PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Patient Advocacy Group Feedback on a pCODR Expert Review Committee Initial Recommendation

Axitinib (Inlyta) for mRCC

March 7, 2013

INQUIRIES

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Feedback on pERC Initial Recommendation

Name of the drug indication(s):	Axitinib (Inlyta) for metastatic renal cell carcinoma
Name of registered patient advocacy	Kidney Cancer Canada

1.1 Comments on the Initial Recommendation

a) Please indicate if the patient advocacy group agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part X disagree

- *Kidney Cancer Canada has learned from our experience with the Votrient/pazopanib recommendation (to which we "Agreed in Part") that there are serious implementation and practicality issues with this type of recommendation that perhaps were not foreseen by pERC at the time of that recommendation.*
- *The prior conditions of "intolerability" or "contraindication" to another agent (Votrient/pazopanib) have resulted in significant delays at the provincial level, with some provinces taking a year to further define those criteria, and many provinces stipulating the duration/dose/toxicity levels of the prerequisite drug.*
- *For patients, having to prove that they are first intolerable to a treatment means that, by virtue of having taken even one tablet, they have "burned through" another line of therapy. Serious repercussions include being excluded from subsequent lines of therapy and clinical trials.*
- *For rarer cancers such as renal cell carcinoma, the requirement for direct comparison trials to a current standard of therapy is unrealistic, especially in a rapidly evolving field. We believe that the only way forward with rarer cancers is to depend upon high-quality indirect comparisons that are performed to CADTH or international standards.*
- *Our Patient Evidence submission to pCODR was in favour of CHOICE and ACCESS. This recommendation as it stands will limit choice, delay access, and increase the burden of eligibility/proof for patients & treating oncologists.*

b) Notwithstanding the feedback provided in part a) above, please indicate if the patient advocacy group would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____	Support conversion to final recommendation.	X	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
1	pERC Recommendation	P1, L4	To the best of our knowledge, there is no medical evidence to support conditional use of axitinib/Inlyta only to those who "*are unable to tolerate ongoing use of an effective dose of everolimus or who have a contraindication to everolimus*". Please clarify the evidence basis for this condition.
1	pERC Recommendation	P1, L4	This "*unable to tolerate*" and "*contraindication*" condition needs further definition from pERC to further guide the provincial drug plans away from trying to define more rigorously "how much everolimus does the patient need to take first", "how intolerable?" (Grade 3 or 4 toxicities only?), and how will "contraindication" be defined? As is, the current recommendation will lead to significant delays in access, and potentially unnecessary and toxic treatments for the patient just to qualify. Worse, implementation of the current recommendation has potential to disqualify kidney cancer patients from future treatments and clinical trials, limiting their PFS and Overall Survival.
2	Summary of pERC Deliberations	P1, L7	Confusion over: "*pERC noted that sorafenib does not have regulatory approval in Canada in the second-line setting, and therefore, its use is limited. As a result, {...} considerable uncertainty when trying to determine the relative effectiveness...*" 1. This statement is incorrect. Sorafenib DOES have regulatory approval in Canada in the second-line setting. Please see Health Canada NOC: "sorafenib is indicated for the treatment of locally advanced / metastatic Renal Cell (clear cell) Carcinoma (RCC) in patients <u>who failed or are intolerant to prior systemic therapy</u>." {emphasis added} 2. We do not understand what pERC is saying here. The AXIS trial was a global study. Why and how does specific Canadian use of the control arm cause "considerable uncertainty" when reviewing the data?
2	Summary of pERC Deliberations	P5, L6	The pricing argument that "*if a higher dose of axitinib were used, as was done in a large proportion of patients on the AXIS study*" needs context. Our reading of the AXIS study is that while 37% of patients increased their dose, almost as many (31%) needed to be down-dosed. Has down-dosing been factored into your cost-effectiveness formula, or only the possibility of increasing dose?
3	Overall Clinical Benefit	P5, L3	"*pERC considered that {...} patients who had received prior sunitinib were the most relevant patient population.*" When considering prior agents with regulatory approval in Canada, we request that pERC provide some words of guidance to the provinces on the reality that many patients will have had first line Votrient (pazopanib) vs. sunitinib. With uncertainty acknowledged, we request pERC provide guidance to the provinces to ensure eligibility from the class of VEGF-TKIs, so to avoid blocking second-line treatment for those patients.

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
4	Overall Clinical Benefit	P1, L1 & P5, L1	"*However, pERC was challenged in determining how axitinib compared with everolimus, which is the most clinically relevant comparator*" & "*The main limitation identified by pERC in the evidence for axitinib is that there are not randomized controlled trials directly comparing it with everolimus, the current standard of care is the second line setting.*" The operative phrase here is "current standard of care". At the time the AXIS global trial began (2008), everolimus was an investigational agent in trials. In 2008, sorafenib was a reasonable treatment of choice following cytokine or sunitinib given the lack of other approved agents. For smaller patient populations, we feel it is unreasonable for pERC to expect head-to-head randomized controlled trials. No such trials for this small patient population are underway.

1.2 Comments Related to Patient Advocacy Group Input

Page Number	Section Title	Paragraph, Line Number	Comments related to initial patient advocacy group input
5	Patient-Based Values	P1, L3	While we appreciate that pERC noted "*a desire for choice in second line therapy*" from our submission, the recommendation as it currently stands will not support any CHOICE for the patient. As the conditions are further defined at the provincial level, patients will be forced to take everolimus first and then demonstrate an unacceptable level of toxicity. They may then be ineligible for 3rd line trials since, having been forced to take everolimus first, axitinib would be considered their third-line treatment. The current recommendation narrows options for our patients rather than facilitates 'a basket of choice' from Health Canada therapies in consultation with their oncologists.

1.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
4	Overall Clinical Benefit	P4, L1 & 26	We agree that well-designed and implemented head-to-head randomized controlled trials provide the most rigorous and valid research evidence to compare the relative effects of different treatments. However, with rarer cancers, evidence from head-to-head comparison trials is often limited or simply unavailable. As the number of available treatments for renal cell carcinoma increases, the costs to conduct head-to-head trials for all possible combinations and all potential sequences has become cost-prohibitive and not practicable for manufacturers or research centres. Internationally,

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			indirect comparisons have become acceptable if conducted to rigorous standards. Much work has been done in Canada to develop CADTH guidelines and to define the methodology for indirect treatment comparisons. We believe that Canadian decision- and policy-makers who make funding recommendations and decisions about health technologies have an obligation to assure Canadians that there is a fair basis for decision-making. That said, when direct evidence is not available, decision makers must accept indirect treatment comparisons as a legitimate method to compare efficacy and cost. Patients with rarer cancers such as mrcc should not face additional hurdles or be denied access to treatment due to reviewers' discomfort with levels of uncertainty. Patients with rarer cancers need pERC to recognize internationally-established standards for indirect comparisons, acknowledge uncertainty where uncertainty exists, but provide CHOICE and ACCESS to life-extending treatments. Thank you.