)
Untreated	Good/ intermediate/ poor risk	Sunitinib Pazopanib Bevacizumab + IFN* Temsirolimus**	High-dose interleukin-2 Sorafenib Observation Sunitinib Pazopanib
Second line	Cytokine refractory	Sorafenib Pazopanib Axitinib	Sunitinib, bevacizumab + IFN*
	Prior VEGF targeted therapy	Everolimus Axitinib	Targeted therapy not previously used
	Prior mTOR		VEGFr TKI
Third line***	Any		Targeted therapy not previously used

IFN: interferon; VEGF: vascular endothelial growth factor; VEGFr: : vascular endothelial growth factor receptor; mTOR: mammalian target of rapamycin; TKI: tyrosine kinase inhibition. *The combination of bevacizumab + IFN has not been approved in Canada but is approved in the United States and Europe. **Temsirolimus is only an option in poorer risk patients as it was only studied in this population. ***At the present time, there is no Health Canada approved third line systemic therapy.

alternate dose and schedule of sunitinib compared to product monograph recommended dosing; they found improved PFS and OS compared to the standard dosing group.[18] A prospective clinical trial conducted across Canada examining this individualized dose titration scheme has completed enrolment and results are pending.

Based on phase III data**, pazopanib** produces an improvement in PFS compared to placebo in both cytokine naïve and refractory patients.[19] As first-line therapy, pazopanib has also been shown to be non-inferior to sunitinib with respect to PFS in the phase III COMPARZ clinical trial.[20] Toxicity profiles were different with sunitinib-treated patients experiencing more fatigue, hand-foot syndrome, and thrombocytopenia whereas pazopanib-treated patients experienced more abnormalities of hepatic transaminases.

Based on phase III data, **temsirolimus** produces an improvement in PFS and OS in poorer risk patients compared to interferon alone or the combination of temsirolimus and interferon.[21] Poorer risk was defined by at least 3 out of the following 6 criteria: Karnofsky Performance Scale (KPS) 60–70, ↑Ca++, ↓hemoglobin, ↑lactate dehydrogenase, <1 year from nephrectomy to treatment, or multiple metastatic sites. If temsirolimus is not available, everolimus should not be substituted. The RECORD-3 trial was a non-inferiority trial that examined sunitinib followed by everolimus at progression or the alternate order of drug administration in all risk groups of patients with metastatic kidney cancer.[22] Non-inferiority was not demonstrated and first-line PFS was inferior for patients starting with everolimus (7.9 vs. 10.7 months, hazard ratio 1.4 (confidence interval 1.2–1.8). Thus, data for first-line mTOR inhibitors only supports the use of temsirolimus. It should be noted that poorer risk patients were treated with VEGF-R TKI therapy on pivotal trials as well. The consensus was that these agents would still be preferentially used in patients whose poor clinical condition was due to extensive RCC and in those who needed a rapid response; individuals with comorbidities, apart from RCC, made them candidates for temsirolimus if it was felt they could not tolerate VEGF-R TKI therapy. In sunitinib intolerant patients, pazopanib or sorafenib remain good options.[23]

There is phase III data demonstrating that the combination of bevacizumab plus interferon improves PFS over interferon alone.[24,25] At this time, there has been no application submitted regarding bevacizumab for kidney cancer in Canada, and so it is not an option for Canadian patients.

In the opinion of attendees, an initial period of **observation** is a reasonable option in select patients given that no systemic therapies are currently considered curative, that all available treatments can be associated with side effects, and that some patients may experience an indolent clinical course with slowly growing asymptomatic metastases. This is supported by prospective observational data presented by Rini and colleagues.[26]

No phase III studies on the use of **interleukin-2** have shown an improvement in survival, and thus it is not considered a standard of care, but may be considered for highly selected patients. Based on phase II data, however, a very select group of patients may be considered for high-dose interleukin-2 (HD IL-2).[27] HD IL-2 must be delivered in specialized and experienced centres and ideally in the context of a clinical trial or investigational setting. Low-dose IL-2 should not be given.[28,29]

