CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Request for Advice

Axitinib (Inlyta) for Metastatic Renal Cell Carcinoma

Kidney Cancer Canada

June 29, 2017

1 Stakeholder Feedback on a pCODR Request for Advice

Name of the drug indication(s): **metastatic renal cell carcinoma**

Name of registered patient advocacy group: Kidney Cancer Canada

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

1.1 Information to inform the Request for Advice

a) Please indicate your affiliation:

____ Submitter/Manufacturer ___X_ Patient Advocacy Group ____ Registered Clinician(s)

Please include name of your organization (or individual names for registered clinicians)
Kidney Cancer Canada

b) Please provide comments on the Request for Advice question(s).

On April 18, 2017, CADTH posted a Request for Advice (RFA) for axitinib (Inlyta) for metastatic renal cell carcinoma (MRCC) which was submitted to the pCODR Expert Review Committee (pERC) by the Provincial Advisory Group.

RFA Question from the Provincial Advisory Group:

Is there evidence to fund axitinib as an alternative to everolimus for the second-line treatment of metastatic clear cell renal carcinoma?

Background: The Kidney Cancer Research Network of Canada and The Canadian Kidney Cancer information system (CKCis)

In 2009, the Kidney Cancer Research Network of Canada (KCRNC), comprised of medical members, and patient members representing Kidney Cancer Canada (KCC), endorsed the establishment of a centralized Canadian kidney cancer database to collect data from medical centres across the country. This database project would be called the Canadian Kidney Cancer information system (CKCis).

CKC is is a web-based national registry supporting the development of clinical and basic research in kidney cancer across Canada. CKCis contains pertinent retrospective, as well as prospective de-identified patient data collected from consented patients who have been diagnosed and treated for renal cell carcinoma. Fifteen Canadian centres actively accrue kidney cancer patients into the CKCis registry. CKCis is a flexible database platform that can integrate different data needs to accommodate creative innovations considered for research. Data fields will be updated as new information emerges concerning the treatment of renal cell carcinoma. The information input into CKCis is used to carry out many research studies.

Supported by Kidney Cancer Canada, CKCis has now been in operation for over 5 years. As of 2017, more than 8000 patients have already been enrolled and their data is being collected. CKCis is now central to the activities of the KCRNC. The data has matured enough to inform the publication of several key manuscripts (see appendix A), with more in the pipeline. The network continues to bring all interested clinicians and researchers in kidney cancer together and supports the development of active kidney cancer research programs in Canada.

On April 19, 2018, Kidney Cancer Canada requested that CKCis investigators make as a research priority the question posed in the RFA: *Is there evidence to fund axitinib as an alternative to everolimus for the second-line treatment of metastatic clear cell renal carcinoma?* Here are their findings:

Title: Comparing outcomes of second line axitinib or everolimus in metastatic renal cell carcinoma patients: the Canadian experience.

Authors: Canadian Kidney Cancer information system Investigators

Background: In Canada, two of the approved therapies for second line (2^{nd}L) treatment of metastatic renal cell carcinoma (mRCC) [post first line (1^{st}L) VEGF targeted therapy (VEGF-TT)] include everolimus (EVE) and axitinib (AX). Although best available evidence suggests similar outcomes with the two drugs, the current pan-Canadian Oncology Drug Review (pCODR) recommendation states AX can only be used if there is intolerance or a contraindication to EVE. This study was designed to demonstrate that AX is an equivalent or superior alternative for the 2^{nd}L treatment so that AX could be equally accessible for mRCC patients across Canada.

Methods: Patient data were collected from the Canadian Kidney Cancer information system (CKCis), a prospective database of patients with mRCC in Canada. Patients who had prior 1^{st}L VEGF –TT, either sunitinib or pazopanib, and were subsequently treated with either 2^{nd}L AX or EVE were analyzed. Patients may have gone on to receive subsequent therapy after 2^{nd}L treatment. Time to treatment failure (TTF- time from starting 2L therapy to stopping 2L therapy or loss to follow up) and overall survival (OS – time from starting 2L therapy to death or loss to follow up) were calculated (Kaplan Meier method). Baseline data were also collected.

Results: CKCis identified 1168 patients treated with 1^{st}L sunitinib or pazopanib. The study cohort who went on to receive either 2^{nd}L AX or EVE consisted of 337 patients; 108 AX and 229 EVE. Baseline characteristics suggest balanced arms with the exception that more males were treated in the EVE group (p=0.015). The median TTF was greater for AX than EVE (5.45 months vs 3.78 months, p=0.034). There was no significant difference in median

OS between AX and EVE (10.91 months vs 14.29 months, p=0.158). More patients received further therapy in the EVE group than the AX group (45% vs 33%, p=0.031).

Conclusions: AX had a statistically better TTF than EVE in the 2nd L setting post 1st L VEGF-TT. Given this improved TTF, 2nd L AX should be considered an option for all patients in Canada post 1st L VEGF-TT without the limitations of the existing pCODR recommendation. Numerically, the EVE group had a better OS although this is not statistically significant. This is numerical difference is likely due to patients in the EVE group receiving more subsequent lines of therapy. As the OS outcome is influenced by treatment effect in both 2nd L and following treatment lines (3rd, 4th lines etc.), further investigation to jointly consider the effect of multiple treatment lines could be informative.

Questions: Should the pCODR Expert Review Committee have any questions regarding this study, please contact [redacted]

APPENDIX A - Journal Publications Informed by CKCis Data (To Date)

Lavallée LT et al. Surgical management of stage T1 renal tumours at Canadian academic centres. Can Urol Assoc J 2015;9(3-4):99-106.

