CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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Request for Advice

Axitinib (Inlyta) for Metastatic Renal Cell Carcinoma (mRCC)

Requestor:
pCODR Provincial Advisory Group (PAG)

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

June 29, 2017

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Drug	Axitinib (Inlyta)
Indication	Metastatic Renal Cell Carcinoma
Manufacturer	Pfizer Canada Inc.

1. Executive Summary

1.1 Context for the Request for Advice

PAG is seeking advice on funding axitinib as an alternative to everolimus for the second-line treatment of metastatic clear cell renal carcinoma, rather than only for patients who are intolerant to or have contraindications to everolimus. At the time of the pERC recommendation, there were no trials directly comparing the clinical effectiveness of axitinib with everolimus.

The interpretation of the pERC recommendation and the resulting funding criteria differs amongst the provinces. In some provinces, patients have a choice of everolimus or axitinib, while in other provinces, patients must have a trial of everolimus prior to requesting funding for axitinib.

pCODR Approach to the Request for Advice

A systematic review was undertaken to look for evidence for axitinib (Inlyta) as an alternative to everolimus (Afinitor) (i.e., evidence comparing axitinib with everolimus) for the treatment of second-line metastatic renal cell carcinoma, after failure of first line TKI.

Stakeholder input was provided by Pfizer Canada Inc., the manufacturer of axitinib, and Kidney Cancer Canada, who had provided input on the original pCODR review of Axitinib (Inlyta) for mRCC.

Results of the systematic review along with the stakeholder input were provided to the clinical guidance panel to provide their interpretation and guidance to PAGs request for advice.

Refer to Appendix 3 for methodology.

1.2 Summary of Findings

Based on the results of the systematic review, there is weak comparative evidence to suggest that axitinib is a reasonable alternative to everolimus in patients with metastatic renal cell carcinoma. The systematic review identified nine retrospective observational studies (four full publications and five abstracts) that reported consistent results to suggest that there is no statistically significant difference in the

effectiveness of axitinib versus everolimus. While there was consistency in the findings there are inherent limitations of retrospective observational studies, including selection biases of the included patient populations, potential for reporting bias of unknown outcomes, lack of confidence in assessment of exposure of each treatment, and the fact that non-randomized data is susceptible to bias from unknown confounding variables. Indirect treatment comparisons are also subject to additional limitations which included the lack of similarity between the intervention population and methodology of the studies, lack of consistency between indirect and direct evidence as well as lack of homogeneity between the treatment populations. Furthermore, as the studies were reported in abstract form only, and had limited or no information regarding important study design points and patient characteristics, it was not possible to adequately critically appraise those studies. Therefore, the results of the abstract-only studies should not be used for decision-making as it is not possible to ascertain whether any important biases or limitations are present or not.

In addition, Kidney Cancer Canada provided data from their Canadian Kidney Cancer Information System which reflects kidney cancer treatment practice in Canada. The data from their database supports the results of the systematic review.

1.3 Clinical Guidance Panel's Interpretation and Conclusion on Request for Advice

Based on the systematic review and input from the patient advocacy group, the Clinical Guidance Panel (CGP) concluded that there is sufficient evidence to conclude that axitinib is a reasonable alternative to everolimus for patients with metastatic renal cell carcinoma in the second-line setting after failure of a previous TKI (either sunitinib or pazopanib).

The CGP noted that there is no comparative randomized phase III study of axitinib versus everolimus and it is highly unlikely that there ever will be. They also noted that the benefit for everolimus and axitinib was shown independent whether first-line therapy consisted of sunitinib or pazopanib.

In making this conclusion, the CGP considered that:

- The randomized phase III AXIS trial[1] of axitinib versus sorafenib demonstrated a benefit for axitinib over sorafenib in the second line setting even when only patients with a prior TKI were considered.

- The real world evidence examining everolimus and axitinib in the second line setting consistently shows at least comparable and similar outcomes for axitinib as compared to everolimus with regards to efficacy after failure of a previous TKI.

- All these real world data sets are all potentially subject to various forms of bias, however they do reflect the real world experience and despite potential biases report consistent and comparable results irrespective of origin, number of patients, patient characteristics, study sponsor, etc.

- There are differences in toxicity between everolimus and axitinib but both drugs are associated with acceptable and manageable toxicity.

- Activity of axitinib and everolimus was similar and comparable independent of the previous TKI and the benefit appeared similar after prior sunitinib or pazopanib.

- Axitinib was associated with an improved time to treatment failure (TTF) as compared to everolimus in the Canadian patient population pretreated with either sunitinib or pazopanib while the toxicity of both drugs was consistent with the literature. These are results from the Canadian Kidney Cancer Information System which reflects kidney cancer treatment practice in Canada.

- Numerous reviews and expert opinions published over the past 5 years list axitinib and everolimus as equal alternatives for second-line therapy after failure of either sunitinib or pazopanib.

2. Background

Burden of Illness and Need

Kidney cancer accounts for approximately 4% of all cancers in Canada with approximately 90-95% being RCC. An estimated 6400 new cases (all stages) were diagnosed in 2016 with approximately 1850 deaths reported, highlighting the unfavourable prognosis of this disease and the need for more effective therapy.[2] At presentation, approximately 25% of patients with RCC have metastatic disease and at least 50% of all patients will eventually develop advanced disease. The estimated five-year survival across all stages is 67% but the prognosis for patients with metastatic disease remains poor with only a very few surviving longer than five years. Males are more frequently affected with a predominance of 1.8 to 1. Surgery remains the only curative treatment option and metastatic patients are generally considered incurable.

The management of metastatic RCC has undergone a significant shift in recent years due to advances in the understanding of the disease biology which has translated into the development of a number of novel targeted therapies as well as most recently immunotherapies. Targeted agents such as the small molecule tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib, axitinib, cabozantinib); the mTOR inhibitors (everolimus and temsirolimus); the monoclonal antibody bevacizumab and the programmed-death receptor 1 inhibitor Nivolumab have shown significant activity in the treatment of this disease.[1,3-10]

First line setting

In the first line setting, sunitinib and pazopanib are considered standard options. Sunitinib, a TKI targeting VEGF receptor types 1, 2, 3, PDGF receptors alpha and beta, c-kit and FLT-3, was tested in a large randomized phase III trial against interferon. Sunitinib demonstrated a median PFS benefit of 11 months versus 5 months for interferon ($P < 0.001$); and a median overall survival of 26.4 months versus 21.8 months ($P = 0.051$).[3,11]
Pazopanib, another multi-kinase inhibitor targeting the VEGF receptor, has also shown clinically significant activity in the first line setting based on superior progression-free survival (PFS) benefit compared to placebo in treatment-naïve or cytokine-pretreated RCC. Pazopanib has also been compared to sunitinib in the first line setting and demonstrated to be non-inferior, with a hazard ratio for PFS of 1.047. Median PFS was 8.4 months for pazopanib compared to 9.5 months for sunitinib. Median overall survival was 28.4 months for pazopanib vs. 29.3 months for sunitinib. Pazopanib did have a somewhat better toxicity profile with less hematologic toxicity, hand-foot syndrome, peripheral edema, taste alteration, rash and fatigue; although patients treated with pazopanib had worse hepatoxicity and weight loss.[9,12]

Second line Setting

In the second line setting where patients have progressed on first-line therapy with tyrosine kinase inhibitors, several therapeutic options exist.

Everolimus, an oral mTOR inhibitor was for a long time considered a standard option. In a randomized Phase III trial (RECORD-1)I, in TKI pre-treated patients, everolimus demonstrated a median PFS of 4.9 months versus 1.9 months for placebo, hazard ratio [HR], 0.33; $p<0.001$, leading to its approval in the second line setting.[4]
More recently, Nivolumab, a programmed death receptor 1 inhibitor has demonstrated superiority over everolimus in the second [after failure of one TKI], and third line [after failure of 2 prior TKIs] setting with a statistically significant and clinically meaningful benefit in overall survival (25.5 months vs. 19.6 months).[8] In addition, Nivolumab was significantly better tolerated then everolimus. Nivolumab is therefore considered a standard of care in the second and third line setting while Everolimus is no longer accepted as a standard second

line treatment option. Nivolumab has received Health Canada approval and was subsequently funded in Canada. A funding recommendation was made for the use of Nivolumab as second-line therapy after TKI failure or as third-line therapy after failure of two lines of TKI therapy.

Axitinib, a potent, highly selective small molecule tyrosine kinase inhibitor of multiple targets, including VEGFR 1-3, platelet derived growth factor receptor (PDGFR) and c-Kit, is considered an alternative treatment option in the second line setting after failure of a first-line TKI. This is based on a randomized phase III trial, which demonstrated a superior progression-free survival of axitinib over sorafenib [PFS 4.8 vs. 3.4months with a HR 0.74, 95% CI: 0.573-0.958, p=0.0107 based on 1-sided log-rank test stratified by ECOG performance status] and improved response rate [ORR 19.4% for axitinib vs. 9.4% for sorafenib; 1-sided p=0.0001].[1] It is important to note that this study chose an active comparator at a time when there was no generally approved second-line therapy after TKI failure. AXIS was the first targeted agent versus targeted agent study. Sorafenib was an appropriate choice for the comparator arm in the AXIS study because it had previously demonstrated superiority over placebo in cytokine pretreated patients and shown activity in patients with RCC refractory to sunitinib, bevacizumab, and ≥1 prior antiangiogenic agent.[13-16] In addition, at that time sorafenib was the most commonly used second-line therapy in clinical practice. At the time of initiation of the AXIS study, everolimus had not yet been evaluated and was not approved in the second line setting.

Axitinib has a Health Canada approved indication for use in patients with metastatic renal cell carcinoma (mRCC) of clear cell histology after failure of prior systemic therapy with a cytokine or sunitinib. The recommended dose is 5 mg administered orally twice daily. Patients who tolerate the starting dose with no adverse events for two consecutive weeks may have their dose increased to 7 mg twice daily and subsequently to a maximum of 10 mg twice daily. If a dose reduction is required, for example in the presence of adverse events, dosage may be reduced to 3 mg twice daily.

pCODR issued a funding recommendation for axitinib "as a second-line treatment for patients with metastatic clear cell renal carcinoma who, based on the mutual assessment of the treating physician and the patient, are unable to tolerate ongoing use of an effective dose of everolimus or who have a contraindication to everolimus".

pCODR Expert Review Committee Final Recommendation
The pCODR Expert Review Committee (pERC) recommends funding axitinib (Inlyta) as a second-line treatment for patients with metastatic clear cell renal carcinoma who, based on the mutual assessment of the treating physician and the patient, are unable to tolerate ongoing use of an effective dose of everolimus or who have a contraindication to everolimus. Funding in a broader patient population was not recommended because there is too much uncertainty that the effectiveness of axitinib is similar to everolimus, due to the lack of direct evidence from randomized comparative trials; however, there is a need for other options amongst patients who are either unable to tolerate or who have a contraindication to everolimus. Therefore, while current evidence is insufficient to recommend funding axitinib broadly, pERC considered that there is a need for axitinib in the subgroup of patients defined above and that this would align with patient values. This recommendation assumes similar pricing of standard dosing of the two therapies. pERC did not recommend axitinib as an alternative to everolimus or as a third-line option for patients whose disease progresses while receiving everolimus because there was insufficient clinical trial evidence to support these options.