There is currently much research underway with new agents that modulate the immune system. Specifically, agents targeting the programmed cell death 1 receptor (PD-1) and its ligand (PD-L1), as well as the cytotoxic leukocyte antigen 4 (CTLA-4) pathways, have been examined. Ongoing trials are looking at these agents either alone or in combination with each other or other standard therapies in both first-line settings and beyond. While there is promising data so far, these agents remain experimental at this time.[30]

In patients with metastatic or advanced RCC with non-clear cell histology, enrolment in clinical trials should be encouraged. Other options include sunitinib, sorafenib, and temsirolimus (Table 2).[31-34] In patients with advanced or metastatic sarcomatoid or poorly differentiated RCC, options include sunitinib, sorafenib, chemotherapy, and temsirolimus (Table 3).[31-33,35] The ESPN trial was a randomized phase II trial of everolimus versus sunitinib as first-line therapy for

Table 2. Other options for patients with metastatic or advanced RCC[31-34]

Therapy	Rationale
Sunitinib	Based on subgroup analyses from the Expanded Access trial showing safety and activity
Sorafenib	Based on subgroup analyses from the ARCCS Expanded Access trial showing safety and activity
Temsirolimus	Based on subgroup analysis of phase III data

RCC: renal cell carcinoma; ARCCS: Advanced Renal Cell Carcinoma Sorafenib.

Table 3. Other options for patients with advanced metastatic sarcomatoid or poorly differentiated RCC[31-33,35]

Therapy	Rationale
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
Chemotherapy	Based on phase II data utilizing agents such as 5-fluorouracil, gemcitabine, doxorubicin, and combinations of these showing activity
Temsirolimus	Based on subgroup analysis from the pivotal phase III trial in which these patients were eligible

RCC: renal cell carcinoma; ARCCS: Advanced Renal Cell Carcinoma Sorafenib.

non-clear cell pathologies with crossover allowed at progression.[36] A futility analysis resulted in early termination of the trial due to inferior overall survival and PFS for everolimus, thus this agent cannot be recommended as first-line treatment for non-clear cell RCC.

When prescribing systemic therapy for advanced or metastatic RCC, several key factors must be taken into account. An oncology specialist knowledgeable about the acute and long-term toxicities, drug interactions, monitoring treatment and response, should prescribe therapy. 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, and their prevention, treatment, and management.

Progression on or intolerance to cytokines

Based on phase III data, **sorafenib** improved PFS compared to best supportive care alone in previously treated patients who had received interleukin-2 or interferon.[37] Overall survival data was confounded by crossover, but reached significance when censored for crossover. **Pazopanib** has also been studied in this patient population and produces an improvement in PFS compared to placebo.[19] **Axitinib** has also shown an improvement in PFS compared to sorafenib in this population. In the AXIS trial, about one-third of the subjects received first-line cytokines at the time of study enrolment and PFS was prolonged with the use of axitinib.[38] **Sunitinib** is an alternate treatment. Based on two phase II trials, **sunitinib** produced significant response rates and increased PFS compared to historical controls.[39]

Progression after first-line targeted therapy

- Clinical trials in this population should be supported as the optimal sequence of therapies is unknown.
- Switch to another targeted agent (Table 1)

Based on phase III data, **everolimus** (oral mTOR inhibitor) produced a significantly longer PFS than placebo, with an acceptable toxicity profile in patients who had failed sunitinib or sorafenib (or both).[40] Should everolimus not be available, temsirolimus should not routinely be substituted given its inferior outcomes when compared to sorafenib in this patient population, as shown in the INTORSECT study.[41]

Based on the phase III AXIS trial**, axitinib** has shown improved PFS compared to sorafenib as second-line therapy in patients progressing after first-line therapy with sunitinib and would be another reasonable second-line option.[38]

At this time, there is no evidence to help determine which second-line therapy after first-line VEGFr TKI is superior, thus everolimus or axitinib would be suitable choices. Treatment choices should be made based on toxicity, patient comorbidities, and patient preference.

In patients with advanced or metastatic RCC post-sunitinib or sorafenib failure, other options include **switching to another VEGFrTKI** (e.g., from sunitinib to sorafenib or from sorafenib to sunitinib) based on emerging data showing activity with sequential therapy.[42] The role of interferon post-targeted therapy is unclear.

