

# pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Request for Advice

## Axitinib (Inlyta) for Metastatic Renal Cell Carcinoma

Pfizer Canada Inc.

June 29, 2017

### 3 Stakeholder Feedback on a pCODR Request for Advice

Name of the drug indication(s): Axitinib (Inlyta) 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.

Organization Providing Feedback Pfizer Canada Inc.

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

#### 3.1 Information to inform the Request for Advice

a) Please indicate your affiliation:

Submitter/Manufacturer     Patient Advocacy Group     Registered Clinician(s)

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

Pfizer Canada

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

**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?**

Axitinib was established as an effective second-line treatment alternative to everolimus in a phase III randomized, comparator-controlled trial (the AXIS trial). Axitinib is recommended as a suitable treatment choice in mRCC with level 1 evidence in both international and Canadian guidelines based on the results of the AXIS trial. The AXIS trial remains the only Phase 3 randomized trial against an active comparator in a purely second-line setting in mRCC patients that have progressed after first-line TKI (sunitinib) or cytokines.

Clinical value of axitinib established in prospective Phase III RCT

The efficacy and safety of axitinib was evaluated in the second-line treatment of patients with mRCC who had previously failed one prior systemic first-line therapy in a phase III randomized trial, that compared axitinib (n = 361) to sorafenib (n = 362). The AXIS trial began enrolling patients in 2008; at the time, international and Canadian RCC treatment guidelines listed sorafenib as the treatment of choice for patients that had failed one prior

therapy (either cytokines or sunitinib). Everolimus was still an investigational agent and had only been compared to placebo.

The primary endpoint of the AXIS trial was met demonstrating a statistically significant improvement in PFS as assessed by a blinded Independent Review Committee (IRC). Axitinib prolonged median PFS by 2 months compared with sorafenib (median PFS 6.7 vs. 4.7 months,  $P < 0.0001$ ), and reduced the risk of disease progression or death by 33.5% (HR, 0.665; 95% CI, 0.544 to 0.812;  $P < 0.0001$ ). Objective response rate was defined as complete response (CR) plus partial response (PR) and was assessed by IRC according to the Response Evaluation Criteria in Solid Tumors (RECIST). Twice as many patients treated with axitinib achieved objective response compared with patients treated with sorafenib (risk ratio, 2.056; 95% CI, 1.408 to 3.003;  $P = 0.0001$ ). (Motzer et al, 2013b; Rini et al, 2011).

The phase III RECORD-1 trial leading to the approval of everolimus was a placebo-controlled trial following first-line treatment with sunitinib and/or sorafenib (Motzer et al, 2010), the study was further compromised by a 'mixed' study population in which a majority of patients had received everolimus as a third-line of treatment or later (327/416=78%) rather than a second-line of treatment (89/416=21%).

#### Comparative effectiveness between axitinib and everolimus

The table below provides a summary of these two trials in the second line setting and outlines the results from the subgroup analysis of patients who were pretreated with sunitinib in first-line which is most clinically relevant in the Canadian setting.

Trial	Subject	Patient group	ORR (%)	Median PFS (months)	Median OS (months)
RECORD-1 (everolimus vs placebo)	512	Overall	1.8% vs 0%	4.9 vs 1.9*	14.8 vs 14.4
		Sunitinib pretreated (43 vs 13)	NA	4.6 vs 1.8*	NA
AXIS (axitinib vs sorafenib)	723	Overall	19% vs 9%	6.7 vs 4.7*	20.1 vs 19.2
		Sunitinib pretreated (192 vs 195)	11.3% vs 8%	4.8 vs 3.4*	15.2 vs 16.5

\* denotes statistically significant differences

As shown on the table above, the sample size used to derive the evidence post TKI (sunitinib) is much larger in the AXIS trial with 387 patients as compared to the RECORD 1 trial, n=56. Pfizer acknowledges that naïve cross-trial comparisons between two agents should be interpreted with caution especially when differences in the patient populations were observed between the trials. The key difference between the two studies was the previous treatments that patients had received. Patients in the Axis study had received and failed either one prior cytokine (34%) or prior sunitinib (54%). While in the RECORD trial, 89

(21%) had received one prior systemic therapy, and 327 (79%) had received more than one treatment.

In the absence of a head-to-head trial, advanced analysis techniques and real world data allow for an indirect comparison of the two agents.