Axitinib access has been implemented differently among provinces. Some provinces reimburse axitinib according to the pERC Final Recommendation while others give the treating physician the choice and reimburse either everolimus or axitinib, but not both sequentially.

In addition, in 2016, METEOR, a randomized phase III trial comparing the efficacy and safety of cabozantinib versus the mTOR inhibitor everolimus was published. The trial enrolled patients with advanced renal cell carcinoma who progressed after previous VEGFR tyrosine-kinase inhibitor treatment. A total of 658 patients were randomly assigned to cabozantinib (n=330) or everolimus (n=328). With a median duration of follow-up of

18.7 months and 18.8 months for cabozantinib and everolimus, respectively, the median overall survival in the everolimus group was 16.5 months (14.7-18.8) and in the cabozantinib group was 21.4 months (95% CI 18.7-NE) with a HR of 0.66 [95% CI 0.53-0.83];p=0.00026. Cabozantinib also resulted in an improvement in PFS, with a HR of 0.51 [95% CI 0.41-0.62];p<0.0001.[17]

The primary conclusions of the Clinical Guidance Panel for the 2013 pCODR clinical review of axitinib (Inlyta) for mRCC were as follows:

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to axitinib in the treatment of patients with refractory metastatic RCC based on the results of the AXIS trial, a Phase III, high-quality randomized controlled trial. On the basis of the AXIS trial, the similar biology and activity of VEGFR TKIs in the first line setting, and the need to provide metastatic RCC patients with effective treatment options, the Panel concluded that all patients receiving any VEGFR TKI in the first line setting should be eligible to receive axitinib in the second line setting.
In making this conclusion, the Clinical Guidance Panel also considered that from a clinical perspective:

- Patients with advanced disease who progress on first line sunitinib or first line pazopanib or other first line VEGFR TKI have limited treatment options and a poor overall prognosis. The only drug approved in the second line setting is everolimus which is not effective in all patients highlighting the need for alternatives in this setting.
- Axitinib has greater efficacy than sorafenib, a multi-targeted TKI in the second line setting. This was seen in both the cytokine pre-treated and the TKI/mTOR pre-treated population subgroups.
- The improved efficacy was not achieved at the expense of increased toxicity and the safety profile of axitinib has been well characterized to ensure that axitinib can be administered safely to patients with advanced RCC.
- Axitinib demonstrates some differences compared with sorafenib; some toxicities are more frequent (e.g. hypertension, dysphonia, and hypothyroidism) and some toxicities are less frequent (e.g. hand-foot syndrome, rash, and alopecia) for axitinib than sorafenib.
- Although the currently standard second line treatment in Canada is everolimus, there are no ongoing or planned direct head to head Phase III trial comparisons of axitinib vs. everolimus. At the time the AXIS trial was initiated everolimus was not available and sorafenib was considered a reasonable choice for second line.
- Most Canadian patients receive sunitinib in the first line setting and some are beginning to also receive pazopanib. Although cross-study comparisons have limitations, in the subset of sunitinib-refractory patients axitinib likely does provides a meaningful benefit in comparison to everolimus for patients who have progressed on sunitinib.
- Patients receiving axitinib on the AXIS trial (comparing axitinib to sorafenib) were limited to one prior regimen which may or may not have contained a TKI and were as a result less heavily pre-treated than patients on the RECORD 1 trial (comparing everolimus vs. placebo). As a result patients on the AXIS trial may have had slightly better outcomes, the limitations of cross trial comparisons notwithstanding.
- Results of the INTORSECT study comparing sorafenib to temsirolimus as second line treatment reported that PFS was not statistically significant.[18] Overall survival was statistically significant favouring the sorafenib patients.[18] Interpretation of these results cannot be made as the details of the trial have not been published but may provide some evidence of no difference in PFS between a VEGFR inhibitor and an mTOR inhibitor.

3. Stakeholder Feedback

Stakeholder Input was provided by two groups. Pfizer Canada Inc., the manufacturer of axitinib (Inlyta) and Kidney Cancer Canada, who had submitted patient input for the axitinib (Inlyta) pCODR review. The information pertaining to the request for advice is provided below as it was provided by the stakeholder.

3.1 Manufacturer Stakeholder Feedback on RFA from Pfizer Canada Inc.

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%CI 0.27-0.48); vs. pazopanib: 0.64 (95% CI: 0.42 - 0.95); vs. sorafenib: 0.70 (95% CI: 0.57 - 0.87); vs. everolimus 0.75 (95% CI: 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% CI: 1.2 to 14.5). [19]

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 axtinib following first-line TKI therapy. After adjusting for patient characteristics, no statistically significant differences were found in OS or PFS between everolimus and axintinib.[20]

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 sunitinb-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.[10,17] 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.[21]

3.2 Patient Advocacy Group Stakeholder Feedback on RFA from Kidney Cancer Canada

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 (2ndL) treatment of metastatic renal cell carcinoma (mRCC) [post first line (1stL) 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 2ndL 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 1stL VEGF –TT, either sunitinib or pazopanib, and were subsequently treated with either 2ndL AX or EVE were analyzed. Patients may have gone on to receive subsequent therapy after 2ndL 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 1stL sunitinib or pazopanib. The study cohort who went on to receive either 2ndL 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 2ndL setting post 1stL VEGF-TT. Given this improved TTF, 2ndL AX should be considered an option for all patients in Canada post 1stL 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 2ndL and following treatment lines (3rd, 4th lines etc.), further investigation to jointly consider the effect of multiple treatment lines could be informative.

Table 1: Toxicity that lead to a dose or schedule change:

	Everolimus (%)	Axitinib (%)	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

Baseline patient characteristics for patients included in the Canadian Kidney Cancer information system were also provided by the Kidney Cancer Canada:

Table 2: 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

4. Systematic Review

4.1 Objectives

To evaluate the effect of axitinib on patient outcomes compared to everolimus as second line treatment of patients with advanced/ metastatic renal cell carcinoma.

4.2 Methods

4.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol for the request for advice was developed jointly by the Clinical Guidance Panel and the pCODR Team. Studies were chosen for inclusion in the review based on the criteria in the table below.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCTS, published: • Non-randomized clinical trials • Observational studies Exclusions: • Case Reports	Patients with advanced renal cell carcinoma who have failed first line treatment <u>Sub-group analysis</u>: By prior treatment	Axitinib monotherapy	mTOR inhibitors • Everolimus*	• Overall survival • Progression free survival • Tumour response • Dosing regimen modifications • QoL • SAE • AE (hypertension, diarrhea, fatigue) • WDAE
AE=adverse events; **BSC**=best supportive care; **mTOR**=mammalian target of rapamycin; **QoL**=quality of life; **RCT**=randomized controlled trials; **SAE**=serious adverse events; **VEGFR**=vascular endothelial growth factor receptor; **WDAE**=withdrawal due to adverse events				

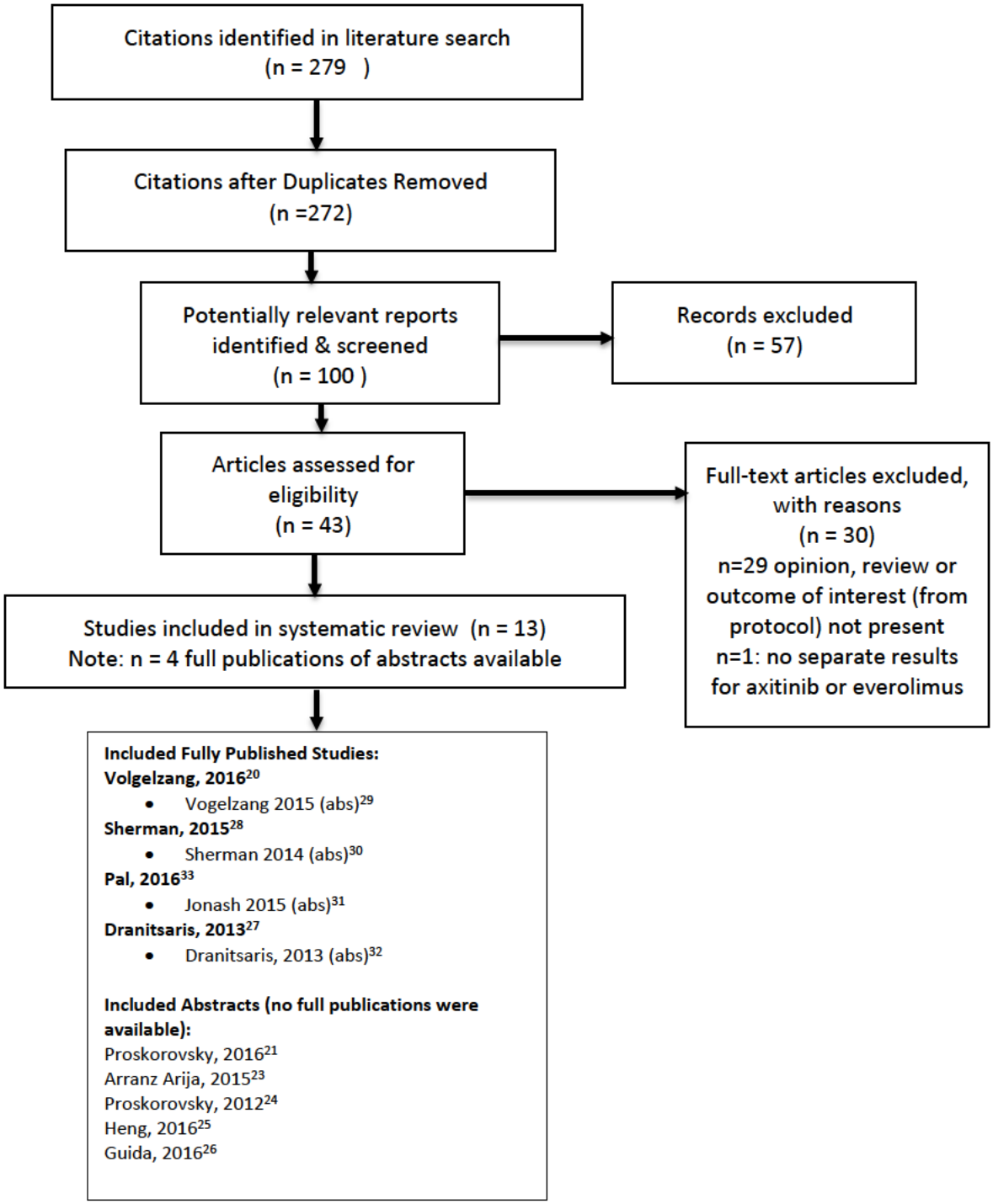
** As per PAG request for advice*

4.3 Results

4.3.1 **Literature Search Results**

Of the 43 potentially relevant reports identified, 9 studies were included in the pCODR systematic review[20-28] and 30 studies were excluded. Studies were excluded because the primary outcome was not of interest or they were opinions and/ or review papers. Of the included studies, four abstracts had full publications available as such nine unique studies were included in the systematic review.

