pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pazopanib hydrochloride (Votrient) for metastatic renal cell carcinoma

January 5, 2012

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, it is 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 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

Pazopanib hydrochloride is a small molecule, multi-target tyrosine kinase inhibitor. It is a potent inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3, platelet-derived growth factor (PDGF) receptors alpha and beta, and stem cell factor receptor (c-KIT). The action of pazopanib at these various receptors reduces the proliferation of cancer cells through inhibition of angiogenesis pathways.

Pazopanib has a Health Canada indication for the treatment of patients with metastatic renal cell (clear cell) carcinoma who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease. The recommended dose of pazopanib is 800 mg administered orally once daily.

The objective of this review was to evaluate the effect of pazopanib on patient outcomes compared to standard therapies or placebo in the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) who have received no prior systemic therapies or who have received prior treatment with cytokines. The scope of the pCODR review included patients with advanced RCC to account for potential clinical use of pazopanib in this population.

1.2 Key Results and Interpretation

One double-blind, placebo controlled randomized controlled trial (RCT), Study VEG105192, met the inclusion criteria for the pCODR systematic review.[1] Study VEG105192 compared pazopanib 800 mg (n = 290) once daily with placebo (n = 145) in 435 patients aged ≥ 18 years with advanced and/or metastatic renal cell carcinoma who were treatment naïve or who received one prior cytokine-based systemic therapy. The study was conducted in 80 different centers in Europe, Asia, South America, North Africa, Australia and New Zealand and was manufacturer-sponsored. Patients with non-clear cell carcinoma and patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 were excluded.

1.2.1 Systematic Review Evidence

Efficacy

- The primary endpoint of the study was progression-free survival (PFS), defined as the time interval between the date of randomization and the date of documented disease progression or death due to any cause. Patients treated with pazopanib demonstrated a statistically significant improvement in median PFS (9.2 months for pazopanib versus 4.2 months for placebo) for an overall median PFS difference of 5 months [hazard ratio (HR) 0.46 (95% confidence interval (CI): 0.34 to 0.62; P<0.001)].
- The secondary endpoint of the study was overall survival, defined as the time interval from randomization to death from any cause. Both an interim analysis as well as a final analysis of overall survival were found to be statistically non-significant. Median overall survival was 21.1 months for pazopanib versus 18.7 months for placebo in the interim analysis [HR 0.73 (95% CI: 0.53, 1.00; P=0.020, pre-specified O'Brien Fleming boundary of P < 0.004 not crossed)]. Median overall survival was 22.9 months for pazopanib versus 20.5 months for placebo in the final analysis results for overall survival [HR: 0.91 (95% CI: 0.71, 1.16; P=0.224)]. In the final analysis of Study VEG105192, 54% of patients in the placebo arm had crossed over to receive pazopanib upon disease progression which may have an impact on the estimation of overall survival benefit of pazopanib.

- Quality of life was assessed in Study VEG105192 using three different instruments and response rates were >90% for each instrument across most of the assessment time points between weeks 6 and 48. There were no statistically significant changes in quality of life scores from baseline in either treatment arm.

Harms

- As of the cut-off date, 38% (n = 109) of the pazopanib treated group had died compared to 46% (n = 67) in the placebo group. Four deaths (1.4%) in the pazopanib group were determined by the investigator to be directly related to pazopanib and were related to abnormal hepatic function, ischemic stroke and peritonitis.
- A total of 24% (n = 60) of patients experienced a severe adverse effect in the pazopanib group compared to 19% (n = 27) of patients in the placebo arm. The most frequently reported serious adverse events with pazopanib were diarrhea, anemia, dyspnea and vomiting.
- More patients in the pazopanib group (92%, n = 268) experienced at least one adverse event compared with the placebo group (74%, n = 107). The most common adverse events occurring in ≥ 10% of patients included diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting, fatigue, asthenia, abdominal pain and headache. Known tyrosine kinase inhibitor-associated adverse events such as hand-foot syndrome, mucositis/stomatitis, proteinuria, thrombocytopenia and hypothyroidism occurred with an incidence < 10% each. Adverse events leading to withdrawal or discontinuation were reported for 15% (n = 44) of patients in the pazopanib arm compared with 5.5% (n = 8) of patients in the placebo arm.
- Dose interruptions were required by 33% of patients in the pazopanib arm versus 9% in the placebo arm and dose reductions were required in 24% of pazopanib patients compared with 3% of placebo patients.

1.2.2 Additional Evidence

Patient Advocacy Group Input

pCODR received input on pazopanib from one patient advocacy group, Kidney Cancer Canada. From a patient perspective, Kidney Cancer Canada highlighted that maintaining quality of life is an important aspect when consideration is given to treatment. Although there are agents currently available on the Canadian market for the first-line treatment of metastatic renal cell carcinoma, they can cause adverse effects which may be significant, in some patients. The side effect profile of pazopanib appears to differ from the currently available agents for metastatic RCC. Patients would like to see an alternative agent, such as pazopanib, available for the first-line treatment of metastatic RCC so that the patient and their physician can have a choice of the most appropriate agent for their individual treatment.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, sunitinib was considered to be the most relevant comparator to pazopanib and the PAG felt it would be important to be aware of any differences between pazopanib and sunitinib with respect to side effect profile and treatment outcomes. Given this, PAG considered that comparative data between the two drugs would be of interest.

Other

- There are currently three ongoing studies of pazopanib that met the inclusion criteria for the pCODR systematic review; however, outcome data for each of these trials is not currently available.[2-4] Of particular interest is the VEG108844 (COMPARZ) trial of pazopanib versus sunitinib in the treatment of locally advanced and/or metastatic RCC, as sunitinib has been identified as the major comparator to pazopanib and current head-to-head comparisons are not available.[2]
- An indirect comparison of pazopanib as first-line treatment of patients with advanced and/or metastatic renal cell carcinoma, compared with sunitinib, interferon-α or best supportive care has been conducted by the manufacturer and was also reviewed by NICE.[5] The results showed no statistically significant difference in PFS or overall survival between pazopanib and sunitinib (HR = 0.949, 95% CI: 0.575 to 1.568). In terms of safety, pazopanib demonstrated statistically significantly less fatigue than sunitinib (HR = 0.21, 95% CI: 0.06 to 0.77). No other statistically significant differences in adverse events were observed.