Nayak JG et al. Clinical outcomes following laparoscopic management of pt3 renal masses: a large, multi-institutional cohort. Can Urol Assoc J 2015;9(11-12): 397-402.

Nayak JG et al. Pathological upstaging of clinical T1 to pathological T3a renal cell carcinoma: a multi-institutional analysis of short-term outcomes. Urology. 2016 Aug;94:154-60. doi: 10.1016/j.urology.2016.03.029.

Mason, R et al. The natural history of renal function after surgical management of renal cell carcinoma: results from the Canadian kidney cancer information system. Urol Oncol. 2016 Nov;34(11):486.e1-486.e7. doi: 10.1016/j.urolonc.2016.05.025. Epub 2016 Jun 22.

Richard PO, et al. Safety, reliability and accuracy of small renal tumor biopsies: results of a multi-institutional registry. BJUI 07 Sep 2016 doi: 10.1111/bju.13630.

Forbes, C et al. Disease progression and kidney function after partial vs. radical nephrectomy for T1 renal cancer. Urol Oncol. 2016 Jul 13. pii: S1078-1439(16)30115-6.

Lalani, AA et al. First-line sunitinib or pazopanib in metastatic renal cell carcinoma: The Canadian experience. Can Urol Assoc J 2017;11(3-4):112-7. http://dx.doi.org/10.5489/cuaj.4398

Appendix

Table 1: Baseline patient characteristics.

	Axitinib (n=108)	Everolimus (n=229)	Fisher exact test P Value
1L pazopanib 1L sunitinib	13% 87%	6.6% 93.4%	0.06
3L therapy	33.3%	45.4%	0.044
Median KPS	80	80	0.61 *
Low KPS	28.2%	28.6%	1
Male	87%	75%	0.015
Median age at 2L (yrs)	64.2	62.8	0.76 *
Elevated neutrophils	8.3%	5.3%	0.388
Elevated platelets	10.7%	11.1%	1
Elevated calcium	23.4%	18.8%	0.52
Low hemoglobin	81.1%	69.1%	0.074

*Wilcoxon non parametric test

Table 2. Toxicity that lead to a dose or schedule change.

	Axitinib (%)	Everolimus (%)	P value
Fatigue	29.6	14.4	0.002
Diarrhea	31.5	5.2	0.000
Nausea	15.7	1.3	0.000
Hypertension	11.1	1.7	0.000
Palmar-plantar erythrodysaesthesia	13.9	0.4	0.000
Abdominal Pain	3.7	0	0.01
Voice hoarseness	3.7	0	0.01
Sensory Changes	2.8	0	0.032
Pneumonitis	0	17.9	0.000
Oral mucositis	3.7	10.9	0.036
Limb edema	0	4.4	0.034
Anorexia	11.1	5.7	0.117
Weight loss	4.6	2.6	0.339
Dysguesia	1.9	0.9	0.596
Constipation	0.9	0.4	0.539
Dyspepsia	1.9	0	0.102
Dyspnea	5.6	6.6	0.813
Cough	0.9	5.2	0.069
Anemia	0	2.6	0.182
Elevated Creatinine	0.9	1.7	1.0
Hyperglycemia	0	1.7	0.310
Proteinuria	1.9	0.4	0.242

Note:

These results are as expected:

- More GI toxicity, rash, palmer-plantar erythrodysaesthesia and hypertension with Axitinib
- More pneumonitis, mucositis, edema with Everolimus

1 About Completing This Template

CADTH's pan-Canadian Oncology Drug Review program invites eligible stakeholders to provide feedback on the Request for Advice made by the pCODR Advisory Committee (PAC) or by the Provincial Advisory Group (PAG).

A Request for Advice is a written request made by PAC or by PAG, to the pCODR Expert Review Committee (pERC) for advice on specific therapeutic, clinical or pharmacoeconomic issues, or regarding a pERC Recommendation, which may result in a new Recommendation. The Request for Advice will be regarding a previous pERC Final Recommendation.

Stakeholders, including the submitter/manufacturer(s) of the drug(s) in question, patient advocacy groups and registered clinician(s) who provided input on the original submission in question are invited to comment or provide information using this template to help inform the question(s) or issue(s) raised by PAC or PAG ten (10) business days from the date of posting on the CADTH website.

When considering a Request for Advice, pERC may address the request by providing one of the following:

a) a revised pERC recommendation that would supersede a previous pERC Final Recommendation

b) a pERC Record of Advice document containing additional context and/or clarifications regarding a pERC Final Recommendation.

In either case, the pERC Record of Advice or revised pERC recommendation and supporting report will be posted ten (10) Business Days following the pERC Meeting on the pCODR section of the CADTH website.

2 Instructions for Providing Feedback on a pCODR Request for Advice

a) Only stakeholders who provided input on the original submission in question are invited to comment or provide information on the Request for Advice.

b) The template for providing *Stakeholder Comments on a pCODR Request for Advice* can be downloaded from the CADTH website. (See https://www.cadth.ca/pcodr/guidelines-procedures-and-templates for a description of the pCODR process and supporting materials and templates.)

c) At this time, the template must be completed in English. The comments should not exceed six (6) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed six pages, only the first six pages will be forwarded to the pERC.

d) Comments should be presented clearly and succinctly in point form, whenever possible. Comments must relate to the question at issue and the information provided must be made fully disclosable.

e) References to support comments may be provided separately.

f) The comments must be submitted via a Microsoft Word document to the pCODR program by the posted deadline date.

g) If you have any questions about the request for advice process, please e-mail info@pcodr.ca