Figure 1. Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



4.3.2 Summary of Included Studies

Nine studies were included, four of which were fully published and five were abstract only publications. All of the included studies were observational retrospective studies.

4.3.2.1 Detailed Trial Characteristics

The table below highlights key trial characteristics between all included studies.

Table 4: Summary of Trial Characteristics of the Included Studies

Study Design	Inclusion Criteria	Intervention and Comparator	Outcomes
Fully Published Studies			
Pal et al., 2016[33] Retrospective Chart Review Each eligible physician randomly selected up to 5 patients meeting pre-specified inclusion criteria N of patients receiving everolimus: 325 N of patients receiving axitinib: 127 Multivariate Cox proportional hazard model was used to compare PFS between everolimus and axitinib. The model was adjusted for age, gender, the presence of hyperchlolesterolemia, ECOG performance status, the presence of aRCC at initial diagnosis, prior nephrectomy, type and duration of first targeted therapy, clinical benefit while on first targeted therapy (physician assessed), duration of aRCC at second targeted therapy initiation, sites of metastases, tumor histological type (clear cell RCC or other), and years of practice treating physician.	Inclusion criteria patients: (1) Age ≥ 18 years (2) Discontinuation of first TKI (sunitinib, sorafenib, or pazopanib) (3) Initiation of axitinib or everolimus as a second targeted therapy during Feb 2012 - Jan 2013 Inclusion criteria oncologist/hematologist (1) Have treated ≥ 3 patients with advanced RCC in the past year	Everolimus (10mg once daily) or Axitinib (5mg twice per day) Note: 14% of patients started at a higher dose of axitinib and 7% of patients started on a lower than recommended dose of everolimus.	PFS Drug Costs
Sherman et al., 2015[28] Indirect Comparison (Bayesian Model) Individual patient level data from RECORD-1 and AXIS trials was used	RECORD 1 & AXIS trial sunitinib refractory second-line treatment populations	Everolimus vs. Axitinib dosing as per trial (AXIS & RECORD 1)	PFS

Study Design	Inclusion Criteria	Intervention and Comparator	Outcomes
A Bayesian latent class mixture model differentiating responders and non-responders and with imbedded Weibull regression on PFS was used to identify sex, Memorial Sloan-Kettering Cancer Center risk score, and time receiving prior sunitinib therapy as prognostic factors for PFS based on posterior probability > 95%. Patients taking everolimus were weighted up or down based on their combination of prognostic variables Weights were calculated by dividing the proportion of patients observed in AXIS for a given characteristic by the proportion observed in RECORD-1 and taking the product of the values derived for all three weighting variables considered. Weighted PFS distributions were derived with bootxrapped 95% CIs and compared with those reported for the AXIS trial RECORD 1 - patients treated with everolimus N = 271 (patients had multiple prior lines of treatment) Of those, n= 43 patients taking everolimus second line who were sunitinib refractory AXIS - patients treated with axitinib N = 194			
Vogelzang 2016[20] Retrospective Chart Review Medical Oncologists and hematologists/oncologists were screened from June 2014 to July 2014 Physicians randomly selected and abstracted data for up to five patient charts	Inclusion Criteria Patients: Patients were ≥ 18 years To have had an mRCC diagnosis Received a TKI (sunitinib, sorafenib, or pazopanib) as first targeted therapy To have discontinued that therapy for medical reasons	Axitinib Everolimus	OS PFS

Study Design	Inclusion Criteria	Intervention and Comparator	Outcomes
To compare effectiveness of everolimus and axitinib , unadjusted multivariable Cox proportional hazards models were used to estimate the hazard ratios and associated 95% CI for OS and PFS Patient data was anonnymized and non-identifiable everolimus n = 325 axitinib n = 127	Patients were required to have initiated either everolimus or axitinib between Feb 1 2012 and Jan 2013 Inclusion Criteria for Physicians: ≥ 3 mRCC patients treated in the last year Exclusion Criteria for patients: Initiated second targeted therapy as part of a clinical research protocol, used interleukin 2 prior to or in combination with the first TKI for the treatment of mRCC Used combination therapy with ≥ 2 targeted agents as first of second targeted therapy		
Dranitsaris 2013[27] Systematic review and Indirect treatment comparison Bayesian MTC models were fitted to assess comparative Effectiveness axitinib n = 361 everolimus n= 272	Inclusion Criteria: Systematic Review of databases from Jan 2005 to June 2013 for randomized controlled trials evaluating at least one of the four agents in 2nd line mRCC	Axitinib Pazopanib Sorafenib Everolimus	Tumour Response PFS Grade II/IV toxicities Treatment Discontinuations
Abstract-only Publications			
Guida et al., 2016[26] Patient characteristics, safety and outcome data from all mRCC pts who received Everolimus or Axitinib as second line from April 2007 to May 2015 have been compared OS and PFS were assessed by KM method and compared with log-rank test	Not Reported	Everolimus Axitinib	Median PFS Median OS Disease Control Rate Partial Response

Study Design	Inclusion Criteria	Intervention and Comparator	Outcomes
everolimus n = 81 axitinib n = 45 Median follow up - 29 months			
Proskorovosky 2016[21] Match Adjusted Indirect Treatment Comparison everolimus n = 328 axitinib n = 76	Patient data from AXIS & Record Trials	Everolimus Axitinib	PFS OS
Heng et al., 2016[25] Retrospective Chart Review Charts were reviewed for adult mRCC patients satisfying the eligibility criteria KM curves were used to estimate OSD everolimus n = 99 axitinib n = 91	Inclusion Criteria (1) Experienced disease progression on 1st targeted therapy with sunitinib or pazopanib (2) Initiated 2nd targeted therapy with EVE, Axi or SOR between 10/2012 and 6/2013	Everolimus Axitinib Sorafenib	Site of Metastases Median OS Rate of Dose Increase
Proskorovsky et al., 2012[24] Simulated Treatment Comparison Sunitinib refractory patients in RECORD1 & AXIS trial were included STC method used to derive OS and PFS curve Parametric survival analysis identified the best fitting distribution and significant predictors of OS and PFS everolimus n = 124 axitinib n = 194	Patients Inclusion (1) Sunitinib refractory patients were included	Everolimus Axitinib	PFS OS

Study Design	Inclusion Criteria	Intervention and Comparator	Outcomes
Arranz Arija et al., 2015[34] SPAZO study - Spain Retrospective Review Study analyzed the effectiveness of 1st line Pazopanib and subsequent therapies in mRCC in daily clinical practice Data from all patients treated with front line pazopanib until June 2014 in 34 centres in Spain were retrospectively collected Second line patients n = 119 patients N everolimus = 48 N axitinib = 27	Not Reported	Everolimus Axitinib	Median OS Median PFS

a) Studies

The majority of included studies were retrospective chart reviews, with the exception of one match adjusted indirect comparison (MAIC), one simulated treatment comparison and an indirect treatment comparison.

The included studies were from US (n=2), UK & Germany & France (n=1), France (n=1), Spain (n=1) and the remainder were indirect treatment comparisons of the AXIS, METEOR or RECORD1 trials.

The included abstracts did not mention funding sources; however, it is important to note that three of the four included full text publications, were funded by Novartis Pharmaceuticals, the manufacturer of everolimus.[20,33,35]

The simulated treatment & match adjusted treatment comparisons were funded by Pfizer.[21,24]

b) Populations

The sunitinib refractory patient populations from the AXIS (range from n=76 to n=194) and RECORD 1 (range from n=43 to n =328) and METEOR (range from n =76 to n = 194) were used for matching in the indirect treatment comparisons.[21,24,28]

For the retrospective chart reviews, patients included were 18 years or older and were eligible for second line targeted therapy after failure of first line TKI targeted therapy. Please see below for a high level overview of patient characteristics from the included full studies:

Table 5: Baseline Patient Characteristics Across Studies

Included Publications	# of patients	Male	Female	Follow-Up Time	Age at Diagnosis	Number of Prior Lines of Therapy	ECOG Status	Clear Cell Renal Cell Carcinoma (RCC)
Pal 2016[33] N = 452	Axi n=127	NR	45 (35%)	Mean:13 (SD: 7)	60 (9%)	1	0: 43 (34%) 1:64 (50%) 2+ :20 (16%)	111 (87%)
	Eve n=325	NR	96 (30%)	Mean:15 (SD: 7)	61 (%)	1	0: 99 (30%) 1: 163 (50%)	274 (84%)

Included Publications	# of patients	Male	Female	Follow-Up Time	Age at Diagnosis	Number of Prior Lines of Therapy	ECOG Status	Clear Cell Renal Cell Carcinoma (RCC)
							2+: 63 (19%)	
Sherman 2015[28] N = 237	Axi: N=194	74	26	NR	61 (20-82)	1	0: 52 1:48 >1:0	NR
	Eve N=43	65	35	NR	58 (32-79)	1	0: 48 1:52 >1:0	NR
Vogelzang 2016[20]	Axi N=127	NR	96 (30%)	13 (7)	60 (9)	1	0:43 (34%) 1:64 (50%) 2+ :20 (16%)	274 (84%)
	Eve N=325	NR	45 (35%)	15 (7)	61 (9)	1	0: 99 (30%) 1: 163 (50%) 2+: 63 (19%)	274 (84%)
Dranitaris 2013[27]	Axi N = 361	NR	NR	NR	61	1	Trials Enrolled patients with ECOG 0-1	As per AXIS trial
	Eve N= 272	NR	NR	NR	61	1	Trials Enrolled patients with ECOG 0-1	As per RECORD1 trial
**Guida 2016[26] N=126	Axi N= 45	NR	NR	NR	54(24-75)	1	≥2: 8	42 (93.3%)
	Eve N = 81	NR	NR	NR	57(26-76)	1	≥2: 12	74 (91.4%)
**Heng 2016[25]	Axi N = 91	65.5%	NR	NR		NR	≤2: 91.8%	NR

Included Publications	# of patients	Male	Female	Follow-Up Time	Age at Diagnosis	Number of Prior Lines of Therapy	ECOG Status	Clear Cell Renal Cell Carcinoma (RCC)
N = 281	Eve N= 99				Mean: 60.6			NR
**Proskorovsky 2012[24] N= 318	Axi N=194	NR	NR	NR	NR	NR	0:52%	As per AXIS Trial
	Eve n = 124						0:60%	As per RECORD 1 Trial
**Arranz Arija 2015[23] N=278	Axi n =27	68.9%	NR	23 months	65 (26-92)	NR	≤ 1: 83.2%	94.1%
	Eve n = 48							
**Proskorovsky 2016[21]	Axi: 76	As per AXIS trial	As per AXIS trial	As per AXIS trial	As per AXIS trial	As per AXIS trial	As per AXIS trial	As per AXIS trial
	Eve: 328	As per METEOR trial	As per METEOR trial	As per METEOR trial	As per METEOR trial	As per METEOR trial	As per METEOR trial	As per METEOR trial

c) Interventions

As the systematic review protocol was developed specifically to identify studies comparing axitnib with everolimus, only studies comparing axitinib with everolimus were included as interventions for the included studies.

