PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Axitinib (Inlyta) for mRCC

March 7, 2013

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s)	**INLYTA (axitinib)** is indicated for the treatment of patients with metastatic renal cell carcinoma (RCC) of clear cell histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI, sunitinib.
Role in Review (Submitter and/or Manufacturer):	Submitter and manufacturer
Organization Providing Feedback	Pfizer Canada Inc.

3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

_____ agrees _____ agrees in part __ X ___ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees, agrees in part or disagrees with the initial recommendation.

Pfizer commends pERC for including the patient perspective in the deliberative process and recognizing the need for therapeutic alternatives, such as axitinib (Inlyta™), for the treatment of advanced metastatic renal cell carcinoma (mRCC). However, Pfizer disagrees with pERC's initial recommendation to restrict funding for axitinib within a subset of second-line mRCC patients who are assessed as being everolimus-intolerant or who have a contraindication to everolimus.

The evidence submitted for review to pCODR supports the use of axitinib as an effective second-line treatment approach for mRCC after failure of front-line therapy. This evidence was recognized by both pERC and the Clinical Guidance Panel (CGP) as generated within a "clinically relevant" subset that is representative of the current Canadian clinical context (i.e. following failure of front-line therapy with a VEGFR TKI). Furthermore, the need for axitinib is supported by the substantial requests obtained from clinicians across the country through the Health Canada special access program (SAP). Therefore, Canadian mRCC patients should have access to unrestricted reimbursement for axitinib as a second-line treatment option.

The first major point of contention is with respect to the restricted recommendation by pERC, citing that:

- " *…the current evidence is insufficient to recommend funding axitinib broadly."*

It is our view that the above statement is in contradiction of the Clinical Guidance Panel's (CGP) evidence-based conclusion stating that:

- *"... all patients receiving any VEGFR TKI in the first line setting should be eligible to receive axitinib in the second line setting."*

Secondly, pERC noted the lack of a direct comparison between axitinib and everolimus as a limitation to funding axitinib in a second-line setting. Pfizer would like to highlight the rigor and appropriateness of the AXIS trial design that established superior efficacy versus an active comparator, sorafenib. This was duly noted by the CGP, which stated:

- *"...sorafenib was a reasonable choice for second-line."*

Contrary to the statement made by pERC, sorafenib has been granted marketing authorisation by Health Canada in the treatment of locally advanced and or metastatic clear cell RCC in patients who failed or are intolerant to prior systemic therapy. Furthermore, at the initiation of patient recruitment for the AXIS trial in 2008, both Canadian[i] and International[ii] guidelines recommended sorafenib as a treatment alternative in cytokine- or sunitinib-refractory patients. It is important to note that everolimus was an investigational agent at the initiation of the AXIS trial. It can be reasonably argued that an inequitable burden of evidence was placed on axitinib, given that everolimus' current standard of care placement is supported by a placebo- controlled trial. In fact, the AXIS trial has provided decision-makers with relevant evidence for patients after failure of front-line sunitinib due to the inclusion of a well-defined second-line population in the AXIS trial when compared to RECORD-1 (i.e. 13% of patients were second-line sunitinib-refractory in RECORD-1, relative to 54% in the AXIS trial).

Despite compelling and relevant direct comparative data, Pfizer provided indirect treatment comparisons between axitinib and everolimus recognizing the rapid and dynamic evolution of the RCC treatment paradigm. This ever-evolving treatment landscape justifies and actually requires the utilisation of analytical methodologies such as indirect comparison to simulate comparative data (i.e. STC) and provide alternative statistical methods where the sunitinib-refractory population is of interest, and mixed treatment comparison is challenging. Pfizer provided several scenarios attempting to adjust for differences between trials demonstrating greater efficacy. However, given the varying limitations of these comparisons, Pfizer conservatively assumed similar efficacy and neutralized axitinib's acquisition costs relative to everolimus. The overall rigor used in addressing potential uncertainty supports axitinib's reimbursement for patients in the second-line setting.

Evidence development and generation in oncology is rapidly dynamic with obvious challenges in study design and comparator selection. Therefore, it is our opinion that the burden of evidence should take into consideration the appropriateness of the study protocol and methodologies at the time of trial initiation. Contrary to pERC's recommendation, we believe the that evidence-based conclusion stated by the CGP did take into context the complexity and uncertainty associated with the ever-evolving landscape and therefore, supports axitinib use in the broad second-line population.

Pfizer acknowledges the need for therapeutic alternatives in everolimus-intolerant and contraindicated patients; however, the restricted initial recommendation must be addressed as the supporting arguments for the decision are not grounded on robust clinical evidence and pragmatic considerations. Firstly, the AXIS trial was not designed to specifically address the efficacy of axitinib in an everolimus-intolerant or contraindicated patient population. Moreover, there is currently no definitive trial data to support the superiority of the sequential approach to VEGF targeted therapy recommended by the pERC (i.e. VEGF targeted therapy to mTOR inhibitor). The rigid treatment algorithm suggested by pERC has the potential to impede the selection of the right treatment for the right patient.

Pfizer believes that there is substantial evidence to support axitinib in a broader second-line mRCC population and reiterate our agreement with the conclusion provided by the CGP that "[...] all patients receiving any VEGFR TKI in the first line setting should be eligible to receive axitinib in the second line setting." We request that pERC's recommendation be amended to reflect the CGP conclusion.

[i] *Canadian Kidney Cancer Forum 2008. Management of kidney cancer: Canadian Kidney Cancer Forum Consensus Statement. Can Urol Assoc J 2008 Jun; 2:175-82.*

[ii] *National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: kidney cancer. Version 1.2008.*

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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.

Recommendation does not require reconsideration by pERC

___X_ Do not support conversion to final recommendation.

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**
p.2	Summary of pERC deliberations	1st paragraph, line 7-10	*pERC noted that sorafenib does not have regulatory approval in Canada in the second-line setting and, therefore, its use is limited.* *Contrary to the statement made by pERC, sorafenib has been granted marketing authorisation by Health Canada. Sorafenib is indicated for the treatment of locally advanced / metastatic Renal Cell (clear cell) Carcinoma (RCC) in patients* ***who failed or are intolerant to prior systemic therapy.***