1.2.3 Interpretation and Guidance

- Approximately 90-95% of all kidney cancers are RCC. An estimated 5100 new cases (all stages) of kidney cancer will be diagnosed in 2011 with approximately 1650 deaths reported, highlighting the unfavourable prognosis of this disease and the need for effective therapy.[6]
- The management of metastatic RCC has undergone significant change in the past five to eight years with the development of various new therapeutic approaches. 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. However, none of the currently available systemic treatment options for metastatic disease are considered curative and all of these therapies are associated with various degrees of side effects.
- Thus, there remains a need for novel therapies in the treatment of metastatic RCC, which are either associated with increased efficacy or have an improved toxicity profile.
- Study VEG105192 appeared to be well conducted. Patient characteristics were well balanced between the two treatment groups and reflect a typical patient population in clinical practice. Patients with non-clear cell renal carcinoma and patients with ECOG performance status ≥ 2 were not included in Study VEG105192.
- The primary endpoint of the VEG105192 study was PFS. The validity of PFS as a primary endpoint for renal cell carcinoma trials is often discussed. A retrospective data analysis reported by Heng et al. 2011 suggests that there is an association between PFS and overall survival in RCC.[7]
- Pazopanib was well tolerated with an overall low incidence of grade 3 and 4 toxicity. The most frequent adverse events related to pazopanib treatment were diarrhea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes and these were well managed in the majority of patients.
- The lack of statistically significant differences between pazopanib and placebo in terms of quality of life, as assessed by three different scales, may be an indication of the favourable toxicity profile for pazopanib.
- Sunitinib is another small molecule tyrosine kinase inhibitor and is considered the standard first-line therapy for metastatic RCC in Canada. There are currently no results from randomized controlled trials directly comparing pazopanib and sunitinib but two studies are ongoing. An indirect comparison of pazopanib and sunitinib suggests the two

treatments may be similar with respect to PFS and pazopanib may have a more favourable toxicity profile.[5]

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to pazopanib in the treatment of advanced and metastatic RCC based on one high-quality randomized controlled trial, Study VEG105192, that demonstrated a clear clinically and statistically significant benefit in PFS for pazopanib compared with placebo.

In making this conclusion, the Clinical Guidance Panel also considered that from a clinical perspective:

- Study VEG105192 supports the use of pazopanib in patients with clear cell histology or clear cell component and good performance status (ECOG 0 and 1).
- While significant advances have been achieved in recent years in the treatment of metastatic kidney cancer, it remains an incurable disease. Approximately one quarter of patients with RCC present with metastases at diagnosis and at least one half of all patients will eventually develop advanced disease.[8]
- Limited treatment options exist for patients with metastatic RCC. Sunitinib is the only drug currently approved and funded in most provinces for patients with good performance status and/or good or intermediate risk disease. While sunitinib, the current standard first-line option in Canada for the vast majority of patients, is an effective therapy, it is also associated with a number of substantial side effects, including hypertension, fatigue, diarrhoea and hand-foot syndrome, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes.
- Pazopanib was well tolerated with an overall low incidence of grade 3 and 4 toxicity. The most frequent adverse events related to pazopanib treatment were diarrhea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes and these were manageable in the majority of patients. Evidence from an indirect comparison suggested that pazopanib may have a similar or more favourable toxicity profile than sunitinib.[5] Two prospective randomized controlled trials comparing pazopanib to sunitinib are currently ongoing, which will provide more definitive information on the relative efficacy and safety of pazopanib.[2,3]

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 pazopanib hydrochloride (Votrient) for metastatic RCC. 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 pazopanib (Votrient) for advanced or metastatic RCC conducted by the pCODR Genitourinary Clinical Guidance Panel and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues or other literature that provides contextual information 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 Clinical Guidance Panel, a summary of submitted Patient Advocacy Group Input on pazopanib for metastatic RCC and a summary of submitted Provincial Advisory Group Input on pazopanib for metastatic RCC are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Pazopanib has a Health Canada indication for the treatment of patients with metastatic (clear cell) renal cell carcinoma (RCC) who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease. The recommended dose is 800 mg administered orally once-daily. Pazopanib is a multi-target tyrosine kinase inhibitor; its targets include VEGF receptor, PDGF receptor, and c-KIT receptor. The action of pazopanib at these receptors reduces the proliferation of cancer cells through inhibition of angiogenesis pathways. Other multi-target tyrosine kinase inhibitors available in Canada for the treatment of advanced RCC include sunitinib and sorafenib. As first-line treatment for advanced RCC, sunitinib is considered the most relevant comparator to pazopanib, as identified by both PAG and the pCODR Clinical Guidance Panel.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of pazopanib on patient outcomes compared to standard therapies or placebo in the treatment of patients with advanced or metastatic RCC who have received no prior systemic therapies or who have received prior treatment with cytokines. The scope of the pCODR review included patients with advanced RCC to account for potential clinical use of pazopanib in this population.

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 pazopanib 800 mg (n = 290) once-daily, was compared to placebo (n = 145) in an international, multicentre, double-blind, RCT (Study VEG105192).[1] The study recruited patients aged ≥18 years with advanced and/or metastatic (clear cell) RCC, ECOG performance status 0 or 1, who were treatment naïve or who received cytokine pre-treatment. The median age was 60 years (range 25 to 85 years), and patients were predominately male and Caucasian. More than 80% of patients had metastasis with ≥ 2 organs involved including lung, lymph nodes, bone or liver. All patients received best supportive care. Two possible limitations to the generalizability of results of the clinical trial to Canadian clinical practice were identified. First, 94% of enrolled patients had 'good' or 'intermediate' prognosis based on Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk scores.[9] Second, there were no study sites in North America.

PFS was assessed over a 20-month period. The median PFS after adjustment for ECOG status and prior therapy was 9.2 versus 4.2 months in the pazopanib versus placebo arm, respectively (HR = 0.46, 95% CI: 0.34 to 0.62, P < 0.0001). The effect was consistent in both pre-specified subgroups: treatment naive (HR = 0.40, 95% CI: 0.27 to 0.60, P < 0.0001) and cytokine pre-treated (HR = 0.54, 95% CI: 0.35 to 0.84, P < 0.001). As of the clinical cut-off date, 40% of patients had died. The difference in overall survival was not statistically significant between the two treatment arms. In the final analysis of overall survival, 54% of patients in the placebo arm had crossed over to receive pazopanib upon disease progression; this aspect of the study is expected to result in underestimation of any beneficial effect of pazopanib on overall survival.[10] Quality of life was assessed using three different scales: the European Quality of Life-5 Dimensions (EQ-5D) Scales[11] and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (version 3).[12] There were no statistically significant differences between treatments in mean changes from baseline at each of the assessment time points from 6 to 48 weeks for any of the scales. In addition, in a *post hoc* analysis based on the proportion of patients to have a ≥20% decline from baseline in the EORTC QLQ-C30 global health status/quality of life scale, no statistically significant differences were observed between treatment groups.[13,14]

The adverse events (≥20%) observed more frequently in patients receiving pazopanib than in patients on placebo were: diarrhea, hypertension, hair colour changes, nausea, anorexia, and vomiting. Hepatic abnormalities associated with pazopanib were identified as a concern by the manufacturer beginning in the early phases of clinical development. In this trial, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin levels increased by 53%, 53% and 36%, respectively in the pazopanib arm while levels in the placebo group increased by 22%, 19% and 10%, respectively. Other known tyrosine kinase inhibitor-associated adverse events such as hand-foot syndrome, mucositis/stomatitis, proteinuria, hypothyroidism, occurred at an incidence of <10% each, with grade 3 or 4 events reported in < 1% of patients receiving pazopanib. Fifty-seven percent of patients who received pazopanib required a dose interruption and/or reduction compared to 12% of patients who received placebo. Overall, 15% of patients receiving pazopanib experienced adverse events leading to discontinuation of treatment or early withdrawal compared to 5.5% in the placebo group.