Of the included indirect treatment comparisons, the dosing schedules of the included trials were assumed.[21,22,27,28]

Of the included retrospective chart reviews, three of the studies did not comment on the dosing regiments of axitinib or everolimus.[20,23,26] Of the two studies that reported on dosing, Pal et al., commented that the large majority of everolimus treated patients (91%) started on the recommended dose of 10mg once per day started on a higher than recommended dose and 7% started on a lower than recommended dose. Of the patients treated with axitinib, 84% started on the recommended dose of 5mg twice per day, while 14% of patients started on a higher than recommended dose and 2% started on a lower than recommended dose.[33] Heng et al. reported that patients receiving axitinib had a higher rate of dose increase (13.2%) compared to everolimus (1.0%), while patients on everolimus had a higher rate of dose decrease (12.1%), compared to axitinib (5.5%).[25]

d) Patient Disposition

Patients included in the retrospective chart reviews were mostly TKI refractory, second-line patients who were being treated either with a TKI or mTOR inhibitor in second line.

Patients included in the Indirect Treatment Comparisons were from the METEOR, RECORD1 and AXIS trials. For a direct comparison, patients who were sunitinib refractory from the RECORD1 trial were used for comparison with the sunitinib refractory AXIS trial patients. Patient characteristics from the METEOR trial were matched to the patient characteristics of the AXIS trial.[21,24,28]

It is important to note that for the Match Adjusted Indirect Comparison, the entire patient population from the METEOR trial was used to match the patient population in AXIS. Of the METEOR patient population 30% of patients received two or more prior VEGFR therapies.[21]

e) Limitations/Sources of Bias

There are no randomized controlled trials evaluating the use of axitinib versus everolimus, the present report summarizes data from retrospective chart reviews and four indirect treatment comparisons.

Below are key limitations of the included studies, separated by type of study included. Further details can be located in Table 1 of Appendix 1.

Limitations of Retrospective Cohort studies:

1. Selection bias
    a. The included studies selected patient populations that are comparable; however, it is unclear how the charts would have been selected for assessment by the oncologists. It is also important to note that the majority of retrospective

reviews included patients who had treated more than three patients with mRCC. The likelihood that these patients would have been seen by the physician is high. Due to the lack of information provided in the abstracts a conclusion on how study evaluators sought to mitigate selection bias cannot be made.

2. Assessment of Blinding
    a. The authors of the included studies did not report whether they considered differences in blinding between the randomized trials and the impact this could have on the results.
3. Lack of confidence in assessment of exposure
    a. The doses and length of exposure for each intervention are not provided for the included retrospective studies. Differences in exposure between interventions have the potential to bias the results.
4. Handling of known confounders in non-randomized studies
    a. It is not clear how potential known confounders were taken into consideration due to the limited amount of information available in the included abstracts.
5. Non-randomized data leading to unknown confounding variables
    a. There exists a potential for bias (of unknown direction and magnitude) due to inability of non-randomized study designs to control for unknown confounding factors.
6. Potential Reporting Bias
    a. There may be outcome measures that were not reported in the included studies as the current systematic review could only assess the available information from the abstracts.
7. Unknown Follow up time of cohorts
    a. The follow-up time of each cohort was unknown. Different follow up times for each study could potentially bias the results to favour one treatment over the other. Without this information, a determination of whether there would be an impact and what that impact might be cannot be made.

Limitations of Indirect Treatment Comparisons:

1. Lack of Similarity between populations
    a. For the fully published included studies, though the study authors attempted to match populations using propensity scoring, the populations were not clinically and methodologically similar. As such, these clinical and methodological differences could bias the study results. For the included abstracts, a comment on similarity between populations could not be made due to the lack of available information.

2. Lack of Consistency between Evidence
    a. There are no direct trials evaluating the use of axitinib versus everolimus. The included studies did not have a common treatment arm either. The AXIS trial compared axitinib to sorafenib, and the RECORD 1 and METEOR trials compared everolimus to placebo and cabozantinib, respectively. Therefore it was not possible to assess consistency between direct and indirect estimates of effect for axitinib compared with everolimus.

3. Lack of Homogeneity between Study Estimates
    a. Both Proskorovsky studies used matching techniques to compare the patient characteristics of everolimus and axitinib. In 2012, the authors used the RECORD1 everolimus population which was sunitinib refractory, which partially aligned with the AXIS trial since 54% of patients had previous systematic therapy with sunitinib; however, in 2016, they used the full METEOR population (n=328) to match to the axitinib population. This is a major limitation, as the METEOR trial included patients with one or more prior lines of therapies, whereas the AXIS trial included patients who progressed on first-line therapy containing sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines. A comment on the treatment effect measures could not be made.
4. How Outcomes were Assessed
    a. A description of the precise criteria used to identify the outcomes and the schedule of outcome assessment for each study were not reported in the included studies

Given the lack of information in the included abstracts it is not possible to assess the important considerations above and conclude if the analyses were appropriately conducted. This is a major limitation since matching will not solve the underlying limitations associated with differences in the areas noted.

4.3.3.3 Detailed Outcome Data and Summary of Outcomes

Table 6 below outlines the overall survival and progression free survival data from the included studies.

Table 6: Summary Table of Outcome Data

Study	Study Design	OS			PFS		
		Axitinib	Everolimus	HR/ p-value	Axitinib	Everolimus	HR/ p-value
Fully Published Studies							
Vogelzang 2016[20] N everolimus= 325 N axitinib = 127	Retrospective Chart Review *Analysis through Multivariate Cox Proportional Hazard Ratios	Rates at 12 months: 83% (95% CI, 74-89%)	Rates at 12 months: 80% (95% CI, 75-84%)	Before Adjusting: HR[95%CI]: 1.02 [0.67 - 1.55] After Adjusting: HR[95%CI]: 1.16 [0.74-1.82]	Rates at 12 months: 56% (95% CI, 47-65%)	Rates at 12 months: 60% (95% CI, 54-65%)	Before Adjusting: HR[95%CI]:1.07 [0.70-1.64] After Adjusting: HR[95%CI]:1.16[0.85-1.59]
Sherman et al., 2015[28] N everolimus = 43 N axitinib = 194	Indirect comparison	NR	NR	NR	Median of 4.8 months (95% CI, 4.5-6.4 months)	Median of 4.7 months (95% CI, 3.5 – 10.6 months)	NR

Study	Study Design	OS			PFS		
		Axitinib	Everolimus	HR/ p-value	Axitinib	Everolimus	HR/ p-value
Dranitsaris 2013[27] N everolimus: 272 N axitinib: 361	Systematic Review *Bayesian MTC	NR	NR	NR	NR	NR	1.32 (95% CrI, 0.88-2.0)
Pal et al., 2016[33] N everolimus = 325 N axitinib = 127	Retrospective Chart Review	NR	NR	NR	NR	NR	HR = 1.16; 95% CI = 0.73 – 1.82
Abstract-only Publications							
Guida et al., 2016[26] N everolimus = 81 N axitinib = 45	Retrospective Chart Review	Median of 14.9 months	Median of 21.5 months	P = 0.23	Median of 7.7 months	Median of 5.3 months	P=0.39
Heng et al., 2016[25] N everolimus = 99 N axitinib = 91	Retrospective Chart Review	Median of 23.5 months	Median of 23.0 months	NR	NR	NR	NR
Proskorovsky et al., 2012[24] N everolimus = 124 N axitinib = 194	Simulated Treatment Comparison	Median of 15.2 months	Median of 10.6 months	NR	Median of 5.1 months	Median of 3.6 months	NR

Study	Study Design	OS			PFS		
		Axitinib	Everolimus	HR/ p-value	Axitinib	Everolimus	HR/ p-value
Proskorovsky 2016[21] N everolimus = 328 N axitinib = 76	Match Adjusted Indirect Comparison	Median of 23.8 (CI[a]: 15.7 – NE) months	Median of 16.5 (CI[a]: 14.7-18.8) months	Adjusted HR = 0.64 (CI[a]: 0.45 – 0.91)	Median of 7.8 (CI[a]: 6.3 – 13.9) months	Median of 3.7 (CI[a]: 1.9-4.2) months	Adjusted HR = 0.48 (CI[a]: 0.32 – 0.73)
Arranz Arija et al., 2015[23] N everolimus = 48 N axitinib = 27	Retrospective Chart Review	Median of 9.4 (7.2-11.6)	Median of 8.5 (6.5 – 10.4)	NR	Median of 6.5 (3.2-9.7)	Median of 4.7 (2.7-6.7)	NR

[a] Size of the confidence intervals was not reported

Summary of Efficacy Outcomes

Progression Free Survival & Overall Survival

Of the included full publications, two studies conducted indirect treatment comparisons. The PFS for everolimus was 4.7 months (3.5-10.6) and axitinib was 4.8 months (4.5-6.4).[28] Dranitsaris (2013), reported the HR for PFS as inconclusive, at 1.32 (0.88-2.0).[27]

Proskorovsky, in 2012 and 2016 conducted two different indirect treatment comparisons. The first was a simulated treatment comparison which showed median OS for axitinib to be 15.2 months and everolimus to be 10.6 months, with a PFS of 5.1 months and 3.6 months, respectively.[24] In 2016, a match adjusted indirect treatment comparison was conducted which showed median OS of 16.5 months (CI: 14.7-18.8) for everolimus and 23.8 months (CI: 15.7 – NE) for axitinib, with a HR: 0.64 (CI:0.45-0.91). The median PFS for the MAIC, was 3.7 months (CI: 1.9-4.2) and 7.8 months (CI 6.3-13.9) for everolimus and axitinib, respectively, with a HR: 0.48 (0.32-0.73).[21]

Of the included fully published retrospective chart reviews, the overall survival rates at 12 months were 83% (95%CI:74-89%) for axitinib and 80% (95%CI 75-84%) for everolimus, with a HR: 1.02 (0.67-1.55) before adjusting and HR= 1.16 (0.74-1.82) after adjusting.[20] The progression free survival at 12 months was 56% (95%CI: 47-65%) and 60% (95%CI: 54-65%) for axitinib and everolimus, respectively.[20] The unadjusted HR for PFS = 1.07(0.74-1.84) and adjusted HR = 1.16(0.55-1.82).[20] Pal et al., 2016, also looked at the comparative efficacy of everolimus vs. axitinib and the adjusted HR for PFS was 1.16 (0.85 – 1.59).[33]

Of the retrospective chart review abstracts, median OS ranged from 8.5 months (6.5-10.4) to 23 months for everolimus and 9.4 months (7.2-11.6) to 23.5 months for axitinib.[23,25,26] Median PFS for everolimus ranged from 4.7 (2.7-6.7) months to 5.3 months and median PFS for axitinib was 6.5 (3.2-0.7) to 7.7 months.[23,25,26] In Arranz-Arija et al (2015), the one year OS was reported at 40.2% (95% CI, 29% to 53%) for everolimus and 32.6% (95% CI, 8% to 56%) for axitinib.[23]

Quality of Life

Quality of life was not reported in any of the publications and abstracts.

Quality of Life data was also not included in either of the stakeholder inputs from the manufacturer or patient advocacy group.

