PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Axitinib (Inlyta) for metastatic Renal Cell Carcinoma

March 7, 2013

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of axitinib (Inlyta) on patient outcomes compared to standard therapies as second line treatment of patients with advanced/metastatic renal cell carcinoma. Axitinib is a potent, highly selective small molecule tyrosine kinase inhibitor of multiple targets, including VEGFR 1-3, platelet derived growth factor receptor (PDGFR) and cKit. Axitinib has a Health Canada 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.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

AXIS was an international, multi-centre, open-label randomized controlled trial that compared the efficacy and safety of axitinib to sorafenib (n=723 randomised, n=714 treated). The study recruited patients with histological or cytological confirmed renal cell carcinoma with a clear cell component and with evidence of metastatic disease. Patients had an ECOG performance status of 0 or 1, a life expectancy of 12 weeks or more, and progressive disease after one previous first-line regimen with sunitinib, temsirolimus, a cytokine, or bevacizumab plus interferon-α. Patients were also ≥18 years with the median age at 61 years (range 20 to 82 years) and were predominantly male and Caucasian. Stage IV cancer was reported in 89% of patients, with lung metastases in >75% of patients. Prior therapy with sunitinib, cytokines, bevacizumab, or temsirolimus was received by 54%, 35%, 8% and 3% patients respectively. At trial end or with disease progression, patients were eligible for continued treatment as assigned at randomization beyond disease progression. Patients could also receive subsequent systemic therapies at physicians' discretion. Cross-over between study drugs was not permitted.

Efficacy

Progression-free survival based on a blinded independent radiology committee assessment was the primary end point of the study. A statistically-significant and clinically-meaningful improvement in PFS was observed with axitinib compared to sorafenib [median PFS 6.7 vs.4.7 months, hazard ratio (HR) 0.665, 95% CI: 0.544-0.812, p<0.0001]. Pre-specified subgroup analyses of PFS supported the primary analysis, with all hazard ratios favouring 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. In the subgroup of patients progressing on sunitinib or cytokines, 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, HR 0.74,95% CI 0.573-0.958, p=0.0107 and 12.1 vs 6.5months, HR 0.464, 95% CI 0.318-0.676, p<0.0001, respectively). Overall response rate (ORR) and overall survival (OS) were secondary endpoints in the study. ORR (complete response [CR] plus partial response [PR]) favoured axitinib compared to sorafenib (19.4% vs. 9.4% respectively) (1-sided p=0.0001) 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. Final OS data, based on 425 events is now available and is similar between the two arms. 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.

Harms

Adverse events in the study were consistent with the expected mechanism of action and were generally mild or moderate in severity and clinically manageable through the use of dosing interruptions, dose reductions, and/or standard medical management. All causality fatal adverse events and non-fatal serious adverse events were of similar incidence in both treatment arms (~30% each group).

1.2.2 Additional Evidence

pCODR received input on axitinib from the following patient advocacy group, Kidney Cancer Canada. Provincial Advisory group input was obtained from seven of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

Results of a phase 3 trial (Study INTORSECT) comparing sorafenib (a VEGFR inhibitor) to temsirolimus (an mTOR inhibitor) as second line treatment in advanced RCC reported that PFS (the primary endpoint), although better in patients treated with temsirolimus, was not statistically significant.[1] Overall survival (a secondary endpoint) was statistically significant favouring the sorafenib patients.[1] Interpretation of these results cannot be made as the details of the trial have not been published but it may provide some evidence of no difference in PFS between a VEGFR inhibitor and an mTOR inhibitor.

In addition, two supplemental questions were identified during the development of the review protocol as relevant to the pCODR review of axitinib and are discussed as supporting information.

- *What is the evidence regarding the effectiveness and safety of everolimus in mRCC? How do AXIS and RECORD-1 trials compare in terms of study design, population, interventions and outcomes?*

  Both axitinib and everolimus are indicated as second line treatment in mRCC. They have different mechanisms of action: Axitinib is a VEGFR inhibitor and everolimus is an mTOR inhibitor.

  The benefits and harms of everolimus were evaluated in a phase 3 trial: RECORD-1 compared everolimus to placebo in a randomized double blind controlled trial in 410 patients after failure of one or multiple therapies. Patients enrolled in RECORD-1 were heavily pre-treated and refractory to treatment. The differences in study design, baseline patient characteristics and comparators make it challenging to compare effectiveness between the two drugs.

- *What are the limitations of conducting an indirect comparison between everolimus and axitinib?*

  The manufacturer submitted unpublished indirect comparisons of axitinib versus everolimus.[2,3] An indirect comparison provides information in instances where trials have not directly compared the specific treatments.

Indirect comparisons may be appropriate in instances when direct evidence is lacking (eg. direct comparison not feasible or not available) however the quality standard of evidence development should be maintained. Conclusions drawn from such indirect comparisons are not as robust as conclusion based on direct, head-to-head trial data. Results need to be considered in light of the limitations and uncertainties of the various indirect comparison methods.

In the manufacturer's submission indirect statistical assessments to determine comparative efficacy amongst the two drugs were performed using different approaches: a side by side comparison, the Bucher fixed effect model, a Bayesian fixed-effect model, and a simulated treatment comparison. The challenge here is in the interpretation of the manufacturer's results given the limitations of the submitted IC and the resulting difficulty in making conclusions based on the uncertainty of those results. A conclusion of 'similarity' in treatment effect cannot simply be derived from a statistically non-significant finding. In general, the details of the IC presented by the submitter were sparse and it was difficult to assess the validity of the findings due to many significant issues identified and therefore, no firm conclusion could reasonably be drawn from these analyses.

1.2.3 Interpretation and Guidance

Kidney cancer accounts for approximately 3% of all cancers in Canada with approximately 90-95% being RCC. An estimated 5600 new cases (all stages) will be diagnosed in 2012 with approximately 1700 deaths reported. 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.

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.

AXIS was an international, multi-centre, open-label randomized controlled trial that compared the efficacy and safety of axitinib to sorafenib. A statistically-significant and clinically-meaningful improvement in PFS was observed with axitinib compared to sorafenib. Pre-specified subgroup analysis of PFS supported the primary analysis, with all hazard ratios favouring axitinib. ORR favoured axitinib compared to sorafenib (19.4% vs. 9.4% respectively) with a median duration of response of 11 months and 10.6 months for axitinib and sorafenib, respectively. Final OS data, based on 425 events is now available and is similar between the two arms.

Adverse events in the study were consistent with the expected mechanism of action and were generally mild or moderate in severity and clinically manageable. All causality fatal adverse events and non-fatal serious adverse events were of similar incidence in both treatment arms (~30% each group).

1.3 Conclusions

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.[1] Overall survival was statistically significant favouring the sorafenib patients.[1] 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.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding axitinib (Inlyta) in metastatic renal cell carcinoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on a systematic review of the literature regarding axitinib (Inlyta) conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on axitinib and a summary of submitted Provincial Advisory Group Input on axitinib are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Axitinib is a potent, highly selective small molecule tyrosine kinase inhibitor of multiple targets, including VEGFR 1-3, platelet derived growth factor receptor (PDGFR) and cKit.[4] Preclinical studies have shown that axitinib has a unique pattern of binding and is more potent and selective against the VEGFR 1-3 than other multitargeted tyrosine kinase inhibitors (TKIs) like sunitinib or sorafenib.[5-7]

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 and further to 2 mg twice daily.

Other oral agents with a Health Canada approve indication for mRCC include: everolimus (after failure of sorafenib or sunitinib), pazopanib (1st line or 2nd line after failure of a cytokine), sorafenib (after failure or intolerance to prior systemic therapy), and sunitinib (not specified).

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect of axitinib (Inlyta) on patient outcomes compared to standard therapies as second line treatment of patients with advanced/ metastatic renal cell carcinoma.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

The efficacy and safety of axitinib 5 mg orally twice daily (n=361) was compared to sorafenib (n=362) 400 mg orally twice daily in an international, multi-centre, open-label randomized controlled trial (Study AXIS).[3,8] The study recruited patients with renal cell carcinoma with a clear

cell component with evidence of metastatic disease, an ECOG performance status of 0 or 1, a life expectancy of 12 weeks or more, and progressive disease after one previous first-line regimen with sunitinib, temsirolimus, a cytokine, or bevacizumab plus interferon-α. The median patient age was 61 years (range 20 to 82 years), and patients were predominantly male and Caucasian. Stage IV cancer was reported in 89% of patients, with lung metastases in >75% of patients. Prior therapy with sunitinib, cytokines, bevacizumab, or temsirolimus was received by 54%, 35%, 8% and 3% patients respectively. Cross-over between study drugs was not permitted. At trial end or with disease progression, patients were eligible for continued treatment as assigned at randomization beyond disease progression. Patients could also receive subsequent systemic therapies at physicians' discretion.

Patient enrolment started on September 15, 2008 and ended July 23, 2010. The median PFS, after adjusting for ECOG status and prior therapy, was 6.7 versus 4.7 months in the axitinib and sorafenib arm respectively (HR=0.67, 95% CI: 0.55, 0.81). PFS benefits were due to a greater response from the sub-group of patients with prior cytokine therapy and less so from the sunitinib pre-treated sub-group. A final overall survival analysis was available and adequately powered. It showed no statistically significant difference between the two treatment arms. A response was seen in 19% of patients (95% CI: 15%, 24%) for axitinib and 9% of patients (95% CI: 7%, 13%) for sorafenib. All were partial responses as there were no complete responders. Patient reported outcomes were measured using the Fact-Kidney Symptom Index. No difference in the overall estimated mean Fact-Kidney Symptom Index scores between the two drugs over time was reported. The majority of axitinib-treated patients required dosage adjustments: only 39% of patients treated with axitinib remained on the initial dose of 5 mg twice daily throughout the study.

The frequency and severity of adverse events were similar between both drugs. A high incidence of diarrhea, hypertension and fatigue was seen with both drugs. Nausea and dysphonia were more frequent with axitinib whereas hand-foot syndrome and rash were more frequent with sorafenib. All causality serious adverse events (fatal and non-fatal) were of similar incidence in both treatment arms.

The results of AXIS are generalizable to patients with clear cell mRCC who have failed first line treatment with sunitinib or a cytokine. There is no evidence presently on the use of axitinib as first line treatment or on the use of axitinib in non-clear cell mRCC. Furthermore, there is no evidence and no on-going trials evaluating the relative effectiveness of axitinib compared to everolimus, another agent used in second-line treatment of mRCC.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

- A Cochrane systematic review searched the literature to identify RCTs of targeted therapies for advanced renal cell carcinoma. Standard Cochrane methods were applied and searches of English language articles were conducted through to June 2011. Of a total of 23 trials meeting the inclusion criteria: 15 trials were conducted with VEGF pathway inhibitors, 3 trials were mTOR inhibitors and 3 trials were conducted with other agents (epidermal growth factor receptor inhibitor and combination therapies). For axitinib, only the AXIS study was identified and reviewed.
- Results of a phase 3 trial (Study INTORSECT) comparing sorafenib (a VEGFR inhibitor and the comparator to axitinib in the AXIS study) to temsirolimus (an mTOR inhibitor) as second line treatment in advanced RCC were made public in a press release by Pfizer and presented in an abstract.[1] It was reported that PFS (the primary endpoint), although better in patients

treated with temsirolimus, was not statistically significant. Overall survival (a secondary endpoint) was statistically significant favouring the sorafenib patients.[1,9] Interpretation of these results cannot be made as the details of the trial have not been published but it may provide some evidence of no difference in PFS between a VEGFR inhibitor and an mTOR inhibitor.

2.1.5 Summary of Supplemental Questions

1. *What is the evidence regarding the effectiveness and safety of everolimus in mRCC? How do AXIS and RECORD-1 trials compare in terms of study design, population, interventions and outcomes?*

Both axitinib and everolimus are indicated as second line treatment in mRCC. They have different mechanism of action: Axitinib is a VEGFR inhibitor and everolimus is an mTOR inhibitor.

The benefits and harms of everolimus were evaluated in a phase 3 trial: RECORD-1 compared everolimus to placebo in a randomized double blind controlled trial in 410 patients after failure of one or multiple therapies. In AXIS, 723 patients who had progressed after first line therapy were randomized to open-label axitinib or sorafenib. Patients enrolled in RECORD-1 were heavily pre-treated and refractory to treatment. Patients in AXIS had disease progression after first line treatment whereas those in RECORD-1 had progression within the last 6 months. Placebo patients could cross-over to everolimus in RECORD-1 whereas cross-over was not permitted in AXIS, but both axitinib and sorafenib patients could receive subsequent treatment upon disease progression or trial discontinuation. The differences in study design, baseline patient characteristics and comparators make it challenging to compare effectiveness between the two drugs.

See section 7.1 for more information.

2. *What are the limitations of conducting an indirect comparison between everolimus and axitinib?*

The manufacturer submitted unpublished indirect comparisons of axitinib versus everolimus. An indirect comparison provides information in instances where trials have not directly compared the specific treatments however the quality standard of evidence development should be maintained.

Indirect statistical assessments to determine comparative efficacy amongst the two drugs were performed using different approaches: a side by side comparison, the Bucher fixed effect model, a Bayesian fixed-effect model, and a simulated treatment comparison.[2,3] Conclusions drawn from such indirect comparisons are not as robust as conclusion based on direct, head-to-head trial data. Results need to be considered in light of the limitations and uncertainties of the various indirect comparison methods. The major limitation of using indirect comparison in this review is the dissimilarities between the patient populations of the trials. The challenge here is in the interpretation of the manufacturer's results given the limitations of the submitted IC and the resulting difficulty in making conclusions based on the uncertainty of those results. A conclusion of 'similarity' in treatment effect cannot simply be derived from a statistically non-significant finding. In general, the details of the IC presented by the submitter were sparse and it was difficult to assess the validity of the findings due to many significant issues identified and therefore, no firm conclusion could reasonably be drawn from these analyses.

See section 7.2 for more information.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

Patient input was provided through a survey conducted by Kidney Cancer Canada. From a patient perspective, prolonging PFS and allowing for extended control of their disease (tumor shrinkage or stability) are important treatment aspects. Patients are aware that all treatments for advanced cancer bear risk and are willing to tolerate moderate to significant side effects during their treatment. Currently available second-line treatment options in Canada are not suitable for all patients. Axitinib is expected to meet the needs of patients who are not suitable for an mTOR inhibitor. Patients with kidney cancer seek choice and flexibility in selecting second-line therapy to manage their disease and to maintain their quality of life.

Of the 103 patients who responded to the survey conducted by Kidney Cancer Canada, nine patients had received axitinib therapy. Only two of these nine patients were prescribed axitinib as second-line therapy. The remainder were first-, third-, fourth-, or fifth-line treated patients which is not in line with the Health Canada approved indication.

PAG Input

Input on the axitinib review was obtained from seven of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that the relationship between everolimus (current standard for the 2nd line treatment of mRCC) and axitinib needs to be explored further since sorafenib is the main comparator in the clinical trials for axitinib. It was also noted that due to axitinib having an oral route of administration, it may be easier to implement for provinces; however, it is important to note that dose escalations and modifications will be a key factor when considering costs to the provinces associated with implementing access to axitinib treatment. As an oral drug, axitinib will not add or burden chemotherapy clinic time and will be relatively accessible to patients.

Other

Trials of therapies for mRCC have typically excluded cancers of non-clear cell histology. There is a possibility that axitinib will be prescribed in these patients despite the lack of evidence.

2.2 Interpretation and Guidance

Burden of Illness and Need

Kidney cancer accounts for approximately 3% of all cancers in Canada with approximately 90-95% being RCC. An estimated 5600 new cases (all stages) will be diagnosed in 2012 with approximately 1700 deaths reported, highlighting the unfavourable prognosis of this disease and the need for more effective therapy.[10] Approximately one quarter of patients with RCC presents with metastases at diagnosis and at least one half 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. Targeted agents such as the small molecule tyrosine kinase inhibitors (sunitinib, sorafenib); the mTOR inhibitors (everolimus and temsirolimus); and the monoclonal antibody bevacizumab have shown significant activity in the treatment of this disease.