No RCT evidence was identified regarding the comparative efficacy and safety of pazopanib with sunitinib, the most relevant comparator in Canada for treatment-naive patients. However, two trials comparing these two agents (COMPARZ and PISCES) are currently ongoing.[2,3] There was also no RCT evidence available on the role of pazopanib in optimal treatment sequences, combination therapy, or as adjuvant therapy following nephrectomy. A phase III RCT to evaluate pazopanib as an adjuvant treatment for localized RCC is currently ongoing.[4]

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.

While both the pCODR Clinical Guidance Panel and PAG have identified sunitinib as the most relevant comparator to pazopanib, there is limited direct evidence comparing the two drugs. An indirect comparison of pazopanib, as first-line treatment of patients with advanced and/or metastatic renal cell carcinoma, compared with sunitinib, interferon-α or best supportive care was reviewed by NICE.[5] This indirect comparison was also the basis of clinical information included in the economic evaluation submitted to pCODR. The indirect comparison included eight RCTs: Study VEG105192 comparing pazopanib with placebo,[1] one RCT comparing sunitinib with interferon-α,[15] and six RCTs comparing interferon-α with either medroxyprogesterone,[16-19] vinblastine,[20] or interleukin-2.[21] Three of the six interferon trials included patients with ECOG status of 2, representing a worse prognosis. One of the six interferon trials included patients with intermediate risk metastatic RCC. The results showed no statistically significant difference in PFS between pazopanib and sunitinib (HR = 0.949, 95% CI 0.575 to 1.568). With regard to overall survival, there was no statistically significant difference between pazopanib and sunitinib (HR = 0.969, 95% CI 0.359 to 2.608). In terms of safety, pazopanib demonstrated significantly less fatigue than sunitinib (HR = 0.21, 95% CI 0.06 to 0.77). No other statistically significant differences in adverse events were observed. Possible sources of bias in the indirect comparison include the different comparators used in the pazopanib and sunitinib trials (placebo/best supportive care versus interferon), changes in best supportive care practices over time, heterogeneity of patient populations across the included trials, and use of different doses of interferon-α across trials.

In a narrative review by Hutson, the clinical efficacy of pazopanib, sunitinib, sorafenib, bevacizumab plus interferon-α , temsirolimus, and everolimus for the treatment of metastatic RCC was discussed.[22] While pazopanib, temsirolimus, sunitinib, and bevacizumab plus interferon-α were considered first-line therapy for metastatic renal cell carcinoma, sorafenib and everolimus were considered second-line options. Based on the results of a single, phase III RCT (Motzer et al., 2007), sunitinib provided significantly longer median PFS (11 versus 5 months, $P < 0.001$) and longer median overall survival (26.4 versus 21.8 months, $P = 0.051$) compared to interferon-α.[15,23] These findings were also reported in other recent reviews.[24-27]

Most clinical trials in advanced or metastatic RCC report PFS as a primary endpoint. In an attempt to evaluate the ability of PFS to predict overall survival, Heng et al. conducted a retrospective study of 1158 patients from 12 centers who received targeted therapy for metastatic renal cell carcinoma.[7] The study population was heterogeneous: thirty-one percent of patients had received previous immunotherapy, 80% had undergone nephrectomy, 77% had >1 metastatic site, and 8% had brain metastasis. Risk scores were also varied. PFS was measured at 3 and 6 months. The median overall survival for patients who progressed at 3 months was 7.8 months compared with 23.6 months for patients who did not progress. The median overall survival for patients who progressed at 6 months was 8.6 months compared with 26.0 months for those who did not progress. The hazard ratios for death adjusted for adverse prognostic factors for patients who progressed at 3 and 6 months, compared with those who did not progress, were 3.05 (95% CI 2.42-3.84) and 2.96 (95% CI 2.39-3.67). Heng et al. concluded that PFS may be used to predict overall survival in patients with metastatic renal cell carcinoma. The quality of the results of this study was limited by the retrospective nature of its design which is susceptible to missing data and selection bias.

2.1.5 Summary of Supplemental Questions

No supplemental questions were developed for this review.

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

- From a patient perspective, maintaining quality of life is an important aspect when consideration is given to treatment.

- Patient advocacy groups have noted that although there are agents currently available on the Canadian market for the first-line treatment of metastatic RCC, they can cause adverse effects, sometimes significant, in some patients. The side effect profile of pazopanib may differ from the currently available agents for metastatic RCC.

- Patient advocacy groups would like to see an alternative agent, such as pazopanib, available for the first-line treatment of metastatic RCC so that the patient and their physician can have a choice of the most appropriate agent for their individual treatment. Treatment choice and availability of treatments with a better efficacy and safety profile than currently available therapies were described as important considerations by patient advocacy groups.

PAG Input

- From a PAG perspective, sunitinib is considered the most relevant comparator and PAG indicated it would be important to be aware of any differences

between pazopanib and sunitinib with respect to side effect profile and treatment outcomes.

- PAG noted that if pazopanib were available, in addition to current therapies such as sunitinib or everolimus, there may sequential use of pazopanib and other agents used to treat metastatic RCC. PAG would be interested to know if there is evidence available to support sequential use of pazopanib and other agents in metastatic RCC.

- PAG noted that pazopanib could be used in other clinical settings, such as the adjuvant treatment of metastatic RCC; therefore, evidence to support use of pazopanib in these settings may be needed if funding were to be provided for this population.

- Jurisdictions have observed dose de-escalations with sunitinib treatment and have considered that this may occur with pazopanib, as well. Therefore, evidence available on the effectiveness of pazopanib at lower doses would be of interest to jurisdictions.

Other

- There is a lack of randomized data for pazopanib in the non-clear cell population. Studies on pazopanib for the treatment of other tumours, such as non-small cell lung cancer, prostate cancer, breast cancer, soft tissue sarcoma, and gynaecologic malignancies are ongoing.

2.2 Interpretation and Guidance

Burden of Renal Cell Carcinoma

Kidney cancer accounts for approximately 3% of malignant diseases in Canada with approximately 90-95% being RCC. An estimated 5100 new cases (all stages) will be diagnosed in 2011 with approximately 1650 deaths reported highlighting the unfavourable prognosis of this disease and the need for effective therapy.[6] The estimated five-year survival across all stages is 67% but the prognosis for patients with metastatic disease remains poor and only very few survive 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.