Dose Modifications

Heng et al, 2016 reported that patients on Axitinib had a higher rate of dose increase (13.2%) compared to everolimus (1.0%). Patients on everolimus had a higher rate of dose decrease (12.1%) compared to axitinib (5.5%).[25]

Harms Outcomes

No Harms Outcomes were identified in the included published studies. However, Dranitaris et al., 2013, did report that patients treated with axitinib would be at a greater risk of fatigue. However, results were inconclusive when compared to everolimus.[27] Adverse event information was also provided by the Kidney Cancer Canada as part of their stakeholder input. Please see Section 3.2.

Additional Outcomes Reported

Additional outcomes of interest are captured in Table 7 below. These included disease control rates, dose modifications, adverse event data, and responses rates, where available.

Table 7: Additional Outcomes Reported Including Harms

Study	Additional Reported Outcomes of Interest
Vogelzang 2016[20] Everolimus, n=325 Axitinib, n=127	N/A
Sherman et al., 2015[28] Everolimus, n=43 Axitinib, n=193	N/A
Dranitsaris 2013[27] Everolimus, n=272 Axitinib, n=361	Odds Ratio for Tumor Response for Eve Vs. Axi: 0.24 (0.02-5.0) Adverse Events: Odds Ratio for everolimus vs. axitinib for drug discontinuations: 4.0 (1.2 to 14.5) Relative Risk for diarrhea, Fatigue, hand-foot syndrome, rash and stomatitis were inconclusive for everolimus and axitinib.
Pal et al., 2016[33] Everolimus, n=327 Axitinib, n=127	N/A
Guida et al., 2016[26]	Disease Control rate was 69% and 73% (p=0.31) and partial response achieved was 4% and 24% (p=0.002) for everolimus and axitinib, respectively
Heng et al., 2016[25]	Patients on Axitinib had a higher rate of dose increase (13.2%) compared to everolimus (1.0%). Patients on everolimus had a higher rate of dose decrease (12.1%) compared to axitinib (5.5%).
Proskorovsky et al., 2012[24]	N/A
Proskorovsky 2016[21]	N/A
Arranz Arija et al., 2015[23]	Response rates were reported with stable disease as percentages. 40.6% for everolimus and 44.4% for axitinib.

5. Discussion

5.1 Clinical Interpretation and Guidance

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

Evidence:
The evidence for axitinib as second-line therapy comprises of the randomized phase III AXIS study as well as a number of real world data sets examining everolimus and axitinib in the second-line setting. In addition, various expert opinions and guidelines from different groups have been published over the past 5 years.

AXIS study: Phase III randomised study of axitinib versus sorafenib in pretreated metastatic RCC patients

1. In the primary analysis of the AXIS study, a statistically-significant and clinically-meaningful improvement in PFS with axitinib compared to sorafenib was observed [median PFS 6.7 vs.4.7 months, hazard ratio (HR) 0.665, 95% CI: 0.544-0.812, p<0.0001)].[1]

2. Pre-specified subgroup analysis of PFS supported the primary analysis, with all hazard ratios favoring axitinib regardless of ECOG performance status, prior therapy (with the exception of bevacizumab, which is not used in Canada), race, gender, age, MSKCC status, and geographic region.[1,36]

3. In the subgroup of patients progressing on sunitinib (N=389), which would represent the majority of Canadian patients, a statistically-significant and clinically-meaningful change in progression free survival was observed in patients treated with axitinib compared to sorafenib [PFS 4.8 vs 3.4months with a HR 0.74, 95% CI: 0.573-0.958, p=0.0107 based on 1-sided log-rank test stratified by ECOG performance status].[1,36]

5. The ORR (complete response [CR] plus partial response [PR]) favoured axitinib; ORR was 19.4% for axitinib vs. 9.4% (1-sided p=0.0001) for sorafenib with a median duration of response of 11 months (95% CI: 7.4, not estimable) and 10.6 months (95% CI: 8.8, 11.5) for axitinib and sorafenib, respectively.[1,36] It is important to note that axitinib did have an objective response. For patients with symptomatic disease, objective responses can lead to symptomatic improvement. In the first line setting, objective responses to sunitinib have been correlated with better overall outcomes.[11]

6. In this study, OS was a secondary endpoint. The median OS was 20.1 months for axitinib arm and 19.2 months for sorafenib, stratified HR 0.969 (95% CI: 0.800-1.174) with a p-value of 0.374 based on a 1-sided log-rank test. Although traditionally considered the endpoint for drug approval, OS is a now challenging endpoint in RCC where there are multiple subsequent treatment options after a patient comes off trial, which could impact OS.

7. Toxicity for axitinib was acceptable and well manageable with this phase III study.[1]

Overall AXIS was a well conducted study. Patients were well balanced in terms of demographics and disease characteristics and would be generalizable to the Canadian population. The majority of patients had received prior sunitinib reflecting not only global practice patterns, but also what is done typically across most centres in Canada. Since sunitinib and other regimens are widely available this study was conducted as a global study including the US, European Union, and Asia, making the results quite generalizable. As discussed above, sorafenib was an appropriate choice for the comparator arm at that time.
Real World Evidence Comparing Axitinib to Everolimus:

A number of real world data sets have been published which examine the efficacy of axitinib and everolimus.

Dranitsaris examined the outcomes of second-line therapies based on data from randomized trials with a Bayesian mixed treatment comparison model. He demonstrated that axitinib and everolimus were superior to placebo in the second-line setting. There was no difference in efficacy between everolimus and axitinib but risk for discontinuation appeared higher with everolimus.[19]

Similar results were reported by Sherman et al. After aligning patient characteristics for patients from the RECORD-1 and AXIS trial using a weight-adjusted indirect comparison no differences in outcomes between everolimus and axitinib treated patients were seen.[28]

Vogelzang undertook a comparative effectiveness analysis between everolimus and axitinib using Cox Proportional Hazard models. Patients treated with everolimus (n=325) and axitinib (n=127) were randomly selected from across the US by oncologists treating more than 3 patients a year. Seventy-three % of patients and 20% were pretreated with suntinib and pazopanib, respectively. After adjusting for patient characteristics no differences were observed in outcomes. Type of first-line TKI (pazopanib or suntinib) did not influence the results.[20]

Heng et al evaluated PFS and OS in 115 everolimus treated and 98 axitinib treated European patients using Kaplan-Meier analyses, and compared across cohorts using multivariable Cox proportional hazards models. Patients had been previously treated with sunitinib (80%) and pazopanib (20%). No statistically significant differences in OS or PFS were observed among patients treated with everolimus or axitinib, and no difference was observed between patients with prior sunitinib or pazopanib.[35]

Similar results were published by Guida et al. Axitinib exhibited a significantly higher response rate of 24.4% versus 3.7% for everolimus, which is in line with other published data.[26]

Arranz et al reported second-line outcomes in a Spanish cohort with 278 patients previously treated with pazopanib. Forty-five % and 24% of patients were treated with everolimus and axitinib, respectively. Tumor control rate and overall survival were similar among patients treated with everolimus and axitinib while progression free survival was numerically longer on the axitinib group. With a tumor control rate of 55%, a median PFS of 5.7 months and an overall survival of 10 months, these results are comparable to the results seen for second-line therapy after sunitinib.[34]

Proskorovsky et al recently conducted a Matching Adjusted Indirect Comparison (MAIC) and Simulated Treatment Comparison of axitinib and everolimus as second-line therapy. MAIC and STC adjust for differences in patient populations and therefore minimize its impact on outcomes. Patient data were extracted from the AXIS and METEOR study, a randomized phase III trial comparing cabozantinib to everolimus in TKI pretreated patients. Axitinib appeared to be associated with a significant longer PFS as compared to everolimus in this analysis.[21]

Of particular interest is a recently performed analysis in a Canadian patient population, since it reflects the current practice in Canada and real world outcomes in Canadian patients across the country. The Canadian Kidney Cancer Information System is a Canada wide data base which collects data on kidney cancer patients and their treatment. The majority of patients were pretreated with sunitinib while a smaller portion of patients underwent first-line pazopanib. Axitinib was given second line in 108 patients while everolimus was used in 229 patients. Time-to-treatment failure was longer in the axitinib group while OS was similar in both groups. Please see section 3.2.

Although multivariate models account for some biases, all of these studies have the limitations of retrospective and non-randomized data. This includes potential patient selection bias, missing data, lack of standardized inclusion criteria, lack of uniform response criteria, missing central review of data and unknown confounding factors due to the lack of randomization.

However, it is noteworthy and remarkable that the results are consistent across all of these studies. All studies report at least similar OS and PFS outcomes for axitinib and consistently improved response rates as compared to everolimus. Most of these studies did not report on toxicity since toxicity is known for both patients and deemed to be acceptable and manageable with either drug.

Published Guidelines:

It is also important to note that virtually every guideline and in particular the most commonly used and internationally accepted guidelines in the world recommend axitinib and everolimus as equal second-line options after prior failure of sunitinib or pazopanib. This includes the European Urology Association Guideline, the European Society of Medical Oncology Guideline, the Canadian Consensus Guideline and the National Comprehensive Cancer Network Guidelines (NCCN).[37-41] All of these guidelines have formed their recommendations based upon the above summarized evidence coupled with a consensus opinion from kidney cancer experts.

6. Clinical Guidance Panel Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit to axitinib in the treatment of patients with refractory metastatic RCC and based on the currently available evidence there is sufficient proof to fund axitinib as an alternative to everolimus in the second-line setting after failure of a previous TKI (either sunitinib or pazopanib).

It is important to note there is no comparative randomized phase III study of axitinib versus everolimus and it is highly unlikely that there ever will be.

However, the Clinical Guidance Panel is of the opinion that there is appropriate real world evidence and expert judgement to justify axitinib as an equal alternative to everolimus in the second line setting.

It is also important to note that the benefit for everolimus and axitinib was shown independent whether first-line therapy consisted of sunitinib or pazopanib.

In making this conclusion, the Clinical Guidance Panel considered that:

- The randomized phase III axis trial of axitinib versus sorafenib demonstrated a benefit for axitinib over sorafenib in the second line setting even if only patients with a prior TKI were considered.

- The real world evidence examining everolimus and axitinib in the second line setting consistently shows at least comparable and similar outcomes for axitinib as compared to everolimus with regards to efficacy after failure of a previous TKI.

- All these real world data sets are all potentially subject to various forms of bias, however they do reflect the real world experience and despite potential biases report consistent and comparable results irrespective of origin, number of patients, patient characteristics and study sponsor, etc.

- There are differences in toxicity between everolimus and axitinib but both drugs are associated with acceptable and manageable toxicity.

- Activity of axitinib and everolimus was similar and comparable independent of the previous TKI and the benefit appeared similar after prior sunitinib or pazopanib.

- Axitinib was associated with an improved TTF as compared to everolimus in our Canadian patient population pretreated with either sunitinib or pazopanib while the toxicity of both drugs was consistent with the literature. These are results from the Canadian Kidney Cancer Information System which reflects kidney cancer treatment practice in Canada.