First line Setting

In the first line setting, sunitinib, a TKI targeting VEGF receptor types 1, 2, 3, PDGF receptors alpha and beta, c-kit and FLT-3, is considered the standard first line treatment for patients with metastatic RCC. In treatment naive patients comparing sunitinib to interferon, sunitinib demonstrated a median PFS of 11 months versus 5 months for interferon ($P < 0.001$); and a median overall survival of 26.4 months versus 21.8 months ($P = 0.051$).[11,12]

Newer VEGFR tyrosine kinase inhibitors, such as pazopanib, have 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 recently 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.

Second line Setting

In the second line setting where patients have progressed on first-line therapy with tyrosine kinase inhibitors, everolimus, an oral mTOR inhibitor is considered standard of care. In a randomized Phase III trial, 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.[13]

Sorafenib is also considered to be a reasonable treatment option in the second line setting as demonstrated in the INTORSECT trial.[9] In this trial, patients with an ECOG PS of 0 or 1, and whose disease progressed after first-line sunitinib therapy were randomized to receive the mTOR inhibitor (temsirolimus) or the VEGFR inhibitor (sorafenib). Median PFS for temsirolimus was 4.28 months compared to 3.91 months with sorafenib. Median OS for temsirolimus was 12.27 months compared to 16.64 months for sorafenib.

Despite these advances 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. It is also not clear which patient population may benefit from the specific treatment options available and further research in this area is likely needed. Thus there remains an ongoing need for better therapy options in the treatment of metastatic RCC, which provide improved efficacy outcomes, reduced toxicity profile or both.

Axitinib

To date, there have been three Phase II studies of axitinib in advanced RCC, that have suggested axitinib has activity in both cytokine-refractory patients (A4061012, A4061035 [Japanese patients only]) and sorafenib-refractory (A4061023) patients. Most patients in the A4061023 Phase II Study also received prior treatment with sunitinib and/or other agents. Based on the results of these Phase II studies, a Phase III randomized, open label, comparative effectiveness study of axitinib

versus an active TKI comparator, sorafenib, was conducted. In this Phase III study, advanced RCC patients failing only 1 prior line of systemic treatment which included sunitinib, bevacizumab and interferon, temsirolimus, or cytokine(s) were randomized to receive either axitinib or sorafenib.

Sorafenib was a reasonable choice for the comparator arm because it had demonstrated activity in patients with RCC refractory to sunitinib, bevacizumab, and ≥1 prior antiangiogenic agent.[9,14-16] At the time of study initiation, everolimus had not yet been evaluated and was not approved in the second line setting.

Effectiveness

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)].

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.

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].

4. In the subgroup of patients progressing on a cytokine (N=251), which is infrequently used in Canada, a statistically-significant and clinically-meaningful change in progression free survival was observed in patients treated with axitinib compared to sorafenib (12.1 vs 6.5months with a HR of 0.464, 95% CI: 0.318-0.676, p<0.0001 based on a 1-sided log-rank test stratified by ECOG performance status).

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. 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.[12]

6. In this study, OS was a secondary endpoint. Final OS data, based on 425 events is now available and is similar between the two arms. 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.

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.[8] Sorafenib was a reasonable choice for the comparator arm because it had demonstrated activity in patients with RCC refractory to sunitinib, bevacizumab, and ≥1 prior antiangiogenic agent.[9,14-16] At the time of study initiation, everolimus had not yet been evaluated and was not approved in the second line setting.

Safety

Adverse events in the study were consistent with the expected mechanism of action and were generally mild or moderate in severity and clinically manageable through the use of dosing interruptions, dose reductions, and/or standard medical management. The most common (>20%) adverse events observed following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia syndrome, decreased weight , vomiting, asthenia, and constipation. Toxicities related to VEGF pathway inhibition were observed with both axitinib and sorafenib. Axitinib had increased incidence of some of these effects (e.g., hypertension, dysphonia, and hypothyroidism). Toxicities unrelated to VEGF pathway inhibition were reported more frequently in the sorafenib arm (e.g., palmar-plantar erythrodysesthesia syndrome, rash and alopecia). Permanent discontinuation of axitinib due to AE was infrequent (9.2%). Toxicities such as thromboembolic events, haematological toxicities such as thromboembolic events, hemorrhage, RPLS, hypertensive crisis, and gastrointestinal perforation were uncommon.

While the safety profile of axitinib has some similarity to that of sorafenib and other approved agents that target the VEGF pathway (based on indirect comparisons), some important differences were observed between axitinib and these other agents. Axitinib appears to be associated with a lower incidence of skin reactions than sorafenib and sunitinib, a lower incidence of myelosuppression than pazopanib and sunitinib, and a lower incidence of liver function test abnormalities than pazopanib and sunitinib. By contrast, axitinib appears to be associated with a higher incidence of dysphonia than sorafenib and sunitinib, a higher incidence of hypothyroidism than sorafenib and pazopanib, and a higher incidence of hypertension than sorafenib. These differences are derived in part from axitinib's greater specificity for VEGFR inhibition than approved multi-targeted TKIs.

2.3 Conclusions

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.[1] Overall survival was statistically significant favouring the sorafenib patients.[1] 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 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2012, there were 5600 new cases and 1,700 deaths due to the disease.[10] About 90% of kidney cancers are renal cell cancers (RCC), which are genetically and histologically distinctly different from carcinomas arising from the renal pelvis which are known as urothelial carcinomas (UC). About 80% of all RCCs are of clear-cell histology, whereas 20% are classified as non-clear cell cancers and include papillary, sarcomatoid, chromophobe subtypes amongst others. At presentation 75% of patients with RCC will have localized disease (confined to the kidney/extensive growth in the area of the kidney but no distant metastases), while about 25% are already metastatic. Of the patients diagnosed with localized disease, 30-50% of patients will eventually relapse and metastasize. The most important prognostic factor for outcome is tumour stage. Survival rates in localized stages range from 70-90% for smaller tumours (stages I and II) but drop significantly to 50-60% for patients with more extensive tumours (stage III). Patients with metastatic disease are rarely cured.[17]

Metastatic RCC is considered refractory to both conventional cytotoxic chemotherapy and conventional radiation therapy. Historically, immunotherapy (cytokines such as interferon or interleukin) were the treatment of choice in the metastatic setting although only a small group of patients derived meaningful benefit and toxicity was an issue. In the era of immunotherapy, median overall survival across all metastatic patients was in the range of 12-14 months.[18-20] Several key prognostic factors have been identified in patients with metastatic disease that can divide metastatic patients into a favourable, intermediate or poor risk groups. The most commonly used classification for mRCC in the era of immunotherapy was the MSKCC criteria which include the presence or absence of five distinct risk factors (performance status, lactate dehydrogenase, corrected calcium, hemoglobin, and time from diagnosis to treatment). This classification has been used both in routine practice to determine prognosis and as part of the eligibility for clinical studies. More recently the Heng criteria which better reflects treatment with targeted agents has come into regular use and for the purposes of clinical trials.[21-23]

Advances in our understanding of RCC biology and the development of new therapeutic agents (targeted therapies / antiangiogenic agents), in particular for the clear-cell subtype of RCC, have resulted in the availability of a number of new treatment options for patients with metastatic RCC. Clear-cell carcinomas are characterized by the presence of inactivating mutations in the von-Hippel-Lindau gene. Loss of functional VHL protein results in the activation of pro-angiogenic and growth factor pathways via constitutive stabilization of the alpha subunits of a group of transcriptionally active proteins called the hypoxia-inducible factors (HIF).[24] HIF plays a central role in renal tumorigenesis by acting as a transcription factor for genes that are involved in angiogenesis, tumor cell proliferation, cell survival and progression, metastatic spread, apoptosis and glucose metabolism. The phosphatidylinositol-3 kinase (PI3K)-AKT-mTOR signal transduction pathway is also involved in controlling HIF. Elucidation of the VHL/HIF pathway has led to the successful evaluation and regulatory approval of agents targeting the VEGF and mTOR pathways. Targeted therapies have a distinct mechanism of action, fundamentally different from classic chemotherapy and also have a different toxicity profile.

Over the past few years, the RCC treatment landscape has changed significantly and continues to evolve rapidly. While these therapies are active in clear cell RCC, the vast majority of tumours eventually become treatment refractory through different, as yet poorly understood, mechanisms. To date, there are no curative treatment options for metastatic RCC.

3.2 Accepted Clinical Practice

Surgery with complete removal of the tumour remains the mainstay of therapy in localized or locally advanced disease. There is currently no role for adjuvant or neoadjuvant therapy although we are currently awaiting the results of a large adjuvant study to better guide practice in this setting.

Until the introduction of targeted therapies, immunotherapy (cytokines) with low dose interferon-α, low dose interleukin-2 or high dose interleukin-2 represented the standard of care for patients with metastatic clear-cell RCC. Although these agents were helpful for a small group of patients, the majority of patients derived no benefit or the clinical benefit was very modest and achieved at the expense of significant toxicity.[11,25,26] Targeted therapies have replaced immunotherapy as standard treatment for patients with metastatic disease and today, high-dose interleukin-2 is only considered for a highly selected, very small subgroup of patients while low-dose interferon and interleukin-2 as single agents are no longer recommended at all.[27]

There are currently three different classes of agents, small molecule tyrosine kinase inhibitors such as sunitinib or sorafenib, inhibitors of mTOR (mammalian target of rapamycin) such as temsirolimus or everolimus and the monoclonal antibody bevacizumab in clinical use for the treatment of metastatic clear-cell RCC. All of these agents interfere with the VEGF pathway and cell signalling, which plays a crucial role in tumour angiogenesis. Tyrosine kinase inhibitors block the intracellular domain of the VEGF receptor, while bevacizumab binds VEGF and mTOR inhibitors interfere with mTOR, which is key regulator within cells.

First Line, Treatment-Naive:

Sunitinib is an oral tyrosine kinase inhibitor with activity against VEGF receptor types 1, 2, 3, PDGF receptors alpha and beta, c-kit and FLT-3. In the pivotal phase III trial in treatment-naive patients with metastatic RCC, there was a statistically significant difference in PFS in patients treated with sunitinib versus interferon (11 vs. 5 months) with a hazard ratio of 0.42 ($P < 0.001$). In addition, this was the first trial to demonstrate a median overall survival of more than 2 years in patients with metastatic RCC. Based on these results sunitinib became the standard first-line treatment for mRCC.[11] More recently a second tyrosine kinase inhibitor, known as pazopanib has been evaluated in a head to head trial known as COMPARZ, against sunitinib, with the final results pending. A patient preference study know as PISCES has shown that patients tended to favour pazopanib over sunitinib, and should the COMPARZ trial be positive, then pazopanib may become the new reference first-line standard. Bevacizumab has also been tested in combination with interferon versus interferon alone and showed a significant PFS benefit compared to interferon alone. Based on these results the combination has been approved for the treatment of advanced RCC in Europe, the US and other countries. The combination has not been filed for approval in Canada yet. For poor risk patients (according to the MSKCC criteria) the mTOR inhibitor temsirolimus, given intravenously once a week, was tested in a randomized trial against interferon and demonstrated superior overall survival outcomes as compared to interferon alone or the combination of both drugs. Temsirolimus is considered an acceptable first line treatment option in patients with poor risk criteria.[28]

Cytokine Refractory

Sorafenib is another oral tyrosine kinase inhibitor with activity against VEGFR-2, VEGFR-3, PDGF-beta, Flt-3, RAF-kinase and c-Kit. Based on the results of the TARGET trial, which randomized patients after failure of cytokine therapy to either sorafenib or placebo and demonstrated superiority in PFS, sorafenib was approved for the treatment of advanced RCC failing cytokines. Sorafenib is considered a treatment option in metastatic RCC failing cytokines but its use has

substantially decreased due to the decreased use of cytokines and the lack of robust randomized data in the first-line treatment naïve setting.[29]

Second Line

In the second line setting where patients have failed first-line therapy with tyrosine kinase inhibitors, everolimus, an oral mTOR inhibitor is considered a standard second line treatment. Everolimus has demonstrated a significant PFS benefit in a randomized phase III trial which compared everolimus to placebo in patients with failure of at least one prior line of tyrosine kinase therapy.[13]

Table 2. Clinical Data from Pivotal Studies: Sunitinib-Refractory Patients with Metastatic RCC

Approved Therapy	Data Source	Comparator	Median PFS (months)	HR (95% CI)	P-value	ORR (%)
Axitinib (Rini et al[8])	Phase 3 randomized study –Patients had received 1 prior systemic therapy - subgroup of patients who had received one prior sunitinib-containing regimen (N=389; 54% of total population)	Sorafenib	4.8 vs. 3.4	0.74 (0.57, 0.96)	0.0107	11.3
Everolimus (Motzer et al[13])	Phase 3 randomized study (RECORD-1) – 79% of patients received more than one prior systemic therapy e -subgroup who had received prior sunitinib-containing regimen (N=184; 44% of total population	Placebo	3.9 vs. 1.8	0.34 (0.23, 0.51)	<0.0001	1.8d

Summary

In the current treatment landscape, sunitinib is considered the reference standard for first-line therapy of patients with good or intermediate risk according to the MSKCC classification and considered a treatment option for poor risk patients with good performance status. Temsirolimus is considered the standard therapy for patients with poor risk criteria. No standard second line therapy exists for patients after failure of first-line temsirolimus. Everolimus is considered standard second line therapy after failure of first line tyrosine kinase inhibitor therapy. There is no standard third or subsequent line therapy.

The use of tyrosine kinase inhibitors is limited by their toxicity which includes fatigue, hand-foot syndrome, hypertension, hypothyroidism, diarrhea, and mucositis as the clinically most relevant. Side effect management is an important component in the overall treatment strategy due to the lack of randomized trials.

In today's clinical practice, these agents are sequenced, meaning if one line of therapy fails, it is replaced by another agent. Eventually almost all patients progress and require a switch to a different therapy. The most commonly used standard sequence in Canada consists of sunitinib as first-line therapy followed by everolimus as second-line therapy. Combinations of these agents are not considered clinically relevant at the present time and for the most part have been shown to be associated with intolerable side effects. For patients that develop intolerable side effects to everolimus, evidence based clinical guidelines do not already define "intolerance to treatment". As such, intolerance to treatment is usually determined by each oncologist based on his/her own clinical experience and discussion with the patient. For example, in instances where patients have poor lung function or poorly controlled diabetes, the oncologist may choose to not use everolimus. Axitinib is also probably not the best drug for patients with poorly controlled hypertension. A more rigid way to define intolerance is to determine if a patient cannot take the Health Canada approved dose of 10 mg everolimus per day continuously without breaks or dose reduction. However, in the clinical setting treatment dosing and schedule may be modified to allow patients to stay on therapy and benefit from the treatment. It is also important to note that there are major inter individual variation in patients tolerance for any drug specially with regards to oral drugs as absorption can vary significantly between patients. Novel agents, such as axitinib and tivozanib are potent VEGF inhibitors that are currently being evaluated in the second line setting and beyond where treatment options remain quite limited and offer the hope of better overall outcomes in this disease.

3.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of axitinib for patients with the following criteria:

- Metastatic or advanced, inoperable renal cell carcinoma
- Clear cell histology or clear cell component
- Failure of one prior systemic therapy

Currently, no clinically useful and reliable biomarkers exist for the prediction of response and/or benefit.

3.4 Other Patient Populations in Whom the Drug May Be Used

Axitinib has not yet been approved for any other indication than advanced RCC anywhere in the world. In most jurisdictions, including the US and the European Union axitinib has been approved for the treatment of mRCC patients who had previously failed one line of systemic treatment.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Kidney Cancer Canada, provided input on axitinib for the treatment of metastatic renal cell carcinoma (mRCC) and their input is summarized below.