Treatments for Renal Cell Carcinoma

The management of metastatic RCC has undergone significant change in the past five to eight years. An increasing understanding of the disease biology has translated into the development of various new therapeutic approaches. 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.

Sunitinib, a small molecule tyrosine kinase inhibitor, is considered the standard first-line therapy in Canada. Sunitinib blocks VEGF receptor types 1, 2, 3, PDGF receptors alpha and beta, c-kit and FLT-3. Sunitinib has demonstrated a median PFS of 11 months versus 5 months ($P < 0.001$) and a median overall survival of 26.4 months versus 21.8 months

(P = 0.051) in the pivotal randomized controlled trial in which it was compared with interferon.[23] None of the currently available systemic treatment options for metastatic disease however (including targeted therapy, immunotherapy (cytokines) or conventional chemotherapy) is considered curative and all of these therapies are associated with various degrees of side effects. Thus, there remains a need for novel therapies in the treatment of metastatic RCC, which are either associated with increased efficacy or have an improved toxicity profile.

Pazopanib is a new small molecule tyrosine kinase inhibitor, which inhibits a broad spectrum of tyrosine kinases including VEGF receptors 1–3, PDGF receptors alpha and beta, and c-Kit. However, the spectrum, selectivity and potency of different kinase inhibitors vary which may explain important differences in the safety profile of these agents.

Given the mechanism of action and proposed indication of first-line therapy, sunitinib is the most valid comparator for pazopanib. No randomized phase III data exist for sorafenib in the first-line setting and the combination of bevacizumab/interferon is not approved in Canada.[28]

Study VEG105192

In Study VEG105192, 435 patients with advanced and/or metastatic RCC (233 treatment naive; 202 cytokine pre-treated) were enrolled between April 2006 and April 2007 from 80 centers in Europe, Asia, South America, North Africa, Australia, and New Zealand.[1] Within the RCT, previously untreated patients or patients previously treated with cytokines, good performance status (ECOG 0 or 1) and clear cell carcinoma were randomly assigned to either pazopanib or placebo. Placebo was chosen as the comparator arm because at the time of study design and initiation, targeted agents were not yet available in most countries and placebo was therefore considered an appropriate comparator. This was a well conducted randomized trial.

Patient Populations

The patient populations in the pivotal pazopanib (Study VEG105192) and sunitinib (Motzer et al. 2009) studies were comparable, with the exception that a higher proportion of patients with a baseline ECOG performance status of 0 (better performance status) were recruited to the sunitinib phase III study than to Study VEG105192 (approximately 60% versus 40%).[1,23] Both studies excluded patients with non-clear cell histology and required either clear cell or predominantly clear cell histology. Average patients' age and proportion having had prior nephrectomy were also similar between both studies. Patient characteristics were well balanced between the two treatment groups and reflect a typical patient population in Canadian clinical practice.

Several points have been raised regarding the generalization and applicability of these results to: patients with non-clear cell carcinoma, the Canadian patient population, and patients with poor performance status.

- Similar to the pivotal sunitinib study, this study included only patients with clear cell carcinoma or a clear cell component. Histology plays a significant role in RCC treatment selection and outcome. About 80% of RCCs are of clear-cell histology, whereas 20% are classified as non-clear cell cancers including papillary, sarcomatoid, chromophobe subtypes amongst others. Importantly, only clear cell RCCs are associated with defects in the von Hippel-Lindau (VHL) gene which appear to be a

major driver of tumour progression in these patients. Approximately 80% of patients with sporadic (non-inherited) clear cell RCC acquire defects of both alleles of the VHL gene with resulting dysfunction of the VHL protein. The VHL protein functions as a tumour suppressor and the VHL protein plays a pivotal role in the control of neo-angiogenesis. Loss of VHL gene function results in enhanced secretion of VEGF, PDGF, and creation of the vascular phenotype characteristic of clear cell RCC. All targeted agents available to date are interfering with the angiogenesis pathway either by inhibiting the VEGF receptor (sunitinib, sorafenib, bevacizumab) or the mTOR pathway (everolimus, temsirolimus). No data are available for pazopanib in non-clear cell cancers, although other tyrosine kinase inhibitors have demonstrated some activity in non-clear cell carcinomas.

- Treatment for patients with poor performance status (i.e., ECOG ≥ 2) remains a challenge. Only patients with ECOG performance status 0 and 1 were included in the pazopanib trial and the efficacy and, most importantly, tolerability of pazopanib in patients with a performance status ≥ 2 remains unknown. The requirement of a performance status of 0 or 1 also led to the inclusion of mostly good and intermediate risk patients according to the MSKCC classification. Only 3% of patients were considered poor risk, which makes the interpretation of the results in poor risk patients difficult. This is also very similar to the pivotal sunitinib study, which also included only ECOG 0 and 1 patients and only a small proportion of poor risk patients.
- Although no North American patients were included in the trial, the results are still applicable because no differences in outcomes are known to exist between North American and European patients with metastatic clear cell cancer. Health Canada determined that the extrapolation of these study results to the Canadian population was appropriate based on the fact that the response rates observed in a Phase II study of pazopanib in North American patients were consistent with those obtained in non-North American patients in that same study, as well as in pazopanib-treated patients in Study VEG105192.[29]

Effectiveness

PFS was the primary endpoint of Study VEG105192. Pazopanib was associated with a statistically significant improvement in PFS in the entire patient population [median PFS 9.2 months vs. 4.2 months, HR = 0.46 P < 0.0001]. In the treatment naive sub-population the difference in median PFS was even larger at 11.1 months versus 2.8 months in favour of pazopanib [HR = 0.40; P < 0.0001] and in the cytokine pre-treated group it was 7.4 versus 4.2 months [HR = 0.54, 95% CI: 0.35 to 0.84, P < 0.001]. In addition, subgroup analyses demonstrate PFS improvement was consistent across multiple clinically relevant subgroups. Importantly, these improvements were seen in pre-specified groups, including both treatment-naïve and cytokine refractory patients.

Although cross trial comparisons have to be interpreted cautiously, the difference in PFS observed for pazopanib resembles the PFS achieved in the pivotal sunitinib trial (11 months vs. 5 months for sunitinib vs. interferon, P < 0.001).[15,23] An indirect comparison to estimate the relative effect of pazopanib versus sunitinib, interferon-α, and best supportive care, has also been conducted, which suggested a similar PFS for pazopanib and sunitinib while PFS was inferior for best supportive care and interferon alfa.[5]

The validity of PFS as the primary endpoint for RCC trials is often discussed. Clinically PFS is a very important objective since a period without tumour progression is often associated with a good quality of life for patients. In addition, observational data from Heng et al., 2011 suggests an association between PFS and overall survival.[7] With the availability of

various active therapies and the option of crossover within the trials, overall survival has become a difficult endpoint for first-line trials in metastatic RCC.