- Numerous reviews and expert opinions published over the past 5 years list axitinib and everolimus as equal alternatives for second-line therapy after failure of either sunitinib or pazopanib

- All important guidelines including the Canadian, European and US NCCN list axitinib and everolimus as equal second-line treatment options after failure of either sunitinib or pazopanib.

- All real world evidence as well as expert opinion and published guidelines do not differentiate between first-line TKIs and recommend axitinib or everolimus as equal options after either sunitinib or pazopanib.

Appendix 1- Critical Appraisal of Included Studies

Select quality characteristics of included studies for the Axitinib mRCC Request for Advice based on the Cochrane Tool to Assess Risk of Bias in Cohort Studies & Modified ISPOR Checklist

The Retrospective Chart Reviews were appraised using the SIGN50 Checklist for Cohort Studies

1. SIGN50 Questions	Volgelzang, 2016[20] (Fully Published)	Pal, 2016[33] (Fully Published)	Guida, 2016[26] (Abstract)	Heng, 2016[25] (Abstract)	Arranz Arija, 2015[23] (Abstract)
	Responses can be from the following: ✓ Yes X No ? Can't Say N/A Not Applicable for Retrospective Studies				
2. The study addresses an appropriate and clearly focused question.	✓	✓	✓	✓	✓
3. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	✓	✓	✓	✓	✓
4. The study indicates how many of the people asked to take part did so, in each of the groups being studied.	?	✓	X	X	X
5. The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	?	?	?	?	?
6. What percentage of individuals or clusters recruited into each	N/A	N/A	N/A	N/A	N/A

arm of the study dropped out before the study was completed.					
7. Comparison is made between full participants and those lost to follow up, by exposure status.	N/A	N/A	N/A	N/A	N/A
8. The outcomes are clearly defined.	✓	✓	✓	✓	✓
9. The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	N/A	N/A	N/A	N/A	N/A
10. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	X	X	X	X	X
11. The method of assessment of exposure is reliable.	✓	✓	✓	✓	✓
12. Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	X	X	X	X	X
13. Exposure level or prognostic factor is assessed more than once.	✓	✓	?	?	?
14. The main potential confounders are identified and taken into account in the design and analysis.	? Unclear if the stratified Analysis of previous sunitinib has been adjusted	?	?	?	?
15. Have confidence intervals been provided?	✓	✓	✓	X	X

16. How well was the study done to minimise the risk of bias or confounding?	High quality (++) ☐ **Acceptable (+) X** Unacceptable – reject 0	High quality (++) ☐ **Acceptable (+) X** Unacceptable – reject 0	High quality (++) ☐ **Acceptable (+) X** Unacceptable – reject 0	High quality (++) ☐ **Acceptable (+) X** Unacceptable – reject 0	High quality (++) ☐ **Acceptable (+) X** Unacceptable – reject 0
17. Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	? Note: wide confidence intervals. Subgroups suggestive but small number of patients. Patient selection, missing data, and unknown and residual confounding	?	? Note: Baseline patient characteristics are different	?	? Note: small number of patients
18. Are the results of this study directly applicable to the patient group targeted in this guideline?	✓	✓	✓	✓	✓
19. **Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	No statistical difference	PFS did not differ significantly between interventions	No statistical difference between OS and PFS between Axi and Eve	Numerically comparable results for Eve and Axi	Both Axitnib and Everolimus are effective after pazopanib

The Indirect Treatment Comparisons were appraised using an adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Metaanalysis

ISPOR Questions	Sherman, 2015[28]	Dranitsaris, 2013[19]	Prokorovsky, 2016[21] (Abstract)	Prokorovsky, 2012[24] (Abstract)
	Responses can be from the following: ✓ Yes X No ? Can't Say N/A Not Applicable for Indirect Treatment Comparison			
1. Is the population relevant?	✓	✓	✓	✓
2. Are any critical interventions missing?	X	X	X	✓
3. Are any relevant outcomes missing?	✓ (only PFS assessed)	✓ (OS not included)	✓ (AEs not included)	X (AEs not included)
4. Is the context (e.g., settings and circumstances) applicable to your population?	✓	✓	✓	✓
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	?	✓ (Systematic Review was conducted)	X (RECORD1 data not Included)	? (METEOR was not included)
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	X	X	N/A	N/A
7. Is it apparent that poor quality studies were included thereby leading to bias?	?	?	N/A	N/A
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	?	✓ Baseline Patient Characteristics Not Reported	✓	✓
9. Are there systematic differences in treatment effect	✓	?	✓	✓

modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?				
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	✓	?	✓ (adjusted for baseline patient characteristics)	✓
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	?	?	?	?
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	X	✓	?	?
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	X	X	N/A	N/A
14. With inconsistency or an imbalance in the distribution of	✓	✓	✓	✓

treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?				
15. Was a valid rationale provided for the use of random effects or fixed effect models?	N/A	N/A	N/A	N/A
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	N/A	N/A	N/A	N/A
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	N/A	?	✓	?
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	X	✓	N/A	N/A
19. Are the individual study results reported?	X	✓	X	No
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	N/A	N/A	N/A	N/A
21. Are all pairwise contrasts between interventions as obtained with the	N/A	✓	✓	X

network meta-analysis reported along with measures of uncertainty?				
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	N/A	✓	N/A	N/A
23. Is the impact of important patient characteristics on treatment effects reported?	X	?	X	X
24. Are the conclusions fair and balanced?	?	?	?	?
25. Were there any potential conflicts of interest?	✓ Funded by Novartis	X	✓ Funded by Pfizer	✓ Funded by Pfizer
26. If yes, were steps taken to address these?	?	X	?	?
27. Comments	Authors report there is no difference between everolimus and axitinib; however, only report median PFS for each group and no Hazard Ratios were calculated. MSKCC was used to weight estimates but it was very different across trials, which would bias estimates	Inconclusive comparison for Eve vs. Axi for Safety and PFS	Sunitinib refractory mRCC patients treated with Axi may have a statistically significant improved PFS and OS compared to patients treated with eve.	Sunitinib refractory mRCC patients treated with Axi may have improved PFS and OS compared to patients treated with eve.

ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; ORR = objective response rate; PFS = progression-free survival; OS = overall survival; AE = adverse event.

Appendix 2: pERC Recommendation
pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Axitinib (Inlyta) **Submittter's Funding Request:** 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.	
Submitted By: Pfizer Canada Inc.	**Manufactured By:** Pfizer Canada Inc.
NOC Date: July 12, 2012	**Submission Date:** August 16, 2012
Initial Recommendation: January 14, 2013	**Final Recommendation:** March 7, 2013

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding axitinib (Inlyta) as a second-line treatment for patients with metastatic clear cell renal carcinoma who, based on the mutual assessment of the treating physician and the patient, are unable to tolerate ongoing use of an effective dose of everolimus or who have a contraindication to everolimus. Funding in a broader patient population was not recommended because there is too much uncertainty that the effectiveness of axitinib is similar to everolimus, due to the lack of direct evidence from randomized comparative trials; however, there is a need for other options amongst patients who are either unable to tolerate or who have a contraindication to everolimus. Therefore, while current evidence is insufficient to recommend funding axitinib broadly, pERC considered that there is a need for axitinib in the subgroup of patients defined above and that this would align with patient values. This recommendation assumes similar pricing of standard dosing of the two therapies. pERC did not recommend axitinib as an alternative to everolimus or as a third-line option for patients whose disease progresses while receiving everolimus because there was insufficient clinical trial evidence to support these options.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps for stakeholders were identified by pERC

SUMMARY OF pERC DELIBERATIONS

pERC noted that the current standard of care and most relevant comparator in the second-line treatment of metastatic renal cell carcinoma is everolimus. However, the one randomized controlled trial included in the pCODR systematic review compared axitinib with sorafenib in the second-line setting (AXIS study, Rini et al 2011). pERC noted that sorafenib has regulatory approval in Canada for use in patients who have failed or are intolerant to prior systemic therapy. pERC discussed that there are only data to support the use of sorafenib after cytokine therapy and that cytokine therapy is rarely used in the first-line setting anymore. Cytokine therapy has been replaced by sunitinib, therefore, pERC considered that sorafenib now has limited relevance as a comparator for axitinib. As a result, pERC encountered considerable uncertainty when trying to determine the relative effectiveness and safety of axitinib compared to everolimus.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC considered overall results from the AXIS study, which demonstrated that there is a statistically significant improvement in median progression-free survival for axitinib compared to sorafenib (6.7 versus 4.7 months, HR=0.665, 95% CI: 0.544 to 0.812, P < 0.001). pERC also noted that a similar but smaller effect was observed in the pre-specified subgroup of patients who had prior treatment with sunitinib, which is most clinically relevant in the Canadian setting (HR=0.74, 95% CI: 0.573 to 0.958, P=0.0107, median PFS 4.8 versus 3.4 months). pERC considered that this demonstrated that there is a biologic effect of axitinib in patients with metastatic renal cell carcinoma and a clinical benefit over sorafenib. However, pERC was uncertain how axitinib compared with everolimus. pERC also discussed unpublished indirect comparisons that had been conducted by the manufacturer but had concerns that interpretations based on cross-trial comparisons are uncertain regarding both the magnitude and direction of benefit. Given this uncertainty, pERC did not support funding axitinib as a second-line treatment option for all patients with metastatic renal cell carcinoma. However, pERC discussed that for a small, defined subset of patients, axitinib may meet a need for an effective treatment option. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer relating to the analysis and conclusions of the submitted indirect comparison. pERC was unable to draw meaningful conclusions based on the results of the indirect comparison because they had methodological concerns that the results were not valid when taking into consideration the differences in study patient populations.

pERC discussed the safety of axitinib compared with sorafenib in the context of the AXIS trial. It was noted that the side effect profile of axitinib appeared consistent with its mechanism of action as a tyrosine kinase inhibitor. pERC also noted that these side effects appeared to differ from those associated with mTOR inhibitors such as everolimus. In reflecting on experience in current clinical practice, pERC noted that everolimus may not be an option for all patients, e.g., those with poor lung function. Additionally, some patients with metastatic renal cell carcinoma experience pneumonitis while on everolimus therapy, which requires discontinuing the treatment. Therefore, pERC considered that making axitinib available as an option for those patients who have intolerance to or a contraindication to everolimus would align with patient values of having more treatment options for patients with poor lung function or who had experienced serious toxicities with everolimus. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer and patient advocacy group that axitinib should be funded as an alternative to everolimus for all patients. pERC reiterated that there is insufficient evidence evaluating axitinib relative to everolimus to support this recommendation. However, recognizing that for some patients, everolimus is not an option and that these patients have a specific clinical need for another treatment option, pERC considered it reasonable to provide this patient population with access to axitinib.

pERC discussed how intolerance to everolimus could best be defined for funding purposes and how patient care could be impacted by the definition of intolerance. pERC noted that it is important that the determination of intolerance to everolimus be based on the assessment of the treating physician, taking into consideration the concerns of the patient. Upon reconsideration of the pERC Initial Recommendation ,the Committee discussed feedback from the patient advocacy group reporting concerns that the definition of intolerance would lead to access delays for patients needing axitinib therapy. pERC noted that in recommending that intolerance to everolimus be based on a mutual assessment by the treating physician and patient, pERC agrees that administrative issues regarding the assessment of intolerance should not be allowed to impact access to appropriate treatment options.

pERC deliberated upon the potential use of axitinib in a first-line population or in patients whose disease progresses while taking everolimus. It was noted that there were no randomized controlled trials evaluating axitinib in these settings. In addition, pERC discussed input from the Provincial Advisory Group that sequential use of axitinib may impact adoption feasibility by increasing the budget impact of axitinib.

pERC also deliberated upon the economic evaluation submitted for axitinib and the critique provided by the pCODR Economic Guidance Panel. pERC discussed the limitations associated with the indirect comparisons that were submitted, comparing axitinib with everolimus. pERC noted that at the Health Canada recommended dose of 5 mg twice daily, the price of axitinib is similar to the price of the Health Canada recommended dose of everolimus (10 mg daily). However, pERC noted that if alternative doses are used, the cost of axitinib may be incrementally higher than the cost of everolimus, e.g. if a higher dose of axitinib were used, as was done in a large proportion of patients in the AXIS study. pERC also noted that costs other than the price of axitinib were not reported in the economic evaluation, which creates uncertainty around the total costs associated with axitinib treatment.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group (Kidney Cancer Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Kidney Cancer Canada)
- the Submitter (Pfizer Canada Inc.)