Kidney Cancer Canada conducted an online survey to gather information about patient and caregiver experiences with the drug under review. The survey contained closed-ended questions with scoring options (ten-point rating scale); limited closed-ended questions (agree/disagree, yes/no, patient/caregiver) and open-ended questions that allowed for free-form commentary. A total of 138 respondents participated in the survey (103 patients and 35 caregivers). Patients and caregivers were recruited through the Kidney Cancer Canada membership database and through social media networks. Nine (9) of the patients had direct experience with axitinib. Of those who participated in the survey, 89% were Canadian. A copy of the survey was provided to pCODR. Cited responses are included verbatim to provide a deeper insight of the patient and caregiver perspective; cited responses are not corrected for spelling or grammar.

From a patient perspective, prolonging progression-free survival and allowing for extended control of their disease (tumour shrinkage or stability) are important aspects when consideration is given to treatment. Patients are aware that all treatments for advanced cancer carry risk and are willing to tolerate moderate to significant side effects during their treatment. Current available second-line treatment options in Canada are not suitable for all patients. Axitinib is expected to meet the needs of patients who are not suitable for an mTOR inhibitor. Patients with kidney cancer seek choice and flexibility in selecting second-line therapy to manage their disease and to maintain their quality of life.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Renal Cell Carcinoma

Patients with mRCC can experience many symptoms, including shortness of breath, coughing, fatigue, severe abdominal or back pain, or bone pain/fractures often involving the pelvis, femur or spine. There is no cure for mRCC presently; it is a fatal disease with a limited number of reimbursed treatment options.

In the first-line setting, new targeted therapies have proven to be successful in shrinking tumours and stopping the progression of the cancer for a period of time. Unfortunately, the cancer eventually becomes resistant to first-line treatment. Without second-line treatment alternatives, patients face certainty of disease progression including worsening of symptoms such as increasing shortness of breath, severe bone pain and fatigue. Depending upon the site of worsening metastases, patients may suffer from seizures, spinal compression leading to paralysis and painful bone fractures often requiring orthopaedic surgery.

From a patient perspective, quality of life while living with mRCC is an important consideration. In the survey of 138 patients and caregivers, the most frequently reported problematic side effects of the disease were: shortness of breath, fatigue, and mobility issues, all of which affect a patient's quality of life. Patients expressed a desire for choice in second-line therapy so that they can continue to manage their disease and side effects, as well as to maintain their quality of life.

Patient input noted that mRCC also affects patients' families and households. Patients rely more on their spouse and/or other family members for support. This reliance can create significant stress on the patient and the whole family leading to anxiety, depression and financial hardships.

"*Shortness of breath and pain are the 2 most important aspects to control. Shortness of breath contributes to fatigue. After climbing up 10 stairs, walking up a hill or walking long distances I am out of breath.*"

"*I have recurrent disease stage 4 have been like this since 2003. I do have shortness of breath and a cough, pain, fatigue. I control my breath and fatigue, as a part of life.*"

"*Fatigue, Pain, mobility and shortness of breath are important for quality of life. Energy is needed to fight.*"

"Yes I am able to still work as a [redacted] but I notice more fatique [sic] then prior to my diagnosis and treatment and surgery"

****The redaction above has been made by the patient advocacy group providing this input.****

4.1.2 Patients' Experiences with Current Therapy for Metastatic Renal Cell Carcinoma

Everolimus is the solely funded, second-line treatment option. Depending on underlying health issues and kidney cancer symptoms, for some patients, the side effects of everolimus could have a significant impact on quality of life and daily activities. Shortness of breath, for example, is a common side effect of this type of cancer and the product monograph for everolimus lists non-infectious pneumonitis as a clinically significant adverse event. While everolimus may be an appropriate treatment choice for some patients, for those with lung impairment, an alternate therapy is necessary. The majority of respondents to the survey indicated that, if given a choice of drugs, it was 'moderately' to 'extremely important' to choose drugs based upon each drug's known side effects with 52.5% who answered this question rating their response as 'extremely important'.

One of the questions on the survey asked respondents should there be a minimum of two funded therapies, how would they rate the importance of flexibility in their choices. A large majority of the respondents (83.9% of 93 respondents who answered this question) indicated that it was 'extremely important' to have this flexibility. When considering a new therapy, 82.4% of the 91 respondents who answered the question confirmed that when considering a new therapy, having a choice was 'very important to choose which drug would be better suited for me'.

Kidney Cancer Canada states that patients face unnecessary hardships in accessing the only-available second-line therapy. In some provinces, patients are not eligible for everolimus if they have taken pazopanib as a first-line therapy. Any patient who has been prescribed first-line temsirolimus, another mTOR inhibitor, has no publicly funded access to an VEGF/TKI agent. Similarly, patients who have participated in first-line clinical trials with new agents are routinely ineligible for second-line therapy in many provinces citing lack of evidence and this practice presents a significant barrier to the acceptance of clinical trials by patients.

The following concerns in relation to current experiences with therapy for mRCC were expressed by the patient advocacy group:

- **Difficulties for Some Patients with Current Treatment:** Patients feel that the current second-line treatment option, everolimus, is not effective for everyone. "*affinito [sic] caused me to become diabetic caused very high colesterol [sic]*"

  One caregiver wrote: "*She responded so poorly on Afinitor (everolimus) - no disease stability, debilitating side effects including pulmonary fibrosis - that her oncologist has advised against taking any type of mTOR inhibitor targeted therapy again. She responded so well on Sutent (sunitinib) that her oncologist will only consider VEGF inhibitor targeted therapies. When Sutent stops responding (it's a "when" not an "if"), she will have to consider an alternative VEGF targeted therapy in order to both prolong life with quality of life. Having access to a third Health Canada approved VEGF inhibitor targeted therapy (i.e. axitinib) gives one more chance at extended life with quality of life for a woman in her 50s with stage IV kidney cancer.*"

- **Lack of Access to Second Line Therapy in General:** When compared to other Western countries, such as Germany, it appears the percentage of kidney cancer patients who receive any second line treatment is significantly lower, conceivably due to lack of options.

- **Patients Require Expert Oncologists / Drug Navigators to Assist with Access:** Kidney cancer specialists spend significant time working on reimbursement/access issues for their patients.
  "*The private insurer was very particular as to how the oncologist prescribed the medication. It took several tries and many phone conversations to get it right."*

- **Excludes some Kidney Cancer Patients Due to Rarer histology:** Patients with non-clear cell kidney cancer are limited in their choices of therapy.
  "*Because I have a rare type of kidney cancer (Papillary), my oncologist cannot get me any of the standard therapies for kidney cancer such as Sutent or Afinitor. We need more flexibility!*"

- **Choice and Access**: Patients placed a very high significance on having a choice with their oncologists in selecting which drug is better suited for their circumstances. The vast majority of respondents want access to new treatments for kidney cancer. A choice in the second-line setting would enable patients and their oncologists to individualize treatments plans according to their disease, treatment history and contraindications enabling the best possible quality of life.

4.1.3 Impact of Metastatic Renal Cell Carcinoma and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of mRCC on caregivers and families is significant. Caregivers provide supportive care to the patient in managing adverse side effects, providing emotional support and assuming additional unpaid work duties in the home. In addition, caregivers of advanced kidney cancer patients suffer from the emotional stress of caring for the patient and from financial anxieties related to disability and costs of treatment.

"*If my husband is suffering, then I am suffering. I suffer a great deal from depression and anxiety as a result of his diagnosis and ongoing fight for his life. I sometimes take time off of work if he is struggling with side effects, or if an emergency comes up (I.e. sudden fever), and to accompany him on all tests and appointments."*

"*My caregiver is concerned about money, thinking we might need our retirement savings for drug costs for me if no one will pay. So, our retirement fund is now our cancer drugs fund.*"

"*in addition to the stress caused by the disease, it has forced my caregiver to increase her workload tremendously to make ends meet financially as I was unable to work and - being self-employed - with no benefits.*"

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Axitinib

Axitinib offers patients an opportunity for an individualized treatment plan in addition to the existing second-line therapy and it may offer patients an enhanced quality of life for an extended period of time.

For patients who anticipate choosing a second-line drug, goals and expectations of second-line therapy are to prolong progression-free survival allowing for extended disease control (tumour shrinkage or stability) with allowable moderate to significant side effects. When considering a new drug treatment, the vast majority (89% of 91 respondents) indicated that it is 'extremely important to see an improvement in their cancer' (tumour shrinkage, tumour stability, pain reduction, improved breathing) and many (69.9% of 93 respondents) indicated that it was 'extremely important to realize an improved quality of life'.

When asked about whether it was important to evaluate the average period of the expected benefit, survey respondents (70.7% of 92 respondents) placed an extremely high degree of importance to this decision. In considering a new therapy, the vast majority of (86% of 90 respondents) indicated that they were willing to tolerate a moderate to high degree of side effects in the range of 5 to 10, where 10 = 'significant side effects'.

The following issues relating to **patient expectations for and experiences to date with** axitinib were expressed by the patient advocacy group:

- **Gap or Unmet Patient Need in Current Therapy (second-line):** Axitinib is expected to meet the needs of patients who are not suitable for an mTOR inhibitor (e.g. those patients with existing lung impairment/shortness of breath, diabetes, previous radiation to the lungs, COPD, or liver toxicity).

- **Gap or Unmet Patient Need in Current Therapy based on First-Line Therapy Selection:** for many patients who have reached a 'dead-end' after first-line therapy due to their / their oncologist's selection of therapy in the first-line setting of an mTOR or a clinical trial drug.

- **Potential Risks Associated With the Drug:** Patients are aware that all treatments for advanced cancer carry risks. Axitinib has risks and known side effects. The product monograph for axitinib contains a list of clinically significant adverse events. Axitinib is an oral therapy that is not administered in a hospital or cancer care centre that allows the patient's ease of use. The management of side effects may require intervention of health care professionals and caregivers similar to other Health Canada approved therapies for mRCC.

A total of nine (9) respondents had direct experience with axitinib, in which 67% were accessing it in either the third, fourth or fifth-line of therapy, two respondents were receiving it in the second-line and one person was receiving axitinib in the first-line. Canadian patient experience with axitinib was limited in the Phase 3 clinical trial (AXIS) due to a small mRCC patient population and competing clinical trials. Some Canadian patients subsequently accessed the drug through Health Canada's Special Access Programme.

When asked about the side effects experienced with axitinib, respondents mentioned fatigue, nausea, diarrhoea and hypertension. In rating the side effects of axitinib, 63% of 8 respondents assigned a score of low to moderate (respondents in the range of 1 'no side effects at all' to 4) and 37% indicated that the side effects were debilitating (respondents in the range of 8 to 10, with one of these respondents (13%) rating the side effects at 10 or 'debilitating side effects that impact daily living'). Of the side effects experienced, respondents indicated 38% were willing to accept them, 25% felt that some were acceptable and others were not, one person (13%) had an adverse event/discontinued usage and two respondents did not answer directly. "*Axitinib is a well tolerated drug with manageable side effects. While on this drug you don't feel very toxic and sick. This has a huge impact on your quality of life.*"

With respect to the patient's view of how axitinib is expected to change their long-term health and well-being, 75% of the 8 respondents are looking for disease stability or tumour reduction in the long term. "*My last CT scan after being on Inlyta™ for 72 days showed a 30-50% decrease in tumor[sic] size. I look at that as being long term health! I hope I can stay on this medicine for quite some time.*"

While axitinib has known risks and side effects, 75% of the 8 respondents rated their quality of life while taking axitinib gave them moderate to high/normal living (respondents in the range of 5 to 8, where 10 = 'high/normal living'). Further, their overall rating of the axitinib experience, in comparison to other drugs taken for kidney cancer, indicated that 75% of 8 respondents scored a similar moderate to high rating (respondents in the range of 6 to 10, where 10 = 'much better').

When asked about the positive and negative impact of axitinib on their kidney cancer, the 9 responses were quite mixed according to the line of therapy. Three (3) patients indicated that the cancer was stable; 2 respondents said that it was too soon to report; 2 respondents did not answer the question directly; and 2 patients (both fifth line use) had seen their cancer progress/no impact.

"*My last two (2) CT Scans (abs/pelvis/thorax) were generally fully stable with no interval increases and with several areas of tumours reductions and no new mets, This is very positive. Only negative effect has been the previously-mentioned hemoptysis bouts and, to the extent that the Axitinib may have been, at least in part, responsible for my current case of hiccups, that as well.*"

"*It needs to be avalable [sic] to patients when doctors, in conjunction with patients, feel this is the best rteatment [sic] for an individual patient. Governments need to be much more flexible to allowing doctors/patients to determine the proper treatment.*"

"*Axitinib is a source of hope, one more targeted therapy that can give prolonged life (with the so-important quality of life). These targeted therapies rarely "cure" the patient of kidney cancer (from what I understand), but they can extend life in its truest sense: quality of life with extra time.*"

"I would like to be able to sitvdown [sic] with my oncologist and discuss WHICH drug would be the best for me."

4.3 Additional Information

Kidney Cancer Canada also surveyed 16 medical oncologists from their Medical Advisory Board who specialize in treating advanced renal cell carcinoma and have experience with axitinib. For this survey, the patient advocacy group specifically sought input from oncologists on how prescribing decisions for second-line treatment are made, key factors that contribute to treatment choice and obstacles to best outcomes for their patients. This survey and the summary of results were provided to pCODR with the patient advocacy group's input.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for axitinib (Inlyta) for metastatic renal cell carcinoma (mRCC). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the axitinib (Inlyta) review was obtained from seven of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that the relationship between everolimus (current standard for the 2nd line treatment of mRCC) and axitinib needs to be explored further since sorafenib is the main comparator in the clinical trials for axitinib. It was also noted that due to axitinib having an oral route of administration, it may be easier to implement for provinces; however, it is important to note that dose escalations and modifications will be a key factor when considering costs to the provinces associated with implementing axitinib. As an oral drug, axitinib will not add or burden chemo chair time and will be relatively accessible to patients.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

The current standard of care in the second line treatment of metastatic renal cell carcinoma is everolimus. The key trial for axitinib compares it to sorafenib which may act as a barrier to understanding its relative place in therapy; however, if cytokines are used in 1st line, sorafenib is a recognized 2nd line comparator for treating mRCC. PAG noted that provinces who fund everolimus as second line agent after first line sunitinib treatment will benefit if axitinib has a different adverse effect profile than everolimus. In the absence of direct head to head efficacy and safety data, it would be helpful if pERC could advise on comparative clinical and cost effectiveness benefits between everolimus and axitinib.

The magnitude of benefit seen with axitinib appears to be greater in patients treated with prior cytokines than in patients treated with prior sunitinib. PAG identified that this will also challenge axitinib's place in therapy. The primary study for axitinib uses 1st line therapies either no longer used (cytokines) or not used at all (bevacizumab). PAG also commented that for provinces like Ontario, where sorafenib is funded as the second line therapy after cytokine treatment, the trial will be of significance.

5.2 Factors Related to Patient Population

PAG noted that the main enabler that will be important in implementing axitinib would be the small population of patients that require the therapy.

However, PAG identified "indication creep" as the most common barrier that could affect implementation. Clinicians may decide to use axitinib as third line, or first line. Although the Health Canada indication is for the treatment of patients with metastatic renal cell carcinoma (RCC) of clear histology after failure of prior systemic therapy with either a cytokine or the VEGFR-TKI sunitinib, there is an ongoing phase III study examining use in first line which may exacerbate the "indication creep" barrier to implementation.

5.3 Factors Related to Accessibility

PAG identified that due to axitinib being an oral drug it will generally be more easily accessed by patients. In some jurisdictions however, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility. For these jurisdictions, patients would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of- pocket expenditure.

5.4 Factors Related to Dosing

PAG noted that axitinib can be delivered in less central and rural areas, which may mean that patients could potentially mistake their dosing regimens. The dosing of axitinib is twice a day (BID) whereas its comparator, everolimus, is once daily; therefore, pill burden and adherence need to be considered. Also, PAG identified dose titration as a potential problem since both 1mg and 5mg tablets might be needed by patients. There may need to be dose modifications for drug interactions and tolerability.