In the intention-to-treat analysis of Study VEG105192, overall survival for pazopanib and placebo was not statistically significant different. Final overall survival data demonstrated a median overall survival of 22.9 months for pazopanib versus 20.5 months for the placebo arm [HR = 0.91; P not significant]. However, it is important to note that the median overall survival of patients randomized to placebo in both the pivotal sunitinib and pazopanib studies was substantially longer than reported for a historical group of patients receiving cytokines. Historically, overall survival rates after interferon or interleukin were in the 10 to 14 months range.[18,30,31] Study VEG105192 likely reflects the confounding effects of subsequent active therapies.

In Study VEG105192, 48% of the placebo patients experiencing progression subsequently received open-label pazopanib. Due to the high rate of crossover to active therapy, the overall survival in the placebo arm was likely higher than if the patients had not crossed over. This may have very likely led to a lack of a clear overall survival benefit in the pazopanib arm. A similar effect was seen in other recently published randomized trials in metastatic RCC, including the pivotal randomized phase III sunitinib trial and the second-line randomized phase III trial of sorafenib versus placebo.[15,32] PFS has therefore become an accepted standard endpoint for first-line trials in metastatic RCC. An analysis adjusting for crossover by using the rank-preserved structural failure time (RPSFT) method was performed by the manufacturer, which showed a consistent overall survival benefit in favour of pazopanib when compared to placebo (HR = 0.501, 95%CI: 0.136 to 2.348).

Tumour response rates and tumour progression were reviewed by an independent review committee and compared to investigator assessments. There was a high concordance between the response rate assessments between the independent review committee and the investigator assessments and median PFS results were similar for both the independent review committee and investigator assessments, demonstrating the robust nature of the findings.

Safety

Ninety-two percent (92%) of patients in the pazopanib arm experienced adverse events and 74% in the placebo arm. The most frequent adverse events related to pazopanib treatment were diarrhoea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes. Pazopanib may have a more favourable toxicity profile than sunitinib except for hepatotoxicity although the absence of a direct comparison makes definitive conclusions challenging. Grade 3 hepatic toxicity may be more frequent with pazopanib than with other tyrosine kinase inhibitors such as sunitinib. However, fatal liver toxicity related to pazopanib is rare (0.05% to 0.1%), and has also been observed with other tyrosine kinase inhibitors such as sunitinib and sorafenib. The adverse event rates for pazopanib, in particular for important side effects such as dyspepsia, mucositis/stomatitis, fatigue, hand-foot syndrome, myelosuppression and altered taste appear generally lower than for other agents in this class such as sunitinib. This may be explained by differences in the spectrum of inhibited kinases. Pazopanib, for example, is not a potent inhibitor of fms-related tyrosine kinase 3, which may explain the low rate (~1%) of grade 3/4 cytopenias. Mucositis, fatigue and in particular hand-food syndrome are amongst the most frequent tyrosine kinase inhibitors e.g. sunitinib related side effects leading to dose reductions or dose delays and may frequently interfere substantially with treatment administration, patients' quality of life and subsequently optimal outcomes. Less than 10% of pazopanib patients were reported to have developed hand-foot syndrome with no patients having had

grade 3 or 4 hand-foot syndrome while in the pivotal sunitinib trial, 29% of patients developed hand-foot syndrome with 9% having grade 3 or 4.[15] Of note, few cardiac adverse events have been reported with pazopanib and preclinical studies suggest differences in effects on myocardium and mitochondria between pazopanib and sunitinib.[33] This may make pazopanib an alternative to sunitinib in patients with pre-existing heart disease.

No significant differences were detected between treatments in terms of quality of life (QoL), assessed by the European Quality of Life-5 Dimensions (EQ-5D) Scale and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), reflecting the favourable toxicity profile for pazopanib compared with placebo.

Evidence Gaps

A number of gaps were identified when reviewing the evidence for pazopanib:

- No data exist for the use of pazopanib in the adjuvant setting after curative resection of the primary tumour. A randomized study in this setting is currently ongoing.[4] At the present time, none of the approved agents should be used in this setting outside of clinical trials.
- No randomized data exist for the sequential use of pazopanib as second or third line option after failure of other anti-angiogenic therapies. Sunitinib, sorafenib, and pazopanib appear to work through the same pathway (VEGF receptor inhibition) to inhibit angiogenesis. It is currently unknown whether resistance to sunitinib or sorafenib will confer similar resistance to pazopanib. A few small phase II and retrospective studies suggest activity of pazopanib after sunitinib but this observation needs confirmation in a larger randomized trial and thus, the use of pazopanib in this setting outside of clinical trials remains experimental.
- No randomized data exist for pazopanib in non-clear cell carcinomas. The most often recommended treatment for these patients is temsirolimus due to the inclusion of non-clear cell carcinoma patients in the pivotal phase III study.[34] Other targeted therapies such as sunitinib or everolimus are currently being tested for non-clear cell carcinoma patients in prospective trials.
- No randomized study directly comparing the efficacy and safety of pazopanib with sunitinib has yet been published. However two trials comparing these two agents (COMPARZ and PISCES) are currently ongoing.[2,3] The COMPARZ clinical trial which directly compares the safety and efficacy of pazopanib and sunitinib will provide the comparative data to conclusively determine whether pazopanib and sunitinib have similar efficacy and if pazopanib has a similar or improved toxicity profile.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to pazopanib in the treatment of advanced and metastatic RCC based on one high-quality randomized controlled trial, Study VEG105192, that demonstrated a clear clinically and statistically significant benefit in PFS for pazopanib compared with placebo.

In making this conclusion, the Clinical Guidance Panel also considered that from a clinical perspective:

- Study VEG105192 supports the use of pazopanib in patients with clear cell histology or clear cell component and good performance status (ECOG 0 and 1).
- While significant advances have been achieved in recent years in the treatment of metastatic kidney cancer, it remains an incurable disease. Approximately one quarter of patients with RCC present with metastases at diagnosis and at least one half of all patients will eventually develop advanced disease.
- Limited treatment options exist for patients with metastatic RCC. Sunitinib is the only drug currently approved and funded in most provinces for patients with good performance status and/or good or intermediate risk disease. While sunitinib, the current standard first-line option in Canada for the majority of patients, is an effective therapy, it is also associated with a number of substantial side effects, including hypertension, fatigue, diarrhoea and hand-foot syndrome, all of which can greatly impact a patient's quality of life, optimal administration of therapy and subsequent outcomes.
- Pazopanib was well tolerated with an overall low incidence of grade 3 and 4 toxicity. The most frequent adverse events related to pazopanib treatment were diarrhea, hair colour change, hypertension, nausea, anorexia and increased liver enzymes and these were manageable in the majority of patients. Evidence from an indirect comparison suggested that pazopanib may have a similar or more favourable toxicity profile than sunitinib. Two prospective randomized controlled trials comparing pazopanib to sunitinib are currently ongoing, which will provide more definitive information on the relative efficacy and safety of pazopanib.[2,3]

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

Cancers of the kidney account for approximately 3% of all cancers in Canada. An estimated 5,100 new cases of kidney cancer and 1,650 deaths from kidney cancer are expected in 2011.[6] About 90% of kidney cancers consist of RCC, which are genetically and histologically distinctly different from carcinomas of the renal pelvis. About 80% of them are of clear-cell histology, whereas 20% are classified as non-clear cell cancers including papillary, sarcomatoid, chromophobe subtypes amongst others.