The pERC Initial Recommendation was to recommend funding axitinib (Inlyta) as a second-line treatment in patients with metastatic clear cell renal carcinoma who, based on the mutual assessment of the treating physician and the patient, are unable to tolerate ongoing use of an effective dose of everolimus or who have a contraindication to everolimus. Feedback on the pERC Initial Recommendation indicated that the manufacturer and patient advocacy group disagreed with the initial recommendation and the pCODR's Provincial Advisory Group agreed in part with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of axitinib on patient outcomes compared to standard therapies in the second line treatment of patients with advanced or metastatic renal cell carcinoma after failure of prior systemic therapy.

Studies included: one study comparing axitinib with sorafenib

The pCODR systematic review included one study, AXIS (Rini et al 2011), an international, multi-centre, open-label randomized controlled trial that compared the efficacy and safety of axitinib to sorafenib in the second-line setting.

The pCODR review also provided contextual information on relevant comparators including everolimus (RECORD-1 study, Motzer et al 2008 and Motzer et al 2010), temsirolimus (INTORSECT study) and an analysis of the submitted indirect comparison of everolimus and axitinib. The RECORD-1 study was a double blind randomized controlled trial, comparing everolimus to placebo. The information summarized on AXIS and RECORD-1, highlighted the differences between the two trials and how this may affect the interpretation of an indirect comparison. pERC discussed these limitations and had concerns that interpretations based on cross-trial comparisons are uncertain regarding both the magnitude and direction of benefit and did not consider them sufficient to determine the overall clinical benefit of axitinib compared with everolimus. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer relating to the analysis and conclusions of the submitted indirect comparison. pERC was unable to draw meaningful conclusions based on the results of the indirect comparison

because they had methodological concerns that the results were not valid when taking into consideration the differences in study patient populations.

Patient populations: majority of patients received prior sunitinib and had lung metastases

The AXIS study included only patients with clear cell renal carcinoma and evidence of metastatic disease. Patients had an ECOG performance status of 0 or 1.

The majority of patients, 54%, had received prior sunitinib as compared to other first line treatments (cytokines, bevacizumab and temsirolimus in 35%, 8% and 3% of patients respectively). pERC considered that this reflected clinical practice in Canada and that patients who had received prior sunitinib were the most relevant patient population. This was a very different study population compared with the RECORD-1 study, which was included in the indirect comparison and evaluated everolimus compared with placebo. In RECORD-1, patients and received multiple prior treatments and may have been more refractory to treatment than those in the AXIS study.

Approximately 75% of patients in the AXIS study had lung metastases. pERC noted that in clinical practice, patients with compromised lung functioning would be less likely to be candidates for everolimus and may need another treatment option.

Key efficacy results: improved progression-free survival compared with sorafenib

The primary endpoint in the AXIS study was progression-free survival, as assessed by a blinded independent radiology committee. Other key efficacy outcomes deliberated upon by pERC included overall survival.

pERC discussed that a statistically-significant improvement in median progression-free survival was observed with axitinib compared to sorafenib in the overall study population [6.7 versus 4.7 months, hazard ratio (HR) 0.665, 95% CI: 0.544-0.812, P<0.0001]. In the pre-specified subgroup of patients who had received prior sunitinb, a similar but smaller improvement in median progression free survival was also observed for axitinib compared to sorafenib (4.8 versus 3.4 months, HR=0.74,95% CI 0.573 to 0.958, P=0.0107). pERC noted that the results in patients previously treated with sunitinib were the most relevant to the Canadian population. pERC further deliberated upon these results and considered that the data demonstrated that axitinib is an active drug in this population. However, pERC was challenged in determining how axitinib compared with everolimus, which is the most clinically relevant comparator.

pERC also noted that median overall survival was similar between axitinib and sorafenib (20.1 versus 19.2 months, HR=0.969, 95% CI: 0.800 to 1.174, P=0.374).

Quality of life: similar between axitinib and sorafenib

In the AXIS study, symptom improvements and quality of life were measured using the Fact-Kidney Symptom Index (FKSI). The FKSI includes 15 questions and a 9-question subscale that measures symptoms of advanced renal cell carcinoma including lack of energy, pain, weight loss, fatigue, shortness of breath, time to deterioration. No difference in the overall mean FKSI-15 scores between axitinib and sorafenib were reported over time. pERC discussed these results and noted that quality of life was valued by patients based on input received from Kidney Cancer Canada.

Safety: adverse events consistent with mechanism of action and manageable

In the AXIS study, the proportions of patients with fatal and non-fatal serious adverse events were similar between the axitinib and sorafenib groups. Diarrhoea, hypertension and fatigue were the most commonly reported adverse events for both axitinib and sorafenib. The adverse events were generally mild or moderate in severity and manageable through dose interruptions, dose reductions, and/or standard medical management. Compared with sorafenib, more patients receiving axitinib experienced dysphonia, nausea, hypothyroidism and hypertension and fewer patients experienced hand-foot syndrome and rash. pERC noted that this side effect profile was consistent with the expected mechanism of action of a tyrosine kinase inhibitor and different from that of a mTOR inhibitor such as everolimus. pERC discussed the challenges of comparing the safety of axitinib with everolimus based on cross-trial comparisons. However, pERC noted that in clinical practice, patients with poor lung function would be less likely to receive everolimus because of concerns about drug-related lung toxicity and that axitinib may be an option for these patients.

Limitations: No direct comparison with everolimus and no ongoing trials

The main limitation identified by pERC in the evidence for axitinib is that there are no randomized controlled trials directly comparing it with everolimus, the current standard of care in the second line setting. pERC also noted that there are no planned or ongoing trials that will compare axitinib with everolimus. pERC also discussed the limitations of conducting an indirect

treatment comparison between axitinib and everolimus, given the available clinical evidence, and the resulting challenges in conducting a cost-effectiveness analysis.

Comparator Information: Uncertainty in results of indirect comparisons

In the absence of trials directly comparing axitinib with everolimus, pERC discussed contextual information provided in the pCODR Clinical Guidance Report on relevant comparators and the limitations of doing an indirect comparison between axitinib and everolimus. pERC noted that because of differences in the study populations and the study designs of the RECORD-1 study and the AXIS study and the lack of a common control group between the studies, the results of the indirect comparison would have a number of limitations and be extremely uncertain.

Need: alternatives for patients intolerant to or with contraindications to everolimus

Currently kidney cancer accounts for approximately 3% of all cancers in Canada with approximately 90-95% being clear cell renal carcinoma. The estimated five-year survival across all stages is 67% but the prognosis for patients with metastatic disease remains poor with only a very few surviving longer than five years. Despite advances in treatment options, none of the currently available systemic treatment options for metastatic RCC (including targeted therapy, immunotherapy, or conventional chemotherapy) is considered curative and all of these therapies are associated with various degrees of side effects.

pERC discussed that everolimus is currently the standard of care in the second-line setting and that there may be patients who have a contraindication to or who are intolerant to everolimus who are in need of another treatment option, e.g. patients with poor lung function. pERC noted that in clinical practice there are often patients who experience serious toxicity with everolimus and who, currently, would not have any other treatment options. Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer and patient advocacy group that axitinib should be funded as an alternative to everolimus for all patients. pERC reiterated that there is insufficient evidence evaluating axitinib relative to everolimus to make this recommendation. However, recognizing that for some patients, everolimus is not an option and that these patients have a specific clinical need for another treatment option, pERC considered it reasonable to provide this small patient population with access to axitinib. pERC also discussed feedback from the patient advocacy group reporting concerns that the definition of intolerance would lead to delays in getting access to axitinib. pERC noted that recommending that intolerance to everolimus be based on a mutual assessment by the treating physician and patient may reduce administrative issues regarding the assessment of intolerance and access to appropriate treatment options. Upon reconsideration of the pERC Initial Recommendation, pERC also noted patient advocacy group concerns that patients found to be intolerant to everolimus and switched to axitinib may be classified as having moved to a third line of therapy. pERC discussed that treating physicians would not likely regard intolerance, for example due to pneumonitis, as equivalent to failing a line of therapy due to disease progression.

PATIENT-BASED VALUES

Values of patients with metastatic renal cell carcinoma: maintaining quality of life and disease stability

pERC considered patient advocacy group input highlighting that patients with metastatic renal cell carcinoma experience many symptoms, including shortness of breath, cough, fatigue, severe abdominal or back pain, bone pain and bone fractures. Patient advocacy group input expressed a desire for choice in second-line therapy so that patients can continue to manage their disease and side effects while maintaining their quality of life. From a patient perspective, prolonging progression-free survival and allowing for extended control of disease (e.g., tumor shrinkage or stability) are important treatment goals.

Patient values on treatment: alternative treatment option and willing to accept side effects

Patient advocacy group input indicated that everolimus is the only second-line treatment option funded in Canada and that for some patients, the side effects of everolimus could have a significant impact on quality of life and daily activities. Patient advocacy group input also noted that for patients with lung impairment, everolimus is not an option and an alternate treatment is required. pERC discussed this and noted that for patients intolerant to or with a contraindication to everolimus, there are no other second-line treatment options. Therefore, pERC considered that providing axitinib as an option for this small subset of patients would align with patient values.

Patient advocacy group input reported that of the small number of patients who had experience taking axitinib, many were willing to accept the associated side effects and the majority considered their quality of life while taking axitinib to be moderate

to high. Patients indicated that they are aware that all treatments for advanced cancer have risks associated with them and that they are willing to tolerate moderate to significant side effects during their treatment. pERC noted this and considered that the side effect profile of axitinib would likely be acceptable to patients and that the side effects appear to be manageable in clinical practice through dose adjustments and interruptions.