For patients whose first-line therapy was an mTOR inhibitor, there is no level I evidence to guide treatment decisions in the second-line setting. The use of a VEGFr TKI in this setting is a reasonable option, however, this recommendation is based on less than level I evidence.[43]

At the present time, Health Canada has not approved any agents specifically in the third-line setting. However, there is data to support use of targeted therapies in this setting. In the RECORD-1 trial of everolimus versus placebo, 25% of subjects randomized had received two prior VEGFR TKI therapies prior to enrolment and there was a significant improvement in PFS for the group receiving everolimus.[40] Thus, everolimus would be a reasonable choice for patients in this setting.

Role of cytoreductive nephrectomy

- Cytoreductive nephrectomy should be considered in appropriately selected patients presenting with metastatic renal cell carcinoma

Recommendations for this section are based on level I evidence in patients treated with interferon. Appropriately selected patients for cytoreductive nephrectomy include: patients with a primary tumour amenable to surgical extirpation and a low risk of perioperative morbidity, patients with good performance status (ECOG 0 or 1), and patients without evidence of brain metastases.[28,43] It is important to ensure that patients undergoing cytoreductive nephrectomy are properly selected to maximize benefit and that there is a low risk of rapid disease progression that would require immediately starting systemic therapy.

Heng and colleagues recently published retrospective data from the International mRCC Database Consortium (IMDC) and found that patients undergoing cytoreductive nephrectomy in the targeted therapy era had improved survival compared to those who did not after controlling for IMDC risk factors (KPS <80%, diagnosis to treatment interval <1 year, hypercalcemia, neutrophilia, anemia, and thrombocytosis). Patients with four or more adverse risk features appeared not to benefit from cytoreductive nephrectomy.[44]

Two separate analyses of the Surveillance Epidemiology and End Results (SEER) database have also found that cytoreductive nephrectomy in the targeted therapy era is associated with improved patients outcomes.[45,46]

At this point, there is no prospective randomized data on the use of cytoreductive nephrectomy in the era of targeted therapy. Decisions are based on extrapolation from the interferon data, retrospective North American data showing improved outcomes in patients with cytoreductive nephrectomy prior to targeted therapy, the fact that most patients (>90%) enrolled in the VEGFr TKI phase III clinical trials had a prior nephrectomy, and clinical judgment.[12,21,35,47-49] Prospective studies on the benefit of cytoreductive nephrectomy are required and several trials are currently underway. Canadian investigators are participating in the EORTC 30073 SURTIME trial.

Given that trial results demonstrate a survival benefit for cytoreductive nephrectomy in the cytokine era and retrospective data showing the same in the targeted therapy era, Forum participants felt that until proven otherwise cytoreductive nephrectomy should be considered the standard of care for eligible patients. Patients being considered for cytoreductive nephrectomy should be reviewed by multidisciplinary tumour teams/boards to appropriately identify best candidates for surgery.

In patients who do not undergo upfront cytoreductive nephrectomy, but have a good response to VEGFrTKI or targeted therapy, limited metastatic disease and good performance status, it is reasonable that cytoreductive nephrectomy be considered in the course of their treatment.

The role of metastatectomy

- In select patients with limited sites of metastatic disease and clinical stability, resection of the metastatic disease may be reasonable.

There are no randomized trials showing the benefit of metastatectomy in RCC. However, among patients with metachronous metastases after nephrectomy, about one-third are eligible for metastatectomy and several large cohorts report 50% 5-year survival following complete resection of metastases.[42,50,51] Based on available observational data, patients most likely to benefit from metastatectomy are those diagnosed with metastases over 2 years following nephrectomy, those with isolated metastases, and those with favourable metastatic locations. A period of observation is reasonable to confirm that the metastatic disease is indolent.

The role of radiation therapy

- Radiation therapy may be considered to control bleeding and pain from the primary tumour, palliate symptoms from metastases, and stabilize brain metastases.

RCC is not a radio-resistant tumour and many patients can achieve palliation of symptoms related to their cancer through radiation therapy. New radiation techniques, such as stereotactic radiation therapy, may improve outcomes compared to traditional external beam radiation therapy; several ongoing trials are in progress.[52] Clinical trials involving radiation should be supported and a Canadian trial of stereotactic body radiation therapy in oligoprogression is underway.