Approximately 75% of patients with RCC have localized disease (confined to the kidney/extensive growth in the area of the kidney but no distant metastases) at the time of diagnosis. About 25% of RCCs are metastatic at the time of diagnosis and approximately 30-50% of patients, who are initially diagnosed with localized disease, will eventually relapse and metastasize.[8]

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 in localized but more extensive tumours (stage III) with survival rates of 50-60%. Patients with metastatic disease are rarely cured.

Metastatic RCC is considered refractory to conventional cytotoxic chemotherapy as well to conventional radiation. Historically, immunotherapy (cytokines) was the treatment of choice in the metastatic setting although only a small group of patients derived meaningful benefit from it. In the era of immunotherapy, median overall survival across all metastatic patients was in the range of 12-14 months.[18,30,31]

Several prognostic factors have been identified in patients with metastatic disease dividing metastatic patients into a favourable, intermediate and poor risk group. The most commonly used classification is the MSKCC model which includes 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 in a number of clinical studies and is used by many in clinical practice to select patients.[35,36]

An increased understanding of RCC biology and the development of new therapeutic agents (targeted therapies / antiangiogenic agents), in particular in the clear-cell subtype, have resulted in the availability of several new treatment options for patients with advanced or 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). HIF plays a central role in renal tumor genesis 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.[37] Elucidation of the VHL/HIF pathway has led to the successful evaluation and regulatory approval of agents targeting the VEGF and mTOR axes.

Targeted therapies have a distinct mechanism of action, fundamentally different from classic chemotherapy and are also associated with a different toxicity profile.

The RCC treatment landscape has changed significantly over the past years and continues to evolve rapidly but RCC therapy continues to be a major challenge. 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.

3.2 Accepted Clinical Practice

Surgery with complete removal of the tumour remains the mainstay of therapy in localized or locally advanced stages. There is currently no role for adjuvant or neoadjuvant therapy.

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 have been helpful for a small group of patients, the majority of patients derive no benefit or the clinical benefit was very modest and achieved at the expense of significant toxicity.[18,30]

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.[38]

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 clear-cell RCC. All these agents interfere with the VEGF pathway, 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.

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 (Motzer et al., 2007) examining 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 ($P < 0.001$).[23] In addition, this was the first trial to demonstrate a median overall survival of more than 2 years in patients with metastatic RCC patients. These results served as the basis for introducing sunitinib as a reference first-line standard of care.

Sorafenib is also an 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.[32] Sorafenib is considered a treatment option in metastatic RCC, although its use has substantially decreased due to the decreased use of cytokines and the lack of robust randomized data in the first-line setting.[28]

The mTOR inhibitor temsirolimus, given intravenously once a week, was tested in a randomized trial which included only poor risk patients according to the MSKCC and Cleveland Clinic criteria. In this trial, temsirolimus demonstrated superior overall survival outcomes as compared to interferon alone or the combination of both drugs.[34] Temsirolimus is considered a standard treatment option for patients with poor risk criteria.

Everolimus, an oral mTOR inhibitor is considered a standard treatment for patients who have failed first-line therapy with tyrosine kinase inhibitors. Everolimus demonstrated a significant PFS benefit in a randomized phase III trial which compared everolimus to placebo in patients with failure to at least one prior line of tyrosine kinase therapy.[39]

Bevacizumab was tested in combination with interferon versus interferon alone within 2 randomized trials. Both trials demonstrated a significant PFS benefit for the bevacizumab combination group.[40,41] 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.

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.

Sorafenib is listed as a first-line option in most clinical practice guidelines although no randomized phase III data exist in treatment-naïve patients.

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 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. 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.

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 part in the overall treatment strategy.[42]

Another limitation is the development of resistance to therapy. Eventually almost all patients progress and require a switch to a different therapy.

Pazopanib is also being evaluated as second-line therapy in metastatic RCC patients previously treated with VEGF-targeted therapy in a single arm phase II study (NCT00731211).[43]

3.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of pazopanib for patients with the following criteria:[1,10]

- Metastatic or advanced, inoperable renal cell carcinoma
- Clear cell histology or clear cell component
- Treatment-naïve patients (first line therapy) or patients after failure of cytokine 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

Pazopanib has not yet been approved for any other indication than advanced RCC anywhere in the world.

In most jurisdictions, including Canada and the European Union, pazopanib has been approved for first-line treatment or treatment of patients who previously had failed cytokines. In the US, pazopanib is approved for the treatment of advanced RCC without indicating line of therapy.

Apart from first-line therapy or second-line therapy after cytokine failure, pazopanib may be used in clinical practice as second-line or third-line therapy after failure of another tyrosine kinase inhibitor and/or mTOR inhibitor. Emerging data suggest activity for re-challenging patients with same class agents in later line of therapy.

There is a large randomized study currently ongoing which examines the role of pazopanib in the adjuvant setting after curatively intended resection (NCT01235962, Study VEG113387).[4]

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Kidney Cancer Canada, provided input on pazopanib for metastatic renal cell carcinoma and their input is summarized below.

Kidney Cancer Canada conducted both a qualitative in-depth study using telephone interviews and a quantitative online survey to gather information about the patient and caregiver experience with the drug under review. There were a total of 6 respondents to the telephone interview conducted by Kidney Cancer Canada. An online survey was hosted by the Canadian Cancer Action Network and consisted of two separate parts. Part one of the survey (120 respondents) collected information regarding patient experience with kidney cancer as well as their view on future drug therapies. Part two of the survey (6 respondents) collected information from patients and caregivers having direct experience with pazopanib. Based on both sources of patient information, 11 unique respondents were identified as having direct experience with pazopanib.

From a patient perspective, maintaining quality of life is an important aspect when consideration is given to treatment. Although there are agents currently available on the Canadian market for the first-line treatment of metastatic renal cell carcinoma, they can cause adverse effects, sometimes significant, in some patients. The side effect profile of pazopanib may differ from the currently available agents for metastatic RCC. Patients would like to see an alternative agent, such as pazopanib, available for the first-line treatment of metastatic RCC so that the patient and their physician can have a choice of the most appropriate agent for their individual treatment.

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 early stage kidney cancer often have no symptoms and as a result, many cases are diagnosed when the cancer has already metastasized. Patients with metastatic RCC 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 metastatic RCC and there are limited treatment options. Patients have found hope in the development of new targeted therapies that shrink tumors and stop the progression of their cancer, sometimes for long periods of time. Without treatment alternatives, patients face disease progression including worsening of symptoms such as increasing shortness of breath, severe bone pain and fatigue. Depending upon the site of untreated metastases, patients may suffer from seizures, spinal compression leading to paralysis and painful bone fractures often requiring orthopedic surgery.