ECONOMIC EVALUATION

Economic model submitted: cost minimization

The pCODR Economic Guidance Panel assessed a cost minimization analysis provided by the submitter, comparing axitinib with everolimus. Because of the lack of head-to-head trials comparing these two drugs, the cost minimization analysis was based on an indirect treatment comparison and assumed similar efficacy and safety for axitinib and everolimus.

pERC discussed the appropriateness of this approach and found that there were considerable challenges in interpreting the cross-trial comparisons and serious limitations with the indirect treatment comparisons. However, pERC noted that these limitations would have also existed in a cost-effectiveness analysis that was informed by the indirect treatment comparison. Therefore, while not ideal, in these circumstances, pERC considered this approach to be reasonable. It was noted that if, in future, the assumption around equal efficacy and safety between axitinib and everolimus was proven incorrect, a cost-minimization approach would no longer be valid and a standard cost effectiveness or cost-utility analysis would be required.

Basis of the economic evaluation: drug costs and indirect treatment comparison

The costs considered in the analysis included only the cost of axitinib and everolimus. pERC noted that there were likely additional costs associated with the treatment and management of these patients but was uncertain about how these costs would differ between the axitinib and everolimus groups. However, based on clinical experience managing patients with advanced cancer and the evidence for these two drugs, pERC was unable to identify any areas where costs were expected to differ substantially.

The clinical effects were based on a submitted and unpublished indirect treatment comparison that included one study comparing axitinib with sorafenib (N=723) and one study comparing everolimus with placebo (N=416). Three different analytical approaches were taken to the conduct of the indirect treatment comparison and similar results were obtained with all three approaches. However, the indirect treatment comparison did not include a robust analysis of potential harms. The results of the indirect treatment comparison indicated that axitinib may have greater efficacy than everolimus, however, for the purposes of the cost minimization analysis, it was assumed that efficacy was similar between the two drugs. pERC discussed this and noted that the manufacturer had made a conservative assumption in the cost-minimization analysis.

Although a conservative assumption was made in the cost-minimization analysis, pERC could not recommend axitinib for patients who can receive everolimus because of the considerable uncertainty around the assumption of similar efficacy and safety between axitinib and everolimus.

Drug costs: alternate doses may increase drug costs of axitinib relative to everolimus

Axitinib costs $18.60 per 1 mg tablet and $93.00 per 5 mg tablet, at the list price. At the recommended dose of 5 mg twice daily, the average cost per day is $186.00 and the average cost per 30-day course is $5,580. Everolimus costs $186.00 per 5 mg and 10 mg tablets, at the list price. At the recommended dose of 10 mg daily, the average cost per day is $186.00 and the average cost per 30-day course is $5,580.

Although the prices of axitinib and everolimus are the same at the Health Canada recommended daily doses, if higher doses of axitinib are used, the cost of axitinib may be greater than the cost of everolimus. pERC noted that the majority of patients receiving axitinib in the AXIS study required dosage adjustments and a large proportion of patients received a dose higher than the recommended 10 mg per day. The submitted economic evaluation did not consider the possibility of axitinib dose adjustments; therefore, the pCODR Economic Guidance Panel conducted a reanalysis using alternative doses of axitinib. This

resulted in incremental costs of between $0 and $335 for axitinib versus everolimus. pERC considered that the impact of axitinib dose adjustments would need to be considered in the budget impact analyses of axitinib.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: additional cost of treating patients intolerant to or with a contraindication to everolimus

pERC noted that the submitted budget impact analysis addressed the use of axitinib in patients currently receiving everolimus but not the use of axitinib in patients who are intolerant to or contraindicated to everolimus. pERC noted that the use of axitinib in this latter population would result in additional costs, since these patients do not currently have treatment options available to them. pERC further noted that the potential for dose adjustments will need to be considered by provinces as this could affect the incremental cost of axitinib relative to everolimus. pCODR's Provincial Advisory Group input also identified sequential use of axitinib as a potential factor that could further increase budget impact. pERC considered that there is no clinical trial evidence to support the use of axitinib in the first-line or in patients whose disease progresses while receiving everolimus.

DRUG AND CONDITION INFORMATION

Drug Information	• Multi-target tyrosine kinase inhibitor • 1 mg and 5 mg reviewed by pCODR • Recommended dosage of 5 mg orally twice daily
Cancer Treated	• Advanced or metastatic renal cell carcinoma with clear-cell histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI, sunitinib
Burden of Illness	• 5600 new cases (all stages) will be diagnosed in 2012 with approximately 1700 deaths reported. • Estimated five-year survival across all stages is 67% but prognosis for patients with metastatic disease remains poor with very few surviving over 5 years • Males are more frequently affected with a predominance of 1.8 to 1.
Current Standard Treatment	• In the first line setting, sunitinib is the current standard of care and more recently pazopanib, both VEGFR inhibitors • Everolimus, an oral mTOR inhibitor is considered standard of care in second line setting. Sorafenib is also a treatment option in the second line setting, after previous cytokine therapy
Limitations of Current Therapy	• None of the currently available treatment options are considered curative and all therapies are associated with various degrees of side effects • Ongoing need for better therapy options in the treatment of metastatic RCC, which improve efficacy outcomes, reduce toxicity or both

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Lister, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Peter Venner who was excluded from deliberations and voting due to a conflict of interest
- Dr. Allan Grill and Dr. Chaim Bell who were absent from the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

All members participated in deliberations and voting on the final recommendation except:

- Jo Nanson and Dr. Bill Evans who were absent from the meeting
- Dr. Peter Venner who was excluded from deliberations and voting due to a conflict of interest

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the pCODR Conflict of Interest Guidelines; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of axitinib (Inlyta) for mRCC, through their declarations, eight members had a real, potential or perceived conflict and based on application of the pCODR Conflict of Interest Guidelines, one of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in this recommendation document.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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Appendix 3: Methodology

APPENDIX 3.1: LITERATURE SEARCH STRATEGY

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2017, **Embase** 1974 to 2017 April 24, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Line #	Searches	Results
1	Everolimus/ or (Afinitor* or everolimus* or Zortress* or Disperz* or Advacan* or Certican* or Votubia* or Xience* or Evertor* or RAD001 or "RAD 001" or RAD001a or RAD 001a or SDZRAD or SDZ RAD or 9HW64Q8G6G or 159351-69-6 or "0159351696" or 1245613-55-1).ti,ab,ot,kf,kw,hw,rn,nm.	29784
2	(axitinib* or Inlyta* or AG013736 or "AG 013736" or C9LVQ0YUXG or 319460-85-0 or 790713-39-2).ti,ab,ot,kf,kw,hw,rn,nm.	4101
3	Kidney Neoplasms/ or Carcinoma, Renal Cell/	92639
4	Kidney/ or (kidney* or renal or hypernephroid or collecting duct* or Grawitz or nephroid).ti,ab,kf,kw.	1940878
5	Neoplasms/ or (cancer* or carcinoma* or adenocarcinoma* or pyelocarcinoma* or neoplasm* or tumor* or tumour* or metast* or malignan*).ti,ab,kf,kw.	6559486
6	(hypernephroma* or nephroma* or reninoma*).ti,ab,kf,kw.	5166
7	(RCC or mRCC).ti,ab,kf,kw.	34305
8	3 or (4 and 5) or 6 or 7	327851
9	1 and 2 and 8	939
10	9 use pmez	129
11	9 use cctr	20
12	*everolimus/ or (afinitor* or everolimus* or Zortress* or Disperz* or Advacan* or Certican* or Votubia* or Xience* or Evertor* or RAD001 or "RAD 001" or RAD001a or RAD 001a or SDZRAD or SDZ RAD or 9HW64Q8G6G).ti,ab,kw.	19450

13	*axitinib/ or (axitinib* or Inlyta* or AG013736 or AG 13736 or C9LVQ0YUXG).ti,ab,kw.	1943
14	kidney tumor/ or kidney cancer/ or kidney carcinoma/	157035
15	exp Kidney/ or (kidney* or renal or hypernephroid or collecting duct* or Grawitz or nephroid).ti,ab,kw.	1988775
16	Neoplasm/ or (cancer* or carcinoma* or adenocarcinoma* or pyelocarcinoma* or neoplasm* or tumor* or tumour* or metast* or malignan*).ti,ab,kw.	6565130
17	(hypernephroma* or nephroma* or reninoma*).ti,ab,kw.	5146
18	(RCC or mRCC).ti,ab,kw.	34262
19	14 or (15 and 16) or 17 or 18	349465
20	12 and 13 and 19	409
21	20 use oemezd	281
22	21 and conference abstract.pt.	135
23	limit 22 to yr="2012 -Current"	123
24	21 not 22	146
25	10 or 11 or 24	295
26	remove duplicates from 25	187
27	26 or 23	310
28	limit 27 to english language	288

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#10	Search **#9 AND publisher[sb]** Filters: **English**	3
#9	Search **#2 AND #3 AND #8** Filters: **English**	109
#8	Search **#4 OR (#5 AND #6) OR #7** Filters: **English**	117407
#7	Search **hypernephroma*[tiab] OR nephroma*[tiab] OR reninoma*[tiab] OR RCC[tiab] OR RCC[tiab]** Filters: **English**	12337
#6	Search **Neoplasms[mh:noexp] OR cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR pyelocarcinoma*[tiab] OR neoplasm*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour[tiab] OR tumours[tiab] OR metast*[tiab] OR malignan*[tiab]** Filters: **English**	2400080
#5	Search **Kidney[mh] OR kidney*[tiab] OR renal[tiab] OR hypernephroid[tiab] OR collecting duct*[tiab] OR Grawitz[tiab] OR nephroid[tiab]** Filters: **English**	719124
#4	Search **Kidney Neoplasms[mh:noexp] OR Carcinoma, Renal Cell[mh]** Filters: **English**	48152
#3	Search **Axitinib[supplementary concept] OR axitinib[tiab] OR Inlyta*[tiab] OR AG013736[tiab] OR AG 013736[tiab] OR 319460-85-0[rn] OR 790713-39-2[rn] OR C9LVQ0YUXG[tiab]** Filters: **English**	607
#2	Search **Everolimus[mh] OR Afinitor*[tiab] OR everolimus*[tiab] OR Zortress*[tiab] OR Disperz*[tiab] OR Advacan*[tiab] OR Certican*[tiab] OR Votubia*[tiab] OR Xience*[tiab] OR Evertor*[tiab] OR RAD001[tiab] OR RAD 001[tiab] OR RAD001a[tiab] OR RAD 001a[tiab] OR SDZRAD[tiab] OR SDZ**	5353

Search	Query	Items found
	RAD[tiab] OR 9HW64Q8G6G[tiab] OR 159351-69-6[rn] OR 0159351696[rn] OR 1245613-55-1[rn] Filters: **English**	

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Afinitor/everolimus, Inlyta/axitinib, renal cell carcinoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Afinitor/everolimus, Inlyta/axitinib, renal cell carcinoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology
http://www.hematology.org/

Search: Afinitor/everolimus, Inlyta/axitinib, renal cell carcinoma - last 5 years

Appendix 3.2: Detailed Methodology of Literature Review

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017 April 24) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017 April 24) via Ovid; The Cochrane Central Register of Controlled Trials (March 2017) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were everolimus/Afinitor, axitinib/Inlyta and renal cell carcinoma.

No filters were applied to limit retrieval to by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of May 30, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

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