The role of bone targeted agents for patients with skeletal metastases

About one-third of patients with metastatic RCC will develop bone metastases, which can lead to skeletal-related events (SRE), as part of their disease.[53] Currently available bone modifying agents have been shown to reduce SREs in this population. In a phase III trial of zoledronic acid versus placebo, a subset analysis of 74 RCC patients showed that administration of zoledronic acid compared to placebo resulted in a significant decrease in SREs in the zoledronic acid group (44% compared to 74% in placebo).[54] Specific results from this subgroup have been published separately and there was a significant reduction of SREs in the group receiving zoledronic acid 4 mg intravenously monthly compared to placebo.[55] Thus, monthly administration of zoledronic acid is a reasonable option. Careful monitoring of renal function is required. Patients receiving bisphosphonates 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 also important. Patients starting on any bone-targeted therapy should ensure they have had a thorough dental exam prior to starting therapy. Patients should also be monitored for osteonecrosis of the jaw while on treatment.

Denosumab is a receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor. In a phase III trial of denosumab versus zoledronic acid for treatment of malignancy with bone metastases (excluding breast or prostate cancer patients), a subset of patients enrolled on this trial had metastatic RCC. This trial demonstrated non-inferiority for denosumab compared to zoledronic acid in terms of SRE reduction for the group overall, although no subgroup analysis for RCC patients was done.[56] Thus, denosumab could also be considered a reasonable option for this population of patients. Calcium and vitamin D supplementation and careful serum calcium monitoring are also required for patients

receiving denosumab, as well as a thorough dental examination and monitoring for osteonecrosis of the jaw while on treatment

Summary

Advanced RCC has seen many treatment advances in the last several years, with the introduction of many targeted therapies. Therapy should be individualized based on patient risk and each agent chosen should be optimized in terms of dose and schedule to obtain maximal benefit. The optimal sequence of agents is still unclear and the subject of ongoing clinical trials. Multidisciplinary care is paramount in maximizing patient benefit. However, despite recent advances, many patients still die of metastatic RCC and ongoing support of clinical trials to further our knowledge in the field is essential.

Competing interests: Dr. North is a member of the advisory board for Astellas. He has also received grants from Astellas, Janssen and Sanofi and is currently participating in clinical trials with Janssen and Sanofi. Dr. Basappa is a member of the advisory boards for Pfizer, Novartis, Astellas, Janssen, Amgen, and Trelstar. He has also received grants from Pfizer, Novartis, Astellas, Janssen, and Amgen. Ms. Basiuk has received grants from Pfizer and Novartis. Dr. Bjarnason has received grants from Pfizer and is currently participating in a clinical trial with Pfizer. Dr. Breau has received a grant from Pfizer. Dr. Canil was a member of the advisory boards for Pfizer and was a member of the Speaker's bureau for Bayer. She has received a travel grant from Novartis and is currently participating in clinical trials with Novartis, Astellas, Pfizer, GSK, BMS and Bayer. Dr. Heng is a member of the advisory boards for Pfizer, Bayer, BMS, and GSK. Dr. Jewett is a member of the advisory boards for Pfizer and Novartis. He has also received grants from Pfizer and Novartis. Dr. Kapoor has received grants from Janssen Oncology, Novartis Oncology, Amgen and Astellas Oncology. He is also participating in multiple multicentre investigator-initiated trials. Dr. Kollmannsberger is a member of the Advisory Boards and Speakers' bureaus for Pfizer and Novartis. He is also currently participating in trials with Pfizer, Novartis, and BMS. Dr. Potvin is a member of the advisory board for Pfizer and has received a grant from Novartis. Dr. Reaume is a member of the advisory boards for Pfizer, Novartis, and GSK. Dr. Ruether is a member of the advisory boards for Pfizer and Novartis. He is also a member of the Speaker's bureau for Astellas. Dr. Venner is a member of the advisory board for Pfizer and has received honoraria from Janssen and Novartis. He is also participating in clinical trials with Pfizer, BMS, Astellas, Lilly, and Medivation. Dr. Wood is a member of the advisory boards for Pfizer and Astellas. She is also participating in clinical trials with Novartis, BMS, Merck, Pfizer, and GSK.

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