Drug wastage at time of dose modification may occur. The main study allowed subjects to escalate the dose beyond the recommended 5mg to 7mg and then 10mg. As such, since the final product monograph only specifies 5mg BID as the recommended dose with dose increase or reduction based on individual safety and tolerability, if the budget impact / cost-effectiveness analysis only focus on 5mg, the escalated dose would not be accounted for in the real or potential budget impact or cost effectiveness if the product is funded.

5.5 Factors Related to Implementation Costs

PAG identified that axitinib as an oral therapy will not add or burden chemo chair utililization since both first and second line comparators are orally administered. However, drug interaction monitoring could act as a barrier to implementation with respect to ensuring adequate health care professional resources and time to support optimal therapy.

There is a potential for sequential use for axitinib and everolimus (or vice versa) and this poses a barrier to implementation in the absence of evidence to support this possible practice.

5.6 Other Factors

PAG identified the need for a treatment algorithm as many new agents are being developed for the treatment of renal cell cancer.

6 SYSTEMATIC REVIEW

6.1 Objectives

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

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 1. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs	Patients with advanced renal cell carcinoma who have failed first line treatment <u>Sub-group analysis</u>: By prior treatment	Axitinib monotherapy at a recommended dose of 5 mg orally twice daily, up to 10 mg twice daily	mTOR inhibitors • Everolimus • Temsirolimus VEGFR inhibitors • Sorafenib • Sunitinib • Pazopanib Immunotherapy • Interferon-α • Interleukin-2	• 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

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions*

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- What is the evidence regarding the effectiveness and safety of everolimus in mRCC? How do AXIS and RECORD-1 trials compare in terms of study design, population, interventions and outcomes? What are the limitations of conducting an indirect comparison between everolimus and axitinib?

6.2.2 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-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2012, Issue 11) 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 concept was axitinib (Inlyta).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or language.

The search is considered up to date as of December 3, 2012.

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 – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. 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 information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.

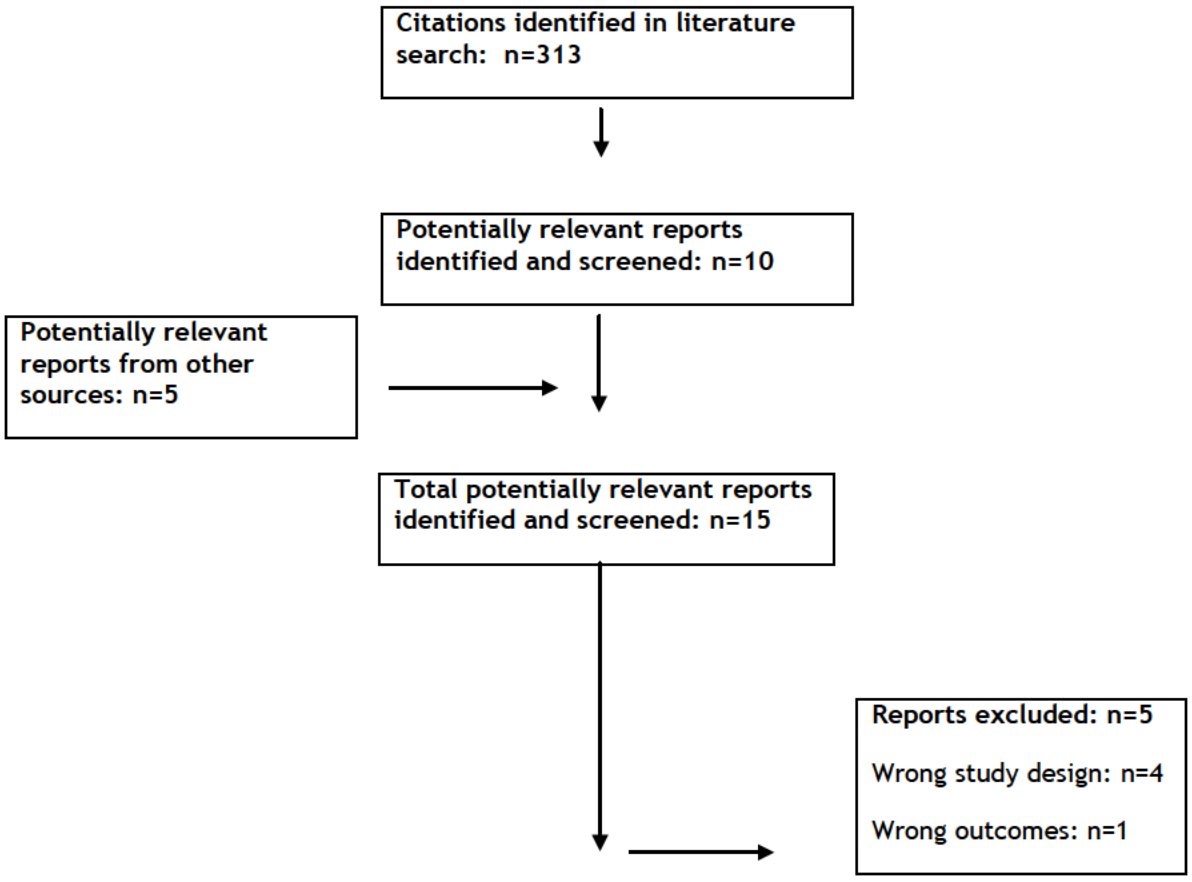
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 15 potentially relevant reports identified, ten reports presenting data from one unique trial were included in the pCODR systematic review[3,8,30-37] and five studies were excluded. Studies were excluded because of wrong study design[38-41] or wrong outcomes.[42]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the included study were also obtained through requests to the Submitter by pCODR[43,44]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2: Summary of Trial Characteristics of the Included Study[3,8]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
AXIS[3,8] 175 centres in 22 countries September 15, 2008 to July 23, 2010 (data cut-off August 31, 2010) Phase 3 RCT, open-label, active control n=723 randomized n=714 treated Funded by Pfizer Inc.	Patients ≥ 18 years with histologically or cytologically confirmed renal cell carcinoma with a clear cell component and evidence of metastatic disease ≥ 1 measurable target lesion documented radiographically and RECIST-defined progressive disease after one previous systemic first-line regimen (sunitinib, bevacizumab + interferon-α, temsirolimus, or cytokine-based) ECOG PS ≤ 1 Life expectancy ≥ 12 weeks	axitinib 5 mg orally twice daily with food versus sorafenib 400 mg orally twice daily without food axitinib dose could be increased to a maximum of 10 mg twice daily in the absence of > grade 2 AEs or decreased to a minimum of 2 mg twice daily if needed sorafenib dose could be decreased to a minimum of 400 mg every other day if AEs no cross-over permitted	<u>Primary</u> Progression-free survival (IRC assessed) <u>Secondary</u> Progression-free survival (investigator assessed) Overall survival Objective response rate Duration of response Time to deterioration (composite endpoint of death, progression, and a decrease in FKSI) Patient reported outcomes (FKSI, FKSI-DRS) Safety

AEs=adverse events; **ECOG PS**=Eastern Cooperative Oncology Group performance status; **FKSI**=Functional Assessment of Cancer Therapy Kidney Symptom Index; **FKSI-DRS**=Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms; **IRC**=independent radiology committee; **RECIST**=Response Evaluation Criteria in Solid Tumours; **RCT**=randomized controlled trial

a) Trials

One multicentre phase 3 randomized controlled trial (study AXIS) was included in this review.[3,8] The trial was conducted in 175 centres in 22 countries and was manufacturer-sponsored.

The trial included patients with histologically or cytologically confirmed renal cell carcinoma with a clear cell component with evidence of metastatic disease. Additional eligibility criteria included at least one measurable target lesion documented radiologically, RECIST-defined progressive disease and 2 weeks or more since one previous systemic first-line regimen with a sunitinib-based, temsirolimus-based, or cytokine-based regimen, or 4 weeks or more with a bevacizumab plus interferon-α-based regimen. Patients were further required to have an ECOG performance status of 0 or 1, a life expectancy of 12 weeks or more, and adequate renal, hepatic and haematological organ functions. Patients were ineligible to enter the study if they had prior treatment with more than one systemic first line regimen, treatment with neoadjuvant or adjuvant systemic therapy,

major surgery < 4 weeks prior to starting study treatment, or radiation therapy < 2 weeks prior to starting study treatment. Further exclusion criteria included: history of malignancy other than RCC; use of drugs known to affect cytochrome P450; HIV/ AIDS; CNS metastasis; uncontrolled hypertension; myocardial infarction, uncontrolled angina, congestive heart failure, or cerebrovascular accident within the previous 12 months; and deep vein thrombosis or pulmonary embolism within the previous 6 months.

Patient enrolment started on September 15, 2008 and ended July 23, 2010. The data cut-off date was August 31, 2010. An initial target sample size of 540 patients was calculated based on 90% power to demonstrate a 40% improvement in PFS using a one-sided, stratified log-rank test with a significance level of 0.025. It was further assumed that sorafenib-treated patients would have a median PFS of 5 months compared to a median of 7 months for axitinib-treated patients, with an enrolment period of 18 months. The initial sample size was later increased to 650 patients because no drop-outs (prior to progression) had been assumed in the original sample size calculations. The amended protocol (November 16, 2009) assumed a 25% drop-out rate at 18 months. The required number of PFS events remained unchanged at 409 events.[45]

The sample size also provided adequate power for overall survival with an estimated 417 events using a log-rank test with a significance level of 0.025 and power of 80% to detect a difference. Lan-DeMets/ O'Brien-Fleming methodologies were used to account for multiple overall survival analyses. Accordingly, the alpha for the interim overall survival analysis (cut-off of August 31, 2010) was 0.002 and the alpha for the final analysis (November 1, 2011) was 0.0244.[37]

Other secondary endpoints were tested at a significance level of 0.025 but no adjustments were made for multiple testing or comparisons.

Trial procedures for randomization and allocation concealment were considered adequate. Allocation to treatment was done randomly using a web-enable centralized registration system.

b) Populations

Patients were randomized in a 1:1 ratio to receive open-label axitinib (n=361) or open-label sorafenib (n=362). The randomization was stratified by ECOG performance status (0 or 1) and by type of previous treatment. Median age was 61 years (range 20 to 82). The study population comprised mostly of men (72%) and patients were predominantly white (76%). The median time since metastatic diagnosis was 59 weeks (range 1 to 752 weeks) for the axitinib group and 62 weeks (range 1 to 883 weeks) for the sorafenib group. Almost all patients had a nephrectomy (>90%). Approximately 64% and 10% of patients were classified in the intermediate and poor risk sub-groups according to the Heng et al. risk factors respectively. Approximately 44% of patients had an ECOG performance status of 1. Stage IV cancer was reported in 89% of patients, with lung metastases in >75% of patients. Prior therapy with sunitinib, cytokines, bevacizumab, or temsirolimus was received by 387 (54%), 251 (35%), 60 (8%) and 25 (3%) patients respectively.

c) Interventions

Axitinib was started at a dose of 5 mg administered orally twice daily with food. Patients tolerating the starting dose for at least 2 weeks (i.e., not experiencing adverse events above grade 2; maintaining a blood pressure of 150/90 mmHg or less or not receiving an antihypertensive agent) could have their dose increased to 7 mg twice daily. Using the same criteria, patients could have their dose subsequently increased to 10 mg twice daily. Conversely, axitinib could be reduced to 3 mg twice daily or 2 mg twice daily as required in the presence of grade 3(non-hematologic) toxicity.

Sorafenib patients received an initial dose of 400 mg orally without food twice daily. In the presence of toxicity, the dose could be decreased to 400 mg orally once daily, and then to 400 mg every other day if required.

Patients were treated until progression of disease, occurrence of unacceptable toxicities, death, or withdrawal of consent. Cross-over between study drugs was not permitted. Patients were eligible for continued treatment as assigned at randomization beyond disease progression. Patients were also eligible for subsequent systemic therapies at physicians' discretion (Table 3).

Table 3: Most Commonly Used Follow-up Systemic Therapy in Patients who Discontinued Study Treatment (November 1, 2011)[46]

Subsequent therapy, %	Axitinib (n=320)	Sorafenib (n=332)
Any systemic therapy	54	57
>1 systemic therapy	26	27
everolimus	35	34
sorafenib	6	8
temsirolimus/ sirolimus	6	10
bevacizumab	5	8
sunitinib	12	16
pazopanib	6	8

d) Patient Disposition

A total of 723 patients were randomized and included in the full analysis (Table 4). Nine patients did not receive treatment after randomization (5 due to protocol violation, 3 refused treatment, and 1 patient's health deteriorated)[3], and thus the safety population (i.e., patients receiving at least one dose of study medication) included 359 and 355 axitinib and sorafenib patients respectively.

Table 4: Number of Patients[8]

	Axitinib	Sorafenib
Randomized	361	362
Received treatment	359	355
Full analysis	361	362
Safety analysis	359	355
Still receiving treatment at end of trial (%)	138 (38)	99 (28)
Discontinued treatment (%)	221 (61)	256 (71)
• Disease progression or relapse	• 160 (44)	• 180 (50)
• Adverse event	• 22 (6)	• 33 (9)
• Protocol violation	• 4 (1)	• 2 (1)
• Patient discontinued treatment (not due to adverse events)	• 10 (3)	• 7 (2)
• Global deterioration of health status	• 9 (3)	• 9 (3)
• Death	• 12 (3)	• 13 (4)
• Lost to follow-up	• 1 (<1)	• 3 (1)
• Other	• 3 (1)	• 9 (3)

At data cut-off (August 31, 2010), 221 (61%) axitinib and 256 (71%) sorafenib patients had discontinued treatment (Table 4). The most common reasons for treatment discontinuation were disease progression (44% and 50% of axitinib and sorafenib patients respectively), adverse events (6% and 9% of axitinib and sorafenib patients respectively), and death (3% and 4% of axitinib and sorafenib patients respectively).

e) Limitations/Sources of Bias

- AXIS was funded by Pfizer Inc.

- RECORD-1 data (which compared everolimus to placebo) were presented at the American Society of Clinical Oncology (ASCO) in June 2008, three months before the start of AXIS.[47] Although it had not yet been approved for use as second line therapy in mRCC at the start of AXIS, everolimus (Afinitor) would have been a more appropriate comparator to axitinib. Therefore, there is no evidence as to the relative effectiveness of axitinib compared to everolimus. Which of these two agents should be used first as second line therapy cannot be established based on evidence. Information on everolimus is provided in the supplemental issues section.

- Patients and investigators were not blinded to study treatment (open-label design) to facilitate dose adjustments. This type of study design may limit the interpretation of the results reported for patient outcomes (symptom improvements and quality of life).

- The actual sample size was 723 patients, higher than the estimated 650 patients. The higher than required sample size was due to patients already at the screening stage when the 650th patient was enrolled.[45] Enrollment at the Japanese centers was also extended to meet regulatory requirements for submission. The final number of PFS events was 402 at data cut-off which is lower but close to the required 409 events.[37]

- PFS is a surrogate outcome for overall survival in patients with advanced RCC who receive targeted therapies. An association between PFS and overall survival has been reported based on observational data.[48]

- There were no statistical adjustments of the level of significance to account for multiple secondary end points and therefore P values are not interpretable for secondary end-points other than overall survival. Similarly, no statistical adjustments were made to account for sub-group analyses including the pre-specified sub-group analyses and therefore these are considered exploratory.[37]

- There was discordance between the independent radiology committee and investigators in 24% of the patient population as to whether a PFS event occurred or not. This may be due to choosing different lesions as target lesions and investigators may have had additional clinical information to assess PFS. Similarly, the total event discordance rate was 23% between radiologists.[36]

- The results of overall survival may have been confounded by subsequent therapies administered to patients who discontinued the trial.