From a patient perspective, quality of life while living with metastatic RCC is one of the most important considerations. Treatment options that reduce worsening of disease, pain, and fatigue can lead to maintaining or resuming normal daily activities. Comments from a survey of patients with metastatic RCC highlighted that, in addition to the physical impact, the emotional and mental impact of cancer can be significant.

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

Current first-line therapies for metastatic RCC include sunitinib, temsirolimus (poor prognosis) and cytokine treatments such as interleukin-2 or interferon-alpha. Across Canada, patients are frequently prescribed sunitinib as first-line therapy. Although sunitinib and other tyrosine kinase inhibitors are considered effective in significantly delaying progression, each has associated side effects which some patients, in varying degrees, find difficult to manage. Depending on the individual patient, other concurrent health issues and the kidney cancer symptoms, the treatment's side effects have a significant impact on 'quality of life' and daily activities of patients and caregivers.

Comments from survey respondents currently receiving sunitinib therapy highlighted the impact of sunitinib side effects including fatigue, nausea, vomiting, and hand/foot syndrome. Patients noted that additional medications were sometimes required to control sunitinib side effects, e.g. antihypertensive for elevated blood pressure, antacids for acid reflux and thyroid hormones for thyroid dysfunction.

While patients are aware of and have direct experience with the serious side effects of current therapies, the survey results indicate that a moderate majority is willing to accept side effects and the serious risks associated with a future, new drug such as pazopanib. Given that metastatic RCC is a life-threatening cancer, patients are willing to accept a higher level of risk even if the treatment is not curative and the benefits are projected to be short-term.

Some qualities that patients are looking for in a new therapy include:

- **Individualized Therapy:** Patients feel that the need for individualized choice in first-line therapy is currently not being met in Canada for metastatic RCC, unlike for other cancers. If multiple choices were available, patients and oncologists would be able to individualize treatment plans to the characteristics of their tumours, any contraindications and their lifestyle enabling the best possible quality of life.
- **Quality of Life:** When considering a new drug treatment, survey respondents placed a very strong emphasis and importance on quality of life.
- **Choice**: Patients placed a very high significance on having a choice with their doctors in selecting which drug is better suited for their circumstances.

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

Patient advocacy group input indicated that the impact of kidney cancer on caregivers 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. A caregiver's paid work; community and social involvement are affected by the physical requirements, time commitments, and emotional stress of caring for a patient.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Pazopanib

Patients without direct experience with pazopanib seek a choice in treatment that would offer similar disease control with minimized impact on their quality of life. While sunitinib will remain a viable option for many patients, pazopanib could provide an additional option for patients and their oncologists.

Similar to other therapies, pazopanib has risks and known side effects. Management of side effects may require intervention of health care professionals and caregivers similar to other Health Canada approved therapies for metastatic RCC. An indication of prior liver impairment (moderate to severe) would prevent a patient from receiving pazopanib and patients will require close monitoring of liver function during pazopanib treatment to allow the oncologist to lower dosage or stop treatment as necessary. One patient that commented on pazopanib disclosed that liver toxicity became an issue with their pazopanib therapy and they were required to discontinue use.

As an oral therapy, pazopanib is not administered in a hospital or cancer care centre and allows the patient ease of use. In addition, as pazopanib is administered daily, it might make it easier for patients and caregivers to follow the administration schedule, without keeping track of the weeks on/off therapy.

Canadian patient experience with pazopanib is limited as Canadian patients were not involved in the pivotal Phase III trial. However, a limited number of patients have had access through subsequent trials or a Patient Assistance Program from the manufacturer. While these patients experienced side effects with pazopanib, the side effects were quite different when compared to other tyrosine kinase inhibitors, such as less severe/no hand/foot syndrome. Pazopanib survey respondents indicated that with respect to their experience with this drug, their quality of life was reasonably good.

Patients receiving pazopanib indicated that it had shrunk their tumours and seemed to have an important role in PFS. Patients indicated that they expect pazopanib to change their long-term health and well-being by providing PFS in managing kidney cancer.

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 pazopanib for metastatic RCC. PAG 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 pCODR review of pazopanib was obtained from all nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, sunitinib is considered the most relevant comparator and PAG indicated it would be important to be aware of any differences between pazopanib and sunitinib with respect to side effect profile and treatment outcomes. Given this, PAG considered that the relative cost and cost-effectiveness of sunitinib and pazopanib was a very important factor and that comparative data between the two drugs would be most relevant.

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

5.1 Factors Related to Comparators

Sunitinib was identified by PAG as the most relevant comparator to pazopanib in the first-line treatment of metastatic RCC and it was noted that sunitinib is funded in many jurisdictions for this indication. Therefore, PAG considered it important to identify any differences in effectiveness, side effects or costs which would make one drug more favourable over the other. PAG indicated that comparative data between pazopanib and sunitinib would be useful to identify any differences but noted that if only placebo-controlled trials for either drugs was available, this may be a barrier. PAG indicated that if the two drugs were determined to have similar clinical effects then the relative costs of pazopanib and sunitinib would a key consideration.

5.2 Factors Related to Patient Population

PAG noted that as metastatic RCC affects a relatively small patient population, there may be a small number of patients accessing pazopanib when considering budget impact, which may be an enabler for jurisdictions if implementing a funding recommendation.

PAG noted that if pazopanib were available, in addition to current therapies such as sunitinib or everolimus, there may sequential use of pazopanib and other agents used to treat metastatic RCC. This may be a barrier to implementation as it could potentially increase costs to the drug program. Therefore, PAG would be interested to know if there is evidence available to support sequential use of pazopanib and other agents in metastatic RCC.

PAG noted that pazopanib could be used in other clinical settings, such as the adjuvant treatment of metastatic RCC; therefore, evidence to support use of pazopanib in these settings may be needed if funding were to be provided for this population.

5.3 Factors Related to Accessibility

PAG input considered that both pazopanib and sunitinib are oral agents that can be given in the community setting without the need for chemotherapy unit resources or the patient having to travel for treatment. This would be beneficial for patients in less central or rural areas.

Pazopanib and sunitinib do not require access to other concomitant drug therapies and specialized molecular tests are not required for a patient to be considered a candidate for pazopanib therapy.

PAG input noted that in some jurisdictions oral therapies are funded under their provincial drug plans and that not all provincial drug plans cover the entire patient population, which may be a barrier to access. Therefore, patients who are not covered under the provincial drug plan would have to receive funding for pazopanib from a private drug plan or pay out of pocket for treatment.

PAG recognized that the same accessibility issues apply to both pazopanib and sunitinib; therefore, when compared with sunitinib, there are no enablers or barriers to access.