Two comparative effectiveness analyses, comparing axitinib and everolimus, have been published subsequent to the original pCODR recommendation in March 2013:

1) A Bayesian mixed treatment comparison of prospective randomized trials was fitted to assess relative effectiveness of four agents: axitinib, pazopanib, sorafenib and everolimus in the second-line setting. All four molecules were superior to placebo with respect to PFS. The indirect comparison suggested that axitinib provided the greatest benefit in term of PFS compared to other treatment options. Axitinib vs placebo: 0.36 (95%CrI: 0.27-0.48); vs pazopanib: 0.64 (95% CrI: 0.42 - 0.95); vs sorafenib: 0.70 (95% CrI: 0.57 - 0.87); vs everolimus 0.75 (95% CrI: 0.50 - 1.14), although no statistically significant difference was found between axitinib and everolimus. In addition, the indirect statistical analysis also revealed that the risk of treatment discontinuation was highest with everolimus and pazopanib. Odd-ratio (everolimus vs axintinib) for drug discontinuation: 4.0 (95% CrI: 1.2 to 14.5). ([Dranitsaris et al, 2013](#))

2) A retrospective chart review study was conducted by Vogelzang and colleagues to compare overall survival and progression-free survival of patients treated with everolimus and axitinib following first-line TKI therapy. After adjusting for patient characteristics, no statistically significant differences were found in OS or PFS between everolimus and axintinib. ([Vogelzang et al, 2016](#))

Further to these published comparisons, Pfizer has included two analyses using recent advanced methodologies that allow the indirect comparison of individual patient data from trials of one treatment to another. These techniques can address limitations that often arise in traditional meta-analyses based only on aggregate data.

Matched-Adjusted Indirect comparison (MAIC) and Simulated Treatment Comparison (STC) methods were used to compare axitinib to everolimus as treatments for sunitinib-refractory patients with mRCC in the second-line setting. The MAIC uses a model that calculates weights to be assigned to patients in the index trial (i.e., AXIS) to balance the populations in METEOR ([Choueiri et al, 2015 and 2106](#)). The STC method makes an adjustment through regression analyses by deriving a model for the outcome of interest based on the index trial and by applying the model to predict outcomes for index treatment in the comparator-like population. A detailed description of both methods is provided in in the appendix.

The effect of axitinib on PFS compared to everolimus was statistically significant using both methods, HR (95% CI) (MAIC: 0.48 (0.32, 0.73); STC: 0.52 (0.38, 0.71)). The analyses also suggested that axitinib was associated with a positive benefit on OS compared to everolimus with HRs range between 0.64 to 0.89, although not statistically significant when alternative MSKCC definition was used. ([Proskorovsky et al, 2016](#))

#### Evidence-based guideline recommendations

The National Cancer Comprehensive Care Network Guidelines (NCCN), recommend axitinib for second-line treatment with the highest level of evidence (category 1). In contrast, NCCN recommends the use of everolimus post-TKI with level 2A evidence, lower evidence

than axitinib.

The European Society of Medical Oncology (ESMO) guidelines (Escudier et al, 2016) recommend the use of both agents with level IIB evidence. The European Association of Urology (EAU) guidelines (Powles et al, 2016) recommend the use of axitinib as second-line option in VEGF-refractory disease, whereas everolimus should be considered only if other drugs are not safe, tolerable or available.

In Canada, the Canadian Kidney Cancer Forum consensus states that at the present time, there is no evidence to help determine which second-line therapy after 1st-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.

Taken together, the sum of the evidence supports the use of axitinib as an alternative treatment option to everolimus in the second-line setting for patients with mRCC previously treated with either sunitinib or cytokines. Pfizer requests that pERC's recommendation be amended by removing restricted reimbursement criteria, i.e. intolerant or contraindicated to everolimus, to make axitinib accessible to a broader second-line mRCC patient population as per the AXIS trial and the axitinib product monograph.

---

#### REFERENCE:

Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *The New England Journal of Medicine*. 2015;373(19):1814-23.

Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncology*. 2016;17(7):917-27.

Dranitsaris G, Schmitz S, Broom R. Small molecule targeted therapies for the second-line treatment for metastatic renal cell carcinoma: a systematic review and indirect comparison of safety and efficacy. *J Cancer Res Clin Oncol* (2013) 139: 1917-1926.

Escudier, B., et al. (2016). Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27(suppl 5): v58-v68.

Motzer RJ, Escudier B, Oudard S, et al and the RECORD-1 Study Group. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. *Cancer*. 2010;116(18).

Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*. 2013b;14(6):552-62.

Powles, T., et al. (2016). "Updated EAU Guidelines for Clear Cell Renal Cancer Patients Who Fail VEGF Targeted Therapy." *Eur Urol* 69(1): 4-6.

Proskorovsky I, Benedict A, Negrier S, Larkin J, et al. Axitinib (axi) and everolimus (eve) in the treatment of sunitinib-refractory (su-r) patients with metastatic renal cell carcinoma (mRCC): results of a matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC). Poster presentation at the 15<sup>th</sup> international kidney cancer symposium, Nov 4-5, 2016, Miami, Florida.

Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomized phase 3 trial. *Lancet*. 2011;378(9807):1931-9. Erratum in: *Lancet*. 2012 Nov 24;380(9856):1818.

Vogelzang N, Pal S, Signorovitch J, et al. Comparative effectiveness of everolimus and axitinib as second targeted therapies for metastatic renal cell carcinoma in the US: a retrospective chart review. *Current Medical Research and Opinion*. 2016; Vol 32. No.4, 741-747.

## 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.

### 1 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](mailto:info@pcodr.ca)