- The majority of axitinib-treated patients in AXIS required dosage adjustments. It would appear that the correct dosing for axitinib has yet to be defined. Toward this end, an on-going trial is evaluating the benefits and harms of dose titration (increase) of axitinib in 200 patients with mRCC.[49]

- The results of AXIS are generalizable to patients with mRCC who have failed first line treatment with sunitinib or a cytokine. However, it is still unclear whether axitinib is the best treatment choice post- sunitinib progression because most PFS benefit came from the sub-group with prior cytokine therapy. Hence, results should be considered in light of the fact that cytokines are used infrequently given that other less toxic therapeutic choices are available. Moreover, sunitinib, sorafenib, and axitinib work through the same pathway (VEGFR inhibition) to inhibit angiogenesis, although axitinib has higher affinity and selectivity to the receptors.[50]

- There is no evidence for the use of axitinib as first line treatment or for the use of axitinib in non-clear cell mRCC.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 5: Summary of Key Outcomes				
EFFICACY (ITT; blinded independent radiology committee)				
Outcome	**Study group**	**Median Months (95%CI)**	**HR (95% CI)**	**P value**
Overall survival	Axitinib Sorafenib	20.1 (16.6, 23.4) 19.2 (17.4, 22.3)	0.97 (0.8, 1.2)	0.37
Progression-free survival	Axitinib Sorafenib	6.7 (6.3, 8.6) 4.7 (4.6, 5.6)	0.67 (0.5, 0.8)	<0.0001
Outcome	**Study group**	**n/N**	**% (95% CI)**	
Partial tumour response*	Axitinib Sorafenib	70/361 34/362	19.4 (15.4, 23.9) 9.4 (6.6, 12.9)	
PATIENT REPORTED OUTCOMES				
Outcome	**Study group**	**Number of patients in analysis**	**Mean Scores**	
FKSI-15	Axitinib Sorafenib	361 362	42.21 41.86	
HARM				
Outcome	**Study group**	**n/N**	**%**	
Fatal SAE	Axitinib Sorafenib	31/ 359 23/ 355	9 7	
SAE	Axitinib Sorafenib	106/ 359 110/ 355	30 31	
AE	Axitinib Sorafenib	325/ 359 336/ 355	91 95	
WDAE	Axitinib Sorafenib	22/ 359 33/ 355	6 9	
AE=adverse events; **CI**=confidence interval; **CR**=complete response; **HR**=hazard ratio; **ITT**=intention to treat; **NR**=not reported; **PR**=partial response; **SAE**=serious adverse events **WDAE**=withdrawal due to adverse events				
*No complete response reported in either arm				

Efficacy Outcomes

Overall Survival

Overall survival was a secondary end point defined as the time from randomization to the time of death due to any cause. In the absence of death, the data was censored at the last date the patient was known to be alive. Patients without data after randomization had their data censored at the date of randomization.

The final overall survival analysis was obtained from the FDA Statistical Review (page 25)[37]. It showed no statistically significant difference between axitinib and sorafenib (Table 6).[37]

Table 6: Overall Survival (final analysis November 1, 2011)[37]

	Axitinib (n=361)	Sorafenib (n=362)	P value
Deaths, n (%)	211 (58)	214 (59)	
Overall survival (95% CI)			
• median, months*	20.1 (16.6, 23.4)	19.2 (17.4, 22.3)	
• HR†	0.97 (0.8, 1.2)		0.37‡

CI=confidence interval; **HR**=hazard ratio

***Kaplan-Meier estimate
†based on stratified Cox model for ECOG performance status and prior therapy factors
‡based on one-sided log-rank test, stratified by ECOG PS and prior therapy, and not adjusted for interim analysis

Progression-free Survival

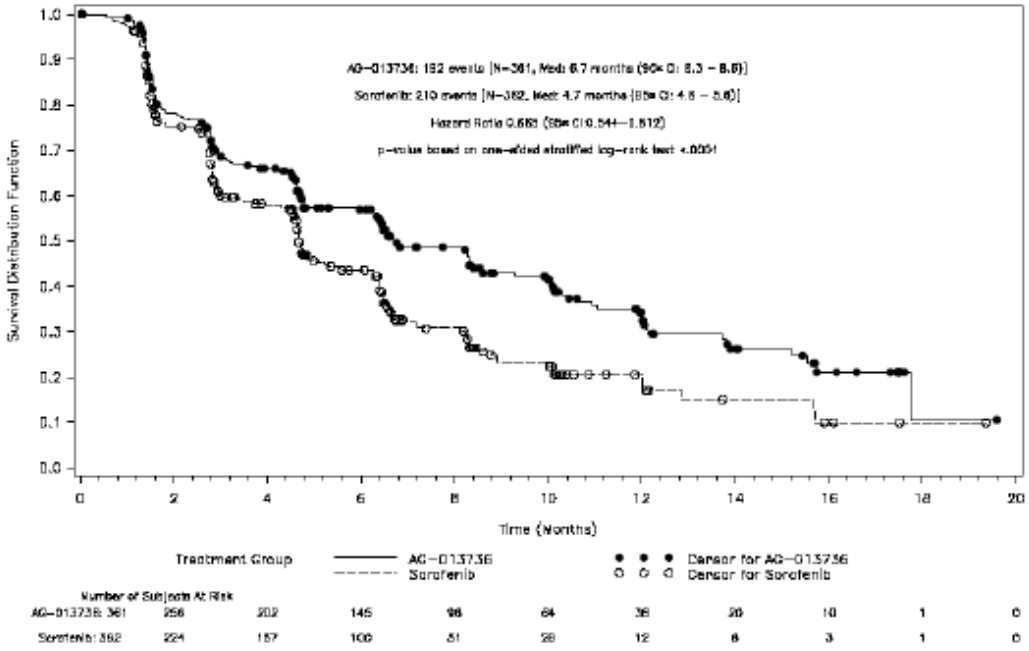
Progression-free survival based on a blinded independent radiology committee assessment was the primary end point. Progression-free survival based on investigator assessment was a secondary end point.

Progression-free survival was defined as the time from randomization to first documentation of objective tumour progression or death due to any cause while on study. Data was censored for patients who were alive and did not experience disease progression during the trial, who missed two or more consecutive tumour assessments before disease progression or death, who started another type of anti-tumour treatment before documented disease progression, or who had at least one disease assessment and discontinued treatment without disease progression or death. Data was censored at randomization in patients lacking an evaluation of their disease at baseline or in those without an evaluation of tumour response after randomization unless death occurred prior to the first planned assessment.

The progression-free survival hazard ratio of axitinib over sorafenib using a stratified Cox model for ECOG performance status and prior therapy factors was 0.67 (95% CI: 0.55, 0.81). The difference in median PFS between the two treatment groups was 2 months.[3]

Table 7: Progression-free Survival (independent radiology committee; final analysis November 15, 2010)[3]			
	Axitinib (n=361)	**Sorafenib (n=362)**	**P value**
Patients with events, n (%)	192 (53)	210 (58)	
• objective progression	180 (94)	200 (95)	
• death without progression	12 (6)	10 (5)	
PFS (95% CI)			
• median, months*	6.7 (6.3, 8.6)	4.7 (4.6, 5.6)	
• HR†	0.67 (0.54, 0.81)		<0.0001‡
CI=confidence interval; **HR**=hazard ratio; **PFS**=progression-free survival			
***Kaplan-Meier estimate †based on stratified Cox model for ECOG performance status and prior therapy factors ‡based on one-sided log-rank test, stratified by ECOG PS and prior therapy			

Figure 2: Kaplan-Meier Curve of Progression-free Survival (independent radiology committee)[3]



Source: A4061032 CSR Figure 14.1.1
Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicated a reduction in favor of sorafenib. Hazard ratio was adjusted for same stratification factors as log-rank test. For the overall stratified analysis, the p-value was from a 1-sided log-rank test of treatment stratified by ECOG performance status and prior treatment.
Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; Med=median; N=number of subjects

Progression-free survival hazard ratio based on investigator assessment was similar to that obtained with the independent radiology committee assessment (data not shown).

Sub-group Analyses of Progression-free Survival

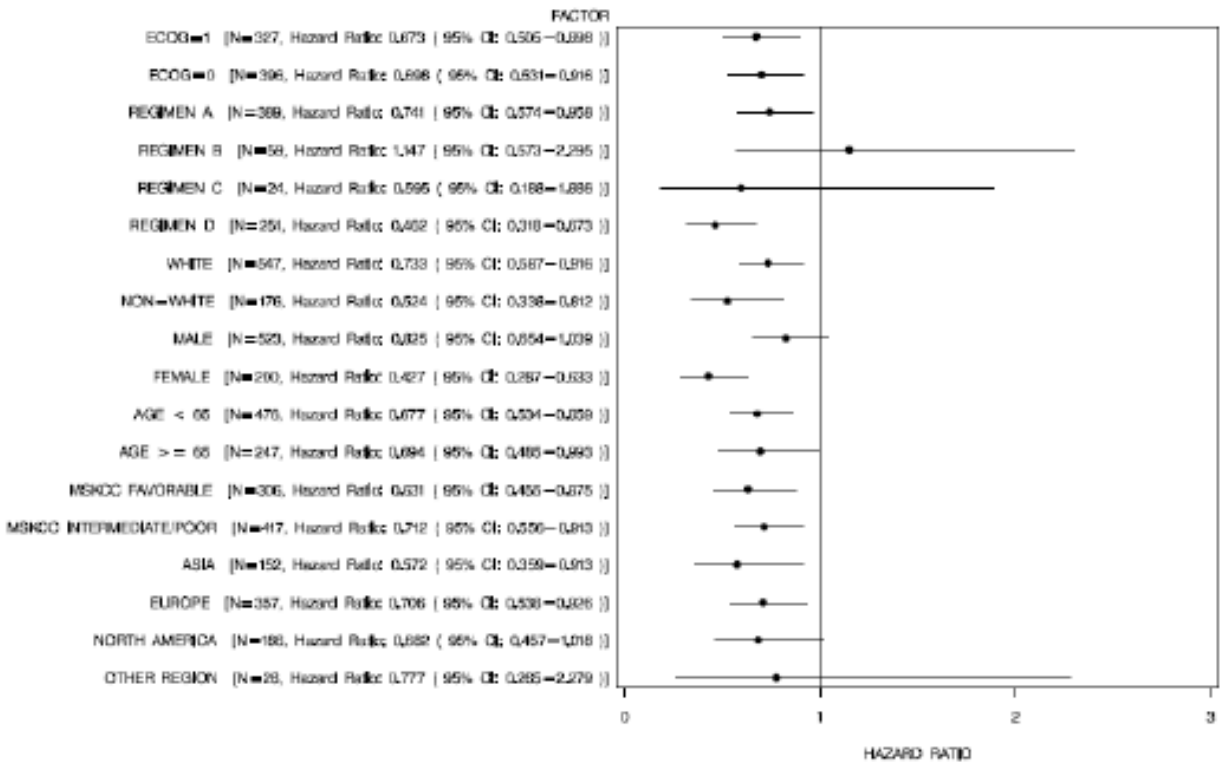
The relative effectiveness of axitinib and sorafenib for PFS was explored in a number of sub-groups (Table 8 and Figure 3). As shown in Table 8, cytokine pre-treated patients may have a better PFS response and much less so in the sunitinib pre-treated patients. However, these findings are considered exploratory because no adjustments were made in Type I error rate for multiple subgroups analyses.[36]

Table 8: Progression-free Survival by Previous Therapy (ITT, independent radiology committee)[8]

Previous therapy	Stratified estimated median PFS, months (95% CI)		HR (95% CI)
Cytokines	Axitinib (n=126)	Sorafenib (n=125)	0.46 (0.32, 0.68)
	12.1 (10.1, 13.9)	6.5 (6.3, 8.3)	
Sunitinib	Axitinib (n=194)	Sorafenib (n=195)	0.74 (0.57, 0.96)
	4.8 (4.5, 6.4)	3.4 (2.8, 4.7)	
Bevacizumab	Axitinib (n=29)	Sorafenib (n=30)	1.15 (0.57, 2.32)
	4.2 (2.8, 6.5)	4.7 (2.8, 6.7)	
Temsirolimus	Axitinib (n=12)	Sorafenib (n=12)	0.51 (0.14, 1.87)
	10.1 (1.5, 10.2)	5.3 (1.5, 10.1)	

CI=confidence interval; **HR**=hazard ratio; **ITT**=intention to treat; **PFS**=progression-free survival

Figure 3: Cox Proportional Hazard Analysis of Progression-free Survival (independent radiology committee)[3]



Source: A4061032, Figure 14.1.3 (See updated information in Module 5, Section 5.3.5.1, A4061032 CSR Erratum, Figure 14.1.3)

Abbreviations: CI=confidence interval, ECOG=Eastern Cooperative Oncology Group; IRC = Independent Review Committee, MSKCC=Memorial Sloan-Kettering Cancer Center; N = number of subjects

Regimen A=sunitinib-containing regimen; Regimen B=bevacizumab-containing regimen; Regimen C=temsirolimus-containing regimen; Regimen D=cytokine-containing regimen

[a] All hazard ratios are unadjusted. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of axitinib; a hazard ratio >1 indicates a reduction in hazard rate in favor of sorafenib.

Tumour Response

Tumour response was a secondary end point. Tumour assessments were done at screening, every 6 weeks for the first 12 weeks, then every 8 weeks, and at the final visit.

Objective response rate was defined as the percentage of patients with confirmed complete response or confirmed partial response according to RECIST criteria. A third-party blinded review of radiographic images was performed retrospectively by an independent radiology committee. Two independent reviewers read the scans. Differences between the two reviewers were resolved by a third reviewer. Patients without a radiographic tumour re-evaluation or those who died, progressed, or dropped out of the trial for any reason before reaching a complete response or a partial response were counted as non-responders. A patient who met the criteria of a partial responder and then became a confirmed complete responder was assigned as a complete responder.

The objective response rate as determined by a blinded independent radiology committee was 70 patients (19%, 95% CI: 15%, 24%) for axitinib and 34 patients (9%, 95% CI: 7%, 13%) for sorafenib (risk ratio=2.1, 95% CI: 1.4, 3.0). All were partial responses as there were no complete responders. The median duration of response was 11 months (95% CI: 7.4, not estimable) for axitinib and 10.6 months (95% CI: 8.8, 11.5) for sorafenib.[3]

Exposure to Study Medication and Dosing Regimen Modifications

Patients' exposure to treatment is provided in Tables 9 and 10.[3] Patients received axitinib for a median duration of 186 days (range 1 to 670) and sorafenib for 141 days (range 1 to 609). More than 75% of study patients required a dose interruption mostly due to adverse events (Table 9). A total of 24% of axitinib-treated patients required a dose reduction from the initial 10 mg dosing. Seventy-one patients (20%) had their axitinib dose escalated then reduced. A total of 139 (39%) of patients treated with axitinib remained on the initial dose of 5 mg twice daily throughout the study (Table 10).

Table 9: Exposure to Treatment[3]

	Axitinib (n=359)	**Sorafenib (n=355)**
Median days on drug (min, max)	186 (1, 670)	141 (1, 609)
Patients with dose interruptions*, n (%)	276 (77)	285 (80)
Patients with dose increase**, n (%)	132 (37)	na
Median daily dose administered (min, max)	9.9 mg (4.4, 19.4)	774 mg (400, 800)
max=maximum; **mg**=milligram; **min**=minimum; **na**=not applicable; **sd**=standard deviation		
*temporary treatment discontinuation, for example one missed dose would count as a dose interruption.[45] ****</**for axitinib, patients who had their total daily dose prescribed above 10 mg (5 mg twice daily) for 2 or more consecutive doses at any time during the study		

Table 10: Axitinib Dose Escalations and Reductions[36]

Dose, n (%)	**Axitinib, n=359**
< 6 mg	30 (8)
6-8 mg	58 (16)
10 mg	139 (39)
12-14 mg	60 (17)
20 mg	71 (20)
Patients escalated then reduced	71 (20)

Patient Reported Outcomes

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 (FKSI-Disease Related Symptoms) that measures symptoms of advanced RCC (lack of energy, pain, weight loss, fatigue, shortness of breath etc.). No difference in the overall estimated mean FKSI-15 scores between the two drugs over time was reported.[3]

Harms Outcomes

Toxicity was assessed based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The assessment of adverse events was conducted up to 28 days after the last dose.

Table 11: Summary of Harm[3]		
Number of Patients (%)	**Axitinib (n=359)**	**Sorafenib (n=355)**
Patients with AEs (all grades)*	325 (91)	336 (95)
Patients with SAEs (fatal and non-fatal)**	106 (30)	110 (31)
SAEs (fatal)†	31 (9)	23 (7)
WDAEs‡	22 (6)	33 (9)
AEs=adverse events; **SAEs**=serious adverse events; **WDAEs**=withdrawals due to adverse events		
***** treatment-related all causality AEs **all causality †all causality ‡ from patient disposition (excludes death) at data cut-off		

Adverse Events

Adverse events were defined as any untoward medical occurrence in a patient during the study, whether or not considered to have a causal relationship to the treatment.

The incidence of treatment-related AEs was similar to those of all-causality. Details are provided in Table 12.[3] The frequency and severity of adverse events were similar between both drugs.[3] A high incidence of diarrhea (>50% both drugs), hypertension (39% for axitinib and 29% for sorafenib) and fatigue (35% for axitinib and 26% for sorafenib) was seen with both drugs. Nausea (29% vs. 18%) and dysphonia (28% vs. 12%) were more frequent with axitinib whereas hand-foot syndrome (51% vs. 27%) and rash (31% vs. 12%) were more frequent with sorafenib.

Serious Adverse Events (Fatal and Non-fatal)

A serious adverse event was defined as any adverse event at any dose that resulted in death, was life-threatening, required hospitalization or prolongation of hospitalization, resulted in a persistent or significant disability or incapacity, or resulted in congenital anomaly or birth defect.

All causality fatal adverse events and non-fatal serious adverse events were of similar incidence in both treatment arms (~30% each group) as reported in Table 13.[3] Nine patients reported dehydration in the axitinib arm. Seven patients reported diarrhea and five patients each reported pyrexia, pulmonary embolism, dyspnea, and pneumonia. This compared to six sorafenib patients who suffered from anemia and five sorafenib patients each who suffered from diarrhea, dyspnea, pneumonia, and pain.

Fatal Serious Adverse Events

All causality fatal adverse events were seen in 31 (9%) axitinib patients compared to 23 (7%) sorafenib patients (Table 14).[3]

Table 12: Treatment-related All Causality Adverse Events Most Commonly Reported (≥5% of Subjects)[3]

	Axitinib (N=359)		Sorafenib (N=355)	
Preferred Term[a]	Grade 3+[b] n (%)	All Grades[c] n (%)	Grade 3+[b] n (%)	All Grades[c] n (%)
Any AE	177 (49.3)	325 (90.5)	189 (53.2)	336 (94.6)
Diarrhea	36 (10.0)	184 (51.3)	25 (7.0)	179 (50.4)
Hypertension	56 (15.6)	141 (39.3)	39 (11.0)	103 (29.0)
Fatigue	35 (9.7)	125 (34.8)	13 (3.7)	93 (26.2)
Nausea	5 (1.4)	103 (28.7)	3 (0.8)	65 (18.3)
Decreased appetite	13 (3.6)	102 (28.4)	6 (1.7)	88 (24.8)
Dysphonia	0	101 (28.1)	0	42 (11.8)
Palmar-plantar erythrodysesthesia syndrome	18 (5.0)	98 (27.3)	57 (16.1)	181 (51.0)
Hypothyroidism	1 (0.3)	66 (18.4)	0	24 (6.8)
Asthenia	15 (4.2)	63 (17.5)	8 (2.3)	44 (12.4)
Vomiting	5 (1.4)	60 (16.7)	0	44 (12.4)
Weight decreased	5 (1.4)	59 (16.4)	4 (1.1)	54 (15.2)
Mucosal inflammation	5 (1.4)	54 (15.0)	2 (0.6)	43 (12.1)
Stomatitis	5 (1.4)	52 (14.5)	1 (0.3)	42 (11.8)
Constipation	0	44 (12.3)	1 (0.3)	45 (12.7)
Rash	1 (0.3)	42 (11.7)	13 (3.7)	109 (30.7)
Headache	2 (0.6)	37 (10.3)	0	24 (6.8)
Dysgeusia	0	37 (10.3)	0	29 (8.2)
Proteinuria	11 (3.1)	37 (10.3)	4 (1.1)	23 (6.5)
Dry skin	0	36 (10.0)	0	35 (9.9)
Pain in extremity	1 (0.3)	32 (8.9)	2 (0.6)	35 (9.9)
Arthralgia	2 (0.6)	31 (8.6)	1 (0.3)	17 (4.8)
Abdominal pain	3 (0.8)	30 (8.4)	1 (0.3)	16 (4.5)
Dyspepsia	0	28 (7.8)	0	6 (1.7)
Dyspnea	1 (0.3)	25 (7.0)	1 (0.3)	13 (3.7)
Abdominal pain upper	1 (0.3)	22 (6.1)	0	7 (2.0)
Pruritus	0	21 (5.8)	0	43 (12.1)
Dizziness	0	20 (5.6)	0	5 (1.4)
Cough	0	19 (5.3)	1 (0.3)	16 (4.5)
Epistaxis	0	19 (5.3)	0	10 (2.8)
Myalgia	3 (0.8)	19 (5.3)	0	7 (2.0)
Alopecia	0	12 (3.3)	0	112 (31.5)
Anemia	1 (0.3)	10 (2.8)	5 (1.4)	20 (5.6)
Erythema	0	8 (2.2)	1 (0.3)	35 (9.9)
Lipase increased	2 (0.6)	8 (2.2)	11 (3.1)	18 (5.1)

AE=adverse event

[a]MedDRA version 13.1 coding dictionary applied; [b]Grade 3+ includes Grades 3, 4 and 5; All Grades include Grades 1 to 5

Table 13: Serious Adverse Events (All Causality/ Treatment-related) Summarized for ≥4 Events[3]

	Axitinib (N=359)	Sorafenib (N=355)
Preferred Term[a]	**Number (%) of Subjects**	
Any all-causality/treatment-related SAE	106 (29.5)/46 (12.8)	110 (31.0)/44 (12.4)
	Number of Events	
Any all-causality/treatment-related SAE	198/64	181/61
Disease progression	24/1	15/0
Metastatic renal cell carcinoma	21/1	12/0
Dehydration	9/7	1/1
Diarrhea	7/6	5/3
Pyrexia	5/1	3/3
Pulmonary embolism	5/2	1/1
Dyspnea	5/0	5/0
Pneumonia	5/3	5/0
Fatigue	4/3	0
Infection	4/1	0
Pleural effusion	3/0	4/0
General physical health deterioration	2/1	4/1
Pain	1/0	5/1
Hypotension	1/0	4/2
Anemia	0	6/4

[a]MedDRA version 13.1 coding dictionary applied

Table 14: Fatal Serious Adverse Events (All Causality/ Treatment-related) Summarized for ≥4 Events[3]

	Axitinib (N=359)	Sorafenib (N=355)
Preferred Term[a]	**Number (%) of Subjects**	
Any all-causality/treatment-related fatal SAE	31 (8.6)/4 (1.1)	23 (6.5)/3 (0.8)
	Number of Events	
Any all-causality/treatment-related fatal SAE	58/5	42/5
Cardiopulmonary failure	2/0	0
Duodenal ulcer hemorrhage	0	1/0
Gastric ulcer	1/0	0
Gastrointestinal hemorrhage	1/1	1/1
Retroperitoneal hemorrhage	0	1/1
Asthenia	1/1	0
Death	0	2/0
Disease progression	23/1	15/0
General physical health deterioration	1/0	1/0
Sepsis	1/1	0
Fall	0	1/0
Blood creatinine increased	0	1/1
C-reactive protein increased	0	1/1
Hyponatraemia	0	1/0
Metastatic renal cell carcinoma	20/1	12/0
Renal cell metastatic	1/0	0
Renal cell carcinoma	2/0	3/0
Cerebrovasacular accident	1/0	1/0
Dyspnoea	2/0	0
Pleural effusion	1/0	0
Pulmonary embolism	1/0	0
Circulatory collapse	0	1/1

[a]MedDRA version 13.1 coding dictionary applied

6.4 Ongoing Trials

Two phase 2 and one phase 3 RCTs identified through trial registries and materials provided by the Submitter met the inclusion criteria for this review: AGILE 1046,[49] AGILE 1051,[51] and NCT 01441414.[52] Key design aspects are reported below (Table 15).

Table 15: On-going Axitinib Randomized Controlled Trials in mRCC

Trial	Design	Population	Intervention	Comparators	Outcomes
Phase 2: Axitinib with or without dose titration in patients with kidney cancer[49] Objective: Axitinib dose titration (giving a higher dose of the drug above its standard starting dose) among certain patients may improve the response to treatment					
NCT00835978 AGILE 1046 Completion date: January 2013	DB N=200	Treatment naïve	Axitinib 5 mg orally twice daily (open label) + axitinib dose titration (blinded)	Randomized: Axitinib 5 mg orally twice daily (open label) + placebo dose titration (blinded) Non-randomized: Axitinib 5 mg orally twice daily (open label)	Primary: ORR Secondary: PFS OS Safety Response duration PCK
Phase 2: CVX-060 in combination with axitinib in patients with previously treated metastatic renal cell carcinoma[52] Objective: To evaluate CVX-060* in combination with axitinib in patients that have received one prior systemic regiment for mRCC versus axitinib alone					
NCT01441414 Completion date: December 2013	open-label N=165	Part 1: patients with 1-3 prior systemic therapy; Part 2: patients with 1 prior VEGF-directed therapy	Axitinib 5 mg orally twice daily	Axitinib + CVX-060 15 mg/ kg/ week IV	Primary: Part 1: Safety Part 2: PFS Secondary: Safety ORR Duration of response PCK

Phase 3: Axitinib for the treatment of metastatic renal cell cancer[51] Objective: To demonstrate that axitinib is superior to sorafenib in delaying tumour progression in patients with mRCC					
NCT00920816 AGILE 1051 Completion date: July 2014	open-label N=492	Treatment-naïve or after failure of first-line sunitinib or a cytokine	Axitinib 5 mg orally twice daily	Sorafenib 400 mg orally twice daily	Primary: PFS Secondary: OS ORR Safety Duration of response Patient reported outcomes
DB=double blind; **IV**=intravenous; **ORR**=overall response rate; **OS**=overall survival; **PCK**=pharmacokinetics; **PFS**=progression free survival; **VEGF**=vascular endothelial growth factor					
*CVX-060 is a monoclonal antibody					

7 SUPPLEMENTAL

The following supplemental questions were identified during the development of the review protocol as relevant to the pCODR review of axitinib (Inlyta) in mRCC:

- Comparison of AXIS and RECORD-1 studies
- Critical appraisal of an indirect comparison of axitinib and everolimus

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Trial Comparison of AXIS and RECORD-1

Both axitinib and everolimus are indicated as second line treatment in advanced/ metastatic renal cell carcinoma (mRCC). They have different mechanism of action: Axitinib inhibits vascular endothelial growth factor (VEGF) receptors 1, 2, and 3 which are implicated in pathologic angiogenesis, tumour growth and metastatic progression of cancer.[3,50] Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that binds to FKBP-12, an intracellular protein, and forms a complex that inhibits the mTOR serine-threonine kinase.[53] These drugs have not been compared in a head to head trial and thus their comparative effectiveness is unknown. The manufacturer conducted an unpublished indirect comparison of axitinib versus everolimus. The indirect comparison was used as the basis for the manufacturer-submitted pharmacoeconomic evaluation. The robustness of the indirect comparison rests on whether or not the trial populations and study designs are similar.

7.1.1 Objective

This supplemental issue will provide information on AXIS and RECORD-1 highlighting the differences between the two trials and how this may affect the interpretation of the results of the indirect comparison. AXIS is the trial under review in this report.[3,8] RECORD-1 is a pivotal trial comparing everolimus and placebo in patients with mRCC.[13,53]

7.1.2 Findings

The data presented is based on published evidence for RECORD-1[13,53] which makes the appraisal of the trial more challenging because of the lack of details provided in the published material.

As shown in the Tables below, there are differences between AXIS and RECORD-1. Patients in AXIS had to have progressed on first line treatment whereas those in RECORD-1 had disease progression within 6 months of stopping treatment (Table 16).

A greater percentage of patients in AXIS had a poor prognosis (33%) compared to those in RECORD-1 (15%), although those with an intermediate/ favourable prognosis were comparable in both trials (Tables 17 and 18).

Table 16: Study Design

AXIS[8]	***RECORD-1***[53]
Inclusion Criteria	
mRCC, clear-cell	mRCC, clear-cell
Presence of measurable disease (as per RECIST)	Presence of measurable disease (as per RECIST)
RECIST-defined progressive disease	Progression ≤6 months of stopping sunitinib, sorafenib, or both
2 weeks or more since the end of one previous	Previous therapy with bevacizumab,

Table 16: Study Design	
AXIS[8]	***RECORD-1***[53]
Inclusion Criteria	
first line regimen with sunitinib, temsirolimus or a cytokine or: 4 weeks or more since the end of bevacizumab+interferon-α therapy	interleukin-2, or interferon-α permitted
ECOG ≤1	Karnofsky PS 70%
Life expectancy of ≥ 12 weeks	
Exclusion Criteria	
History of malignancy other than RCC	Receiving chemotherapy, immunotherapy, radiotherapy or who have received these ≤4 weeks prior to randomization
Use or anticipated use of a drug that affects cytochrome P450	Previous therapy with an mTOR inhibitor
CNS metastasis	Untreated CNS metastases
Uncontrolled hypertension	
MI, uncontrolled angina, CHF, or cerebrovascular accident within previous 12 months	Uncontrolled medical conditions (unstable angina pectoris, symptomatic CHF, recent MI, diabetes)
DVT or PE within previous 6 months	
HIV/ AIDs	
Stratification factors	
ECOG performance status (0 vs. 1)	MSKCC prognostic score (favourable vs. intermediate vs. poor)
Previous treatment (sunitinib, cytokine, temsirolimus or bevacizumab+interferon-α)	Previous VEGFR inhibitor (one vs. two)
Intervention	
2nd line treatment	≥2nd line treatment
Randomized 1:1 to axitinib 5 mg tablets twice daily (dose may be increased to 10 mg twice daily or decreased to 4 mg per day as required) or to sorafenib 400 mg tablets twice daily (dose may be decreased to 400 mg daily). n=723	Randomized 2:1 to everolimus 2 x 5 mg tablets daily; dose may be decreased to 5 mg in case of AEs or placebo 2 tablets daily, identical to study drug. Each group received BSC; n=410
Open-label	Double blind
Treatment discontinuation	
Treatment discontinued if disease progression, occurrence of unacceptable toxic effects, death, or withdrawal of patient consent	Treatment discontinued if disease progression, unacceptable toxicity, death, or other reasons
Cross-over	
Not permitted	Patients receiving placebo could cross-over to receive open-label everolimus
Primary End Point	
Progression free survival assessed by a blinded independent central review (time from randomisation to the first documentation of disease progression or death due to any cause)	Progression free survival assessed by a blinded independent central review (time from randomisation to the first documentation of disease progression or death due to any cause)
Secondary End Points	
Progression free survival assessed by the investigator, safety, objective tumour response, overall survival, disease-related symptoms, QoL	Safety, objective tumour response, overall survival, disease-related symptoms, QoL

Table 16: Study Design	
AXIS[8]	***RECORD-1***[53]
Inclusion Criteria	
AEs=adverse events; **BSC**=best supportive care; **CHF**=congestive heart failure; **CNS**=central nervous system; **DVT**=deep vein thrombosis; **ECOG**=Eastern Cooperative Oncology group; **MI**=myocardial infarction; **mRCC**=metastatic renal cell carcinoma; **MSKCC**=Memorial Sloan-Kettering Cancer Centre; **mTOR**=mammalian target of rapamycin; **PE**=pulmonary embolism; **PF**=performance status; **QoL**=quality of life; **RECIST**=Response Evaluation Criteria in Solid Tumours	

Table 17: Baseline Characteristics of Patients in AXIS[3,8]		
	Axitinib n=361	**Sorafenib n=362**
Median age, y (range)	61 (20-82)	61 (22-80)
Male gender, n (%)	265 (73)	258 (71)
Common sites of metastases, n (%)		
lymph nodes	209 (58)	203 (56)
lung	274 (76)	292 (81)
bone	119 (33)	107 (30)
liver	102 (28)	103 (29)
other	139 (39)	130 (36)
Number of disease sites, n (%)		
	n/r	n/r
MSKCC prognostic score, n (%)		
favourable	100 (28)	101 (28)
intermediate	134 (37)	130 (36)
poor	118 (33)	120 (33)
missing	9 (2)	11 (3)
ECOG performance status, n (%)		
0	195 (54)	200 (55)
1	162 (45)	160 (44)
>1	1 (<1%)	0

Table 17: Baseline Characteristics of Patients in AXIS[3,8]		
	Axitinib n=361	**Sorafenib n=362**
Karnofsky performance status		
	n/r	n/r
Previous treatment		
VEGFR inhibitors		
-sunitinib	194 (54)	195 (54)
-sorafenib	n/a	n/a
-both	n/a	n/a
Interferon-α	126 (35)	125 (35)
Interleukin-2		
Temsirolimus	12 (3)	12 (3)
Bevacizumab	29 (8)	30 (8)
Previous surgery (nephrectomy)	327 (91)	331 (92)
Previous radiotherapy	75 (21)	73 (20)
ECOG=Eastern Cooperative Oncology group; **MSKCC**=Memorial Sloan Kettering Cancer Center; **n/a**=not applicable; **n/r**= not reported; **VEGFR**=vascular endothelial growth factor receptor		

Table 18: Baseline Characteristics of Patients in RECORD-1[53]		
	Everolimus n=272	**Placebo n=138**
Median age, y (range)	61(27-85)	60 (29-79)
Male gender, n (%)	212 (78)	105 (76)
Common sites of metastases, n (%)		
lymph nodes	203 (75)	98 (71)
lung	199 (73)	112 (81)
bone	100 (37)	43 (31)
liver	94 (35)	49 (36)
Number of disease sites, n (%)		
1	26 (10)	14 (10)
2	67 (25)	35 (25)
3	87 (32)	41 (30)
≥4	88 (32)	45 (33)
MSKCC prognostic score, n (%)		
favourable	79 (29)	39 (28)
intermediate	153 (56)	78 (57)
poor	40 (15)	21 (15)
Karnofsky performance status, n (%)		
100	75 (28)	40 (29)
90	98 (36)	53 (38)
80	70 (26)	30 (22)
70	28 (10)	15 (11)
missing	1 (<1%)	0
ECOG performance status, n (%)		
	n/r	n/r
Previous treatment		

Table 18: Baseline Characteristics of Patients in RECORD-1[53]		
	Everolimus n=272	**Placebo n=138**
VEGFR inhibitors		
-sunitinib only	124 (46)	60 (43)
-sorafenib only	77 (28)	42 (30)
-both	71 (26)	36 (26)
Interferon	138 (51)	72 (52)
Interleukin-2	60 (22)	33 (24)
Chemotherapy	36 (13)	22 (16)
Bevacizumab	24 (9)	14 (10)
Previous surgery (nephrectomy)	262 (96)	131 (95)
Previous radiotherapy	83 (31)	38 (28)
ECOG=Eastern Cooperative Oncology group; **MSKCC**=Memorial Sloan Kettering Cancer Center; **n/a**=not available; **n/r**= not reported; **VEGFR**=vascular endothelial growth factor receptor		

In RECORD-1, all patients had received past treatment with either sunitinib or sorafenib. A total of 26% patients had received both. More than 70% of patients had received previous cytokine therapy (Table 18). The sequence of treatments is not reported in the publication of RECORD-1. But we can see that everolimus was not a true second line treatment for all patients. Patients had received multiple treatments before being enrolled in RECORD-1 and this may point to a group of patients being more refractory to treatment.

Everolimus was compared to placebo in a double-blinded fashion. Placebo-treated patients were permitted to cross-over to everolimus in case of disease progression which would impact the results for overall survival in favour of the placebo group. Axitinib was compared to an active comparator with no cross-over permitted. Post progression or after trial discontinuation, axitinib patients could receive subsequent treatment (for example everolimus) which would affect overall survival results.

Table 19: Drug Exposure in AXIS[3,8]

	Axitinib n=361	**Sorafenib n=362**
Duration of exposure: Median days (min, max)	186 (1, 670)	141 (1, 609)
Patients with dose interruptions, n (%)	276 (77)	285 (80)
Patients with dose increase*, n (%)	132 (37)	n/a
Discontinued treatment (%) • Disease progression or relapse • Adverse event • Protocol violation • Patient discontinued treatment (not due to adverse events) • Global deterioration of health status • Death • Lost to follow-up • Other	221 (61) • 160 (44) • 22 (6) • 4 (1) • 10 (3) • 9 (3) • 12 (3) • 1 (<1) • 3 (1)	256 (71) • 180 (50) • 33 (9) • 2 (1) • 7 (2) • 9 (3) • 13 (4) • 3 (1) • 9 (3)
max=maximum; **min**=minimum; **n/a**=not applicable		
***for axitinib, patients who had their total daily dose prescribed above 10 mg (5 mg twice daily) for 2 or more consecutive doses at any time during the study		

Table 20: Drug Exposure in RECORD-1[13,53]

	Everolimus n=272	**Placebo n=138**
Duration of exposure: Median days (min, max)	141 (19, 451)	60 (21,195)
Patients with at least one dose interruption, n (%)	104 (38)	15 (11)
Patients with dose increase, n (%)	n/a	n/a
Patients with at least one dose reduction, n (%)	19 (7)	1 (1)
Discontinued treatment (%) • Disease progression or relapse • Adverse event • Protocol violation • Withdrawal of consent • Global deterioration of health status • Death	202 (74) • 137 (69) • 36 (13) • 2 (<1) • 13 (5) • 0 • 7 (3)	133 (96) • 124 (90) • 2 (1) • 1 (<1) • 2 (1) • 0 • 4 (3)

Table 20: Drug Exposure in RECORD-1[13,53]		
	Everolimus n=272	**Placebo n=138**
• Lost to follow-up • Other	• 4 (1) • 3 (1)	• 0 • 0
max=maximum; **min**=minimum; **n/a**=not applicable		

Dose interruptions were more frequent with axitinib (Tables 19 and 20); however it may be challenging to give interpretation to this finding because definitions for dose interruptions for RECORD-1 were not available. A total of 37% of axitinib-treated patients required dose increases.

At final analysis, everolimus had a median PFS of 4.9 months (95% CI: 4.0 to 5.5 months) compared to 1.9 months (95% CI: 1.8 to 1.9) for the placebo group (HR 0.33, 95% CI: 0.25 to 0.43) by central radiology review.

Harm

In both studies, toxicity was assessed based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

The proportion of patients who discontinued treatment due to adverse events was lower with axitinib (6%) in AXIS compared with everolimus (13%) in RECORD-1 (Tables 19 and 20).

In AXIS, the most frequent adverse events related to axitinib treatment were diarrhea (51.3%), hypertension (39.3%), fatigue (34.8%), decreased appetite (28.4%), nausea (28.7%) and dysphonia (28.1%); the most common adverse event of grade 3 or higher were hypertension (15.6%), diarrhea (10%) and fatigue (9.7%). The rates of all-cause adverse events in the axitinib arm were slightly higher than that of the treatment-related adverse events in this study.[3]

In RECORD-1, the most common adverse events reported in the everolimus group were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), diarrhea (30%) and cough (30%). They were mostly grade 1 or 2. Grade 3 or higher adverse events were rare: stomatitis ~5%, infections 10%, asthenia ~4%, and fatigue 5%.

Table 21 presents the harm profiles of the two drugs.

Table 21: AE profiles in the AXIS and RECORD-1 studies		
	Axitinib n=359	**Everolimus n=274**
All-cause AE (treatment-related and not treatment-related), n (%)	342 (95)	NR
Most common AEs (all grades)	• Diarrhea (55%) • Hypertension (40%) • Fatigue (39%) • Decreased appetite (34%) • Nausea (32%) • Dysphonia (31)	• Stomatitis (44%) • Infections (37%) • Asthenia (33%) • Fatigue (31%) • Diarrhea (30%) • Cough (30%)
AE=adverse event; **NR**=not reported		

7.1.3 Summary

Evidence from a direct, head-to-head trial comparing axitinib and everolimus is required to provide more compelling evidence regarding the relative effectiveness between the two drugs.

Although there were some similarities in study design, the patients enrolled in RECORD-1 were heavily pre-treated and refractory to treatment. Patients in AXIS had disease progression after first line treatment whereas those in RECORD-1 had progression within the last 6 months. The confounding in overall survival (one cohort could cross-over, the other could receive subsequent treatment) and the differences in baseline patient characteristics make it challenging to conduct any kind of comparison.

There are differences in the study drug toxicity profiles: hypertension was a common adverse event in axitinib-treated patients but not frequently reported in everolimus-treated patients; infection (all cause) was a concern in everolimus-treated patients but not common in axitinib-treated patients. Grade 3 toxicities or higher were more prevalent with axitinib.

7.2 Critical Appraisal of an Indirect Comparison of Axitinib with Everolimus

The manufacturer submitted an unpublished indirect comparison of axitinib versus everolimus.[3,43,44] An indirect comparison provides information in instances where trials have not directly compared the specific treatments.

7.2.1 Objective

Indirect statistical assessments for efficacy amongst the two drugs were performed using different approaches: a side by side comparison, the Bucher fixed effect model, a Bayesian fixed-effect model, and a simulated treatment comparison. A critical appraisal of the different methods of indirect comparison is presented here.

7.2.2 Findings

1) Side by side comparison

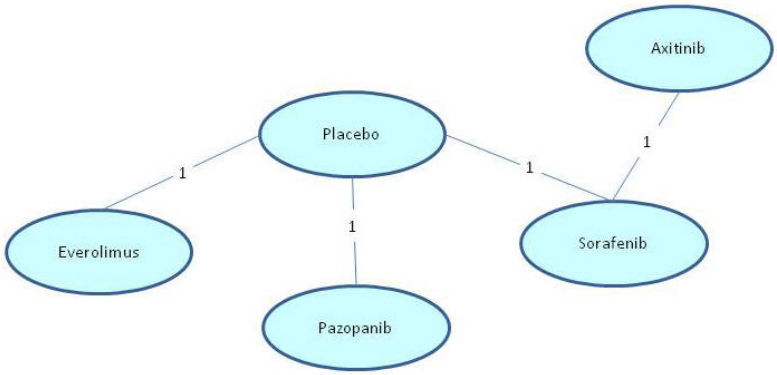
Side by side comparison is an unadjusted (also called naïve) method of comparison. It may be used as an initial step to compare effectiveness but is not a statistically valid method.

2) Bucher method

The Bucher method is an adjusted (also called anchored) indirect comparison approach that uses aggregate data. The effect measure comparing two treatments within a randomized controlled trial is used rather than the individual results for each treatment group, which partially maintains the strength of randomization.[54] The indirect comparison is based on the paired comparison of the direct estimates of the drugs against a common comparator and as such, this method assumes independence between pairwise comparisons. One assumption of this model is that the relative efficacy of a treatment is similar in all trials included in the indirect comparison.

The comparison was made possible through the link between control groups in the AXIS and RECORD-1 trials (Figure 4). The missing link between control groups (placebo and sorafenib) was established from the TARGET trial.[55] The strength of evidence from this indirect comparison is low due to imprecision (insufficient statistical power) and dissimilarities between trials and patient populations (see Bayesian method below).

Figure 4: Network diagram for second line studies[3]



3) Bayesian method

The Bayesian method is a more complex method that may be used when the relevant trials have multiple treatments. It involves using prior probability distribution (prior belief about possible values of parameters which are sometimes arbitrary) to obtain a posterior probability distribution of the parameters which could be interpreted in terms of probabilities (% probability that treatment A results in a better response than treatment B). It can also derive summary measures for parameters and a credible interval (CrI).[56,57]

Three assumptions of comparability need to be considered in network meta-analysis: homogeneity (trials are estimating a common treatment effect or study-specific treatment effects are distributed around a common value); similarity in covariates that may act as treatment effect modifiers (such as patient characteristics, interventions, settings, length of follow-up, and outcomes measured – an indirect comparison cannot adjust for imbalances in patient characteristics); and consistency (indirect evidence is consistent with direct evidence).[56-58]

The manufacturer acknowledges that the Bayesian method in this case is not scientifically robust. The disparity between studies (AXIS and RECORD-1) in terms of effect modifiers and in study design would affect our confidence in the results of the analysis:

- Patients in AXIS had to have progressed on first line treatment whereas those in RECORD-1 had disease progression within 6 months of stopping treatment.
- A greater percentage of patients in AXIS had a poor prognosis (33%) compared to those in RECORD-1 (15%), although proportion of patients with an intermediate/ favourable prognosis were comparable in both trials.
- In RECORD-1, all patients had received past treatment with either sunitinib or sorafenib. A total of 26% patients had received both. More than 70% of patients had received previous cytokine therapy. The sequence of treatments is not reported in the publication of RECORD-1. But we can see that everolimus was not a true second line treatment for all patients. Patients had had multiple treatments before being enrolled in RECORD-1 and this may point to a group of patients being more refractory to treatment.
- Everolimus was compared to placebo in a double-blinded fashion. Placebo-treated patients were permitted to cross-over to everolimus in case of disease progression which would impact the results for overall survival in favour of the placebo group. Axitinib was compared to an active comparator with no cross-over permitted. After trial

discontinuation, axitinib patients could receive subsequent treatment which would affect overall survival.

Assumptions inherent to Bayesian indirect treatment comparison method cannot be met and hence the strength of evidence from this indirect comparison is low.

Table 22: PFS in Patients Pre-treated with Sunitinib using the Bucher and Bayesian Fixed-effect Models[2,3]

Treatment	Bucher fixed-effect model		Bayesian fixed-effect model	
	HR	95% CI	Median HR	95% CrI
Axitinib vs. Everolimus	[redacted]	[redacted] – [redacted]	[redacted]	[redacted] – [redacted]

CI=confidence interval; **CrI**=credible interval; **HR**=hazard ratio; **ITT**=intention to treat; **PFS**=progression free survival

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

Table 23: Overall Survival After Any First Line Treatment using the Bucher and Bayesian Fixed-effect Models (intention to treat)[2,3]

Treatment	Bucher fixed-effect model		Bayesian fixed-effect model	
	HR	95% CI	Median HR	95% CrI
Axitinib vs. Everolimus	[redacted]	[redacted] – [redacted]	[redacted]	[redacted] – [redacted]

CI=confidence interval; **CrI**=credible interval; **HR**=hazard ratio

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

4) Simulated treatment comparison

Simulated treatment comparison (STC) uses a missing data imputation technique (using simulation) to explore what results might likely look like if some 'index trial' (in this case AXIS) had hypothetically also enrolled patients to receive another treatment (in this case everolimus).

It is based on equations that generate predictions of outcomes with both treatments and calculates effect measures.[59] At least one trial for each of the interventions being compared must be available. Although the trials may not be identical, they must have similar relevant aspects such as design, patient characteristics and end points. Individual patient data is required for the

index trial and preferred for the other trial(s). An advantage of STC is that it replicates the detail of the study design which reduces the impact of possible discrepancies in study designs, enrolled population and other differences.[59] However, compared to indirect or mixed treatment comparison analyses, STC is not based on real data (based on hypothetical cohort).

Patients in the AXIS trial were pure 2nd line treatment patients whereas patients in RECORD-1 were not; some patients had received up to 5 lines of treatment. This is a major problem because the treatment effect or any of the predictor variables included in the STC adjustment interacts with the 'line of treatment'. The STC revealed that 'MSKCC score' and 'age' were predictors of PFS, and 'prior duration of sunitinib' and 'MSKCC score' were predictors of overall survival. It seems likely that the ability of a low MSKCC performance score to predict a bad outcome will be augmented when patients are receiving later stage treatments. If so, the STC adjustment will be biased, and thus, would lower our confidence in the produced results.

Table 24: Simulated Treatment Comparison Results in Patients Pre-treated with Sunitinib (Log-normal Distribution)[2,3,44]

	PFS (median months)	OS (median months)
Axitinib (n=194)	[redacted]	[redacted]
Everolimus (n=124)	[redacted]	[redacted]

OS=overall survival; **PFS**=progression free survival; **STC**=simulated treatment comparison

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

Other limitations of using STC in this case include:

- Patient level data, other than that available for AXIS, was not used. Without such data, the STC method has limited ability to simulate an adequately matching hypothetical cohort of patients that would be receiving everolimus.
- The method treats the simulated data as direct whereas the sources, on which the missing data are based, are indirect. This would produce artificially narrow confidence intervals.
- It is incorrect to rely only on point estimates and one should consider what lies within the confidence interval because the STC can only give us an approximation of results if we were to do a new trial. Yet, only point estimates can be calculated as the methods to determine variance are still being developed.

7.2.3 Summary

Indirect statistical assessments for efficacy amongst the two drugs were performed using different approaches: a side by side comparison, the Bucher fixed effect model, a Bayesian fixed-effect

model, and a simulated treatment comparison. Conclusions drawn from such indirect comparisons are not as robust as conclusion based on direct, head-to-head trial data. All four methods have serious limitations which need to be considered when interpreting the results.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available axitinib (Inlyta) in metastatic renal cell carcinoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information, which was provided to pERC for their deliberations, and this information has been redacted in this publicly available Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Genitourinary Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Embase 1980-present (oemezd) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) (pmez)

#	Searches	Results
1	(axitinib* or Inlyta* or AG-013736 or AG013736 or AG-13736 or AG13736).ti,ot,ab,sh,rn,hw,nm.	1592
2	319460-85-0.rn,nm.	1218
3	or/1-2	1592
4	3 use pmez	218
5	*axitinib/	153
6	(axitinib* or Inlyta* or AG-013736 or AG013736 or AG-13736 or AG13736).ti,ab.	502
7	or/5-6	523
8	7 use oemezd	336
9	4 or 8	554
10	exp animals/	34803090
11	exp animal experimentation/ or exp animal experiment/	1662016
12	exp models animal/	1056396
13	nonhuman/	3955681
14	exp vertebrate/ or exp vertebrates/	33900138
15	or/10-14	35959502
16	exp humans/	26801421
17	exp human experimentation/ or exp human experiment/	318454

18	or/16-17	26803498
19	15 not 18	9157591
20	9 not 19	524
21	remove duplicates from 20	353

2. Literature search via PubMed

Search History

Search	Add to builder	Query	Items found
#3	Add	Search **(#1 AND #2)**	10
#2	Add	Search **publisher[sb]**	418789
#1	Add	Search **((Axitinib OR Inlyta OR AG-013736 OR AG013736 OR AG-13736 OR AG13736 OR 319460-85-0[rn]))**	220

3. Cochrane Central Register of Controlled Trials (Central)

Issue 11 of 12, Nov 2012

"There are 12 results from 677429 records for your search on #1 - axitinib* or Inlyta* or AG-013736 or AG013736 or AG-13736 or AG13736 in title abstract keywords in Trials"

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: (axitinib OR Inlyta) AND (renal OR kidney)

Select international agencies including:

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

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Search terms: (axitinib OR Inlyta)

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: (axitinib OR Inlyta) AND (renal OR kidney)/ last 5 years (2008-2012)

REFERENCES

1. Pfizer provides topline results from phase 3 study of Torisel® as second-line treatment in advanced renal cell carcinoma (RCC) [Internet]. New York: Pfizer; 2012 May 15. [cited 2012 Aug 28]. Available from: http://press.pfizer.com/press-release/pfizer-provides-topline-results-phase-3-study-torisel-second-line-treatment-advanced-r

2. Proskorovsky I, Benedict A, Negrier S, Larkin J, Sandin R, Chen C. Axitinib (AXI) and everolimus (EVE) in the treatment (TX) of sunitib-refractory (SU-R) patients (PTS) with metastatic renal cell carcinoma (MRCC): results of a simulated TX comparison (STC) analyses [abstract]. Ann Oncol. 2012;23(Suppl. 9):280.

3. pan-Canadian Oncology Drug Review manufacturer submission: Inlyta™ (axitinib); Company: Pfizer Canada. Pointe-Claire/Dorval (QC): Pfizer Canada; 2012 Aug.

4. Morabito A, De Maio E, Di Maio M, Normanno N, Perrone F. Tyrosine kinase inhibitors of vascular endothelial growth factor receptors in clinical trials: current status and future directions. Oncologist. 2006;11(7):753-64.

5. Hu-Lowe DD, Zou HY, Grazzini ML, Hallin ME, Wickman GR, Amundson K, et al. Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3. Clin Cancer Res. 2008 Nov 15;14(22):7272-83.

6. Solowiej J, Bergqvist S, McTigue MA, Marrone T, Quenzer T, Cobbs M, et al. Characterizing the effects of the juxtamembrane domain on vascular endothelial growth factor receptor-2 enzymatic activity, autophosphorylation, and inhibition by axitinib. Biochemistry. 2009 Jul 28;48(29):7019-31.

7. Kania RS. Structure-based design and characterization of axitinib. In: Rongshi L, Stafford JA, editors. Kinase inhibitor drugs. Hoboken (NJ): Wiley; 2009. p. 167-201.

8. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011 Dec 3;378(9807):1931-9.

9. Hutson T. Randomized phase 3 trial of temsirolimus versus sorafenib as second-line therapy in metastatic RCC (mRCC): results from the INTORSECT trial. Late breaking abstract #LBA22_PR. Abstract presented at: 37th Congress of the European Society for Medical Oncology (ESMO); 2012 Sept 28 - Oct 2; Vienna.

10. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian cancer statistics 2012 [Internet]. Toronto: Canadian Cancer Society; 2012 May. [cited 2012 Oct 24]. Available from: http://www.cancer.ca/Canada-wide/About%20cancer/~/media/CCS/Canada%20wide/Files%20List/English%20files%20heading/PDF%20-%20Policy%20-%20Canadian%20Cancer%20Statistics%20-%20English/Canadian%20Cancer%20Statistics%202012%20-%20English.ashx

11. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med [Internet]. 2007 Jan 11 [cited 2012 Dec 5];356(2):115-24. Available from: http://content.nejm.org/cgi/reprint/356/2/115.pdf

12. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with

metastatic renal cell carcinoma. J Clin Oncol [Internet]. 2009 Aug 1 [cited 2012 Dec 5];27(22):3584-90. Available from: http://jco.ascopubs.org/content/27/22/3584.full.pdf+html

13. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer [Internet]. 2010 Sep 15 [cited 2012 Aug 28];116(18):4256-65. Available from: http://onlinelibrary.wiley.com/doi/10.1002/cncr.25219/pdf

14. Tamaskar I, Garcia JA, Elson P, Wood L, Mekhail T, Dreicer R, et al. Antitumor effects of sunitinib or sorafenib in patients with metastatic renal cell carcinoma who received prior antiangiogenic therapy. J Urol. 2008 Jan;179(1):81-6.

15. Garcia JA, Hutson TE, Elson P, Cowey CL, Gilligan T, Nemec C, et al. Sorafenib in patients with metastatic renal cell carcinoma refractory to either sunitinib or bevacizumab. Cancer. 2010 Dec 1;116(23):5383-90.

16. Di Lorenzo G, Carteni G, Autorino R, Bruni G, Tudini M, Rizzo M, et al. Phase II study of sorafenib in patients with sunitinib-refractory metastatic renal cell cancer. J Clin Oncol. 2009 Sep 20;27(27):4469-74.

17. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008 Jul 1;113(1):78-83.

18. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. N Engl J Med. 1998 Apr 30;338(18):1272-8.

19. Negrier S, Perol D, Ravaud A, Chevreau C, Bay JO, Delva R, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. Cancer. 2007 Dec 1;110(11):2468-77.

20. Gleave ME, Elhilali M, Fradet Y, Davis I, Venner P, Saad F, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. N Engl J Med. 1998 Apr 30;338(18):1265-71.

21. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002 Jan 1;20(1):289-96.

22. Mekhail TM, Abou-Jawde RM, Boumerhi G, Malhi S, Wood L, Elson P, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol [Internet]. 2005 Feb 1 [cited 2012 Dec 5];23(4):832-41. Available from: http://www.jco.org/cgi/reprint/23/4/832

23. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009 Dec 1;27(34):5794-9.

24. Rini BI. VEGF-targeted therapy in metastatic renal cell carcinoma. Oncologist. 2005 Mar;10(3):191-7.

25. Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev. 2005;(1):CD001425.

26. Kammula US, White DE, Rosenberg SA. Trends in the safety of high dose bolus interleukin-2 administration in patients with metastatic cancer. Cancer. 1998 Aug 15;83(4):797-805.

27. Jewett MA, Knox JJ, Kollmansberger C, Basiuk J. Canadian kidney cancer forum 2008. Can Urol Assoc J [Internet]. 2008 Jun [cited 2012 Dec 5];2(3):183. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2494888

28. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007 May 31;356(22):2271-81.

29. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009 Jul 10;27(20):3312-8.

30. Cella D, Escudier B, Rini BI, Chen C, Bhattacharyya H, Tarazi JC, et al. Patient-reported outcomes (PROs) in a phase III AXIS trial of axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol. 2011;29(15 Suppl 1). (Presented at ASCO Annual Meeting 2011 Chicago, IL. 2011 Jun 3-7).

31. Rini BI, Escudier B, Tomczak P, Kaprin A, Hutson TE, Szczylik C, et al. Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): results of phase III AXIS trial [abstract]. J Clin Oncol. 2011;29(15 Suppl 1). (Presented at ASCO Annual Meeting 2011. Chicago, IL. 2011 Jun 3-7).

32. Cella D, Escudier B, Rini B, Chen C, Bhattacharyya H, Tarazi J, et al. Time to deterioration (TTD) in patient-reported outcomes in phase 3 axis trial of axitinib vs sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC) [abstract]. Eur J Cancer. 2011;47 Suppl 1:S224. (Presented at 2011 European Multidisciplinary Cancer Congress. Stockholm, Sweden. 2011 Sep 23-27).

33. Michaelson D, Rini BI, Escudier BJ, Clark J, Redman B, Tarazi JC, et al. Phase III AXIS trial of axitinib versus sorafenib in metastatic renal cell carcinoma: updated results among cytokine-treated patients [abstract]. J Clin Oncol. 2012;Suppl. (Presented at ASCO Annual Meeting 2012. Chicago, IL. 2012 Jun 1-5).

34. Rini BI, Escudier BJ, Michaelson MD, Negrier S, Gore ME, Oudard S, et al. Phase III AXIS trial for second-line metastatic renal cell carcinoma (mRCC): effect of prior first-line treatment duration and axitinib dose titration on axitinib efficacy [abstract]. J Clin Oncol. 2012;Suppl. (Presented at ASCO Annual Meeting 2012. Chicago, IL. 2012 Jun 1-5).

35. Motzer RJ, Escudier B, Tomczak P, Negrier S, Gore ME, Tarazi J, et al. Axitinib vs sorafenib for advanced renal cell carcinoma: phase III overall survival results and analysis of prognostic factors. Abstract presented at: ESMO Congress. 2012 Sep 28 - Oct 2; Vienna.

36. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Inlyta (axitinib) tablets. Company: Pfizer Inc. Application no.: 202324s000. Approval date: 1/27/2012. Rockville (MD): The Center; 2012 [cited 2012 Aug 1]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202324Orig1s000TOC.cfm.

37. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Inlyta (axitinib) tablets. Company: Pfizer Inc. Application no.: 202324s000. Approval date: 1/27/2012. Rockville (MD): The Center; 2012 [cited 2012 Aug 1]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202324Orig1s000TOC.cfm.

38. Vickers MM, Choueiri TK, Rogers M, Percy A, Finch D, Zama I, et al. Clinical outcome in metastatic renal cell carcinoma patients after failure of initial vascular endothelial growth factor-targeted therapy. Urology. 2010;76(2):430-4.

39. Grunwald V, Fishman MN, Hutson TE, Bair A, Chen Y, Kim S, et al. A randomized phase 2 study of axitinib dose titration in patients with advanced renal cell carcinoma (RCC): preliminary pharmacokinetic and ambulatory blood pressure (BP) monitoring results [abstract]. Eur J Cancer. 2011;47:S517.

40. Taneja SS. Re: Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. J Urol. 2012 Aug;188(2):412-3.

41. Ozer-Stillman I, Keyser R, Ambavane A, Cislo P. Sorafenib versus axitinib for second-line treatment of sunitinib-refractory patients with advanced renal cell carcinoma (RCC) in the United States (US). Abstract presented at: ESMO Congress. 2012 Sep 28 - Oct 2; Vienna.

42. Escudier B, Loomis AK, Kaprin A, Motzer R, Tomczak P, Tarazi J, et al. Association of single nucleotide polymorphisms (SNPs) in VEGF pathway genes with progression-free survival (PFS) and blood pressure (BP) in metastatic renal cell carcinoma (mRCC) in the phase 3 trial of axitinib versus sorafenib (AXIS trial) [abstract]. Eur J Cancer. 2011;47 Suppl 1:S505.

43. Pfizer response to September 13, 2012 request for additional information regarding the indirect treatment comparison for pCODR Inlyta review [additional manufacturer's information]. Kirkland (QC): Pfizer Canada; 2012 Sep 21.

44. Pfizer response to September 28, 2012 request for additional information regarding the simulated treatment comparison for pCODR Inlyta review [additional manufacturer's information]. Kirkland (QC): Pfizer Canada; 2012 Oct 2.

45. Pfizer response to October 10, 2012 checkpoint meeting questions regarding the pCODR Inlyta review [additional manufacturer's information]. Kirkland (QC): Pfizer Canada; 2012 Oct 10.

46. Rothenberg M, Pfizer Oncology. Inlyta® (axitinib) [Internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2011 Dec 7. Follow-up systemic therapy use (discontinued patients) overall (Nov. 1, 2011 data cutoff), E 243. [cited 2012 Oct 10]. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM283657.pdf Slides presented at FDA Oncologic Drugs Advisory Committee Meeting.

47. Kenney PA, Wood CG. Words of wisdom. Re: Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Eur Urol. 2012 Jul;62(1):182-3.

48. Heng DY, Xie W, Bjarnason GA, Vaishampayan U, Tan MH, Knox J, et al. Progression-free survival as a predictor of overall survival in metastatic renal cell carcinoma treated with contemporary targeted therapy. Cancer. 2011 Jun 15;117(12):2637-42.

49. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT00835978, Axitinib (AG-013736) with or without dose titration (increase) in patients with kidney cancer; 2012 Sep 13 [cited 2012 Sep 28]. Available from: http://clinicaltrials.gov/ct2/show/NCT00835978

50. Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. Drugs R D. 2011;11(2):113-26.

51. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT00920816, Axitinib (AG-013736) for the treatment of metastatic renal cell cancer; 2012 Sep 24 [cited 2012 Sep 28]. Available from: http://clinicaltrials.gov/ct2/show/NCT00920816

52. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01441414, PF-04856884 (CVX-060) in combination with axitinib in patients with previously treated metastatic renal cell carcinoma; 2012 Sep 10 [cited 2012 Sep 28]. Available from: http://clinicaltrials.gov/ct2/show/NCT01441414

53. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56.

54. Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect evidence: indirect treatment comparisons in meta-analysis [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009 Mar. [cited 2012 Aug 28]. Available from: http://www.cadth.ca/media/pdf/H0462_itc_tr_e.pdf

55. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med [Internet]. 2007 [cited 2012 Oct 10];356(2):125-34. Available from: http://content.nejm.org/cgi/content/abstract/356/2/125

56. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health. 2011 Jun;14(4):429-37.

57. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28.

58. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ. 2009;338:b1147.

59. Caro JJ, Ishak KJ. No head-to-head trial? Simulate the missing arms. PharmacoEconomics. 2010;28(10):957-67.