5.4 Factors Related to Dosing

PAG noted that there are differences between pazopanib and sunitinib with respect to dosage and schedule that may affect the feasibility of implementing a funding recommendation.

Pazopanib is given in a continuous daily fashion whereas treatment with sunitinib requires a two-week break in therapy during each cycle. PAG input considered that diagnostic scans to assess the effectiveness of metastatic RCC therapy must not be performed during the two week break period with sunitinib, which may cause scheduling issues in cancer treatment centers. PAG observed that this would be an enabler to the use of pazopanib as there is no break period in its treatment schedule.

PAG also noted that patient compliance with pazopanib may be affected by the greater pill burden required, which may impact the effectiveness of pazopanib and be a barrier to implementation. The recommended dosage of pazopanib is 800 mg daily taken as 4 x 200mg tablets. This differs from sunitinib which can be dosed as a single 50 mg tablet. However, given that pazopanib is taken in a continuous daily fashion without a need for treatment breaks, there is a possibility that compliance could be enhanced. Information on patient compliance may be useful to jurisdictions.

In addition, jurisdictions have observed dose de-escalations with sunitinib treatment and have considered that this may occur with pazopanib, as well, therefore, evidence available on the effectiveness of pazopanib at lower doses would be of interest to jurisdictions.

5.5 Factors Related to Implementation Costs

Other than drug costs, additional implementation costs were not identified for pazopanib.

5.6 Other Factors

No other input was provided by PAG although it was noted that some jurisdictions will have to decide whether pazopanib should be funded under the provincial drug program or specific Cancer Care Programs.

6. SYSTEMATIC REVIEW

6.1.Objectives

To evaluate the effect of pazopanib on patient outcomes compared to standard therapies or placebo in the treatment of patients with advanced RCC who have received no prior systemic therapies or who have received prior treatment with cytokines.

6.2. Methods

6.1.1. Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the pCODR Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those highlighted in bold. Protocol amendments made after the review protocol was finalized are listed below the table.

Table 1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished DB RCT	Patients with advanced renal cell carcinoma who have received no prior systemic therapies or who have received prior treatment with cytokines for metastatic disease	Pazopanib (oral) as monotherapy at recommended 800 mg once daily	Targeted therapies for advanced RCC (i.e., VEGF inhibitors, mTOR inhibitors) • Sunitinib • Sorafenib • Bevacizumab + interferon • Temsirolimus • Everolimus Immunotherapy (i.e., interferon-alpha (IFN-a), interleukin-2 (IL-2)) Placebo	• Progression-free survival • Overall survival • Response rate • **QoL** • SAE • AE (**hand-foot syndrome, fatigue, mucositis/ stomatitis, diarrhea, hypertension**) • WDAE
AE=adverse events; **DB**=double blind; **mTOR**=mammalian target of rapamycin; **QoL**=quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **WDAE**=withdrawal due to adverse events; **VEGF**=vascular endothelial growth factor				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions) Patient advocacy group input indicated the importance of having therapeutic choices.*

Protocol amendments:

- Subgroup analysis of PFS by age (< 65 vs. ≥ 65 years of age), gender, ECOG performance status (0 vs. 1), and MSKCC risk category (favourable vs. intermediate). These were pre-specified subgroup analyses in the single RCT included in the review, and as such were considered to be relevant.
- Dose reduction/interruption added as a separate outcome based on input from PAG.
- Key laboratory abnormalities (ALT, AST, total bilirubin increase, and hematologic outcomes) were added as outcomes of interest since hepatic abnormalities were identified as a concern by the Submitter beginning in the early phases of clinical development.

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 (2010, Issue 2) 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 pazopanib (Votrient).

Retrieval was not limited by publication year. Retrieval was not limited by language.

The initial search was completed on July 19, 2011 and was updated during the review. The search is considered up to date as of October 13, 2011.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health clinicaltrials.gov and 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 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 additional 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 review protocol (See section 6.2.1). 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 Clinical Guidance Report

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

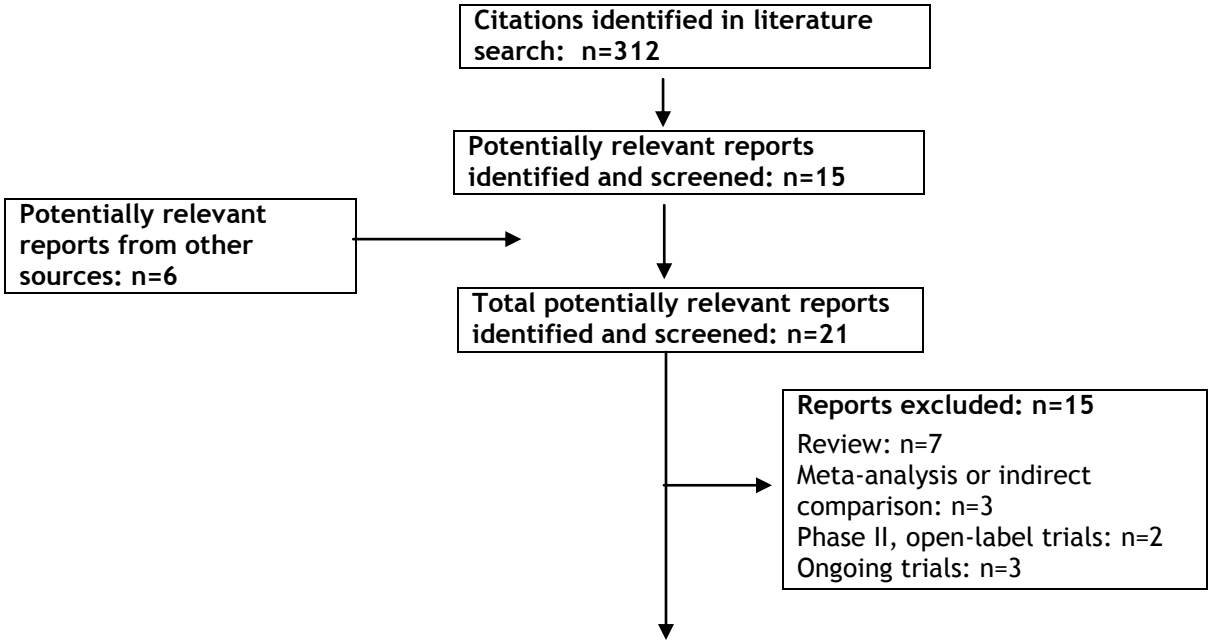
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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 21 potentially relevant reports identified, 6 reports relating to 1 study were included in the pCODR systematic review,[1,10,14,44-46] and 15 reports were excluded. Studies were excluded because they were phase II, open-label trials,[47,48] ongoing trials,[2-4] reviews [22,25,49-53] or meta-analyses.[54-56]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6 reports presenting data from 1 unique RCT

STUDY VEG105192
Sternberg CN 2010[1]
Sternberg CN 2010 (abstract)[10]
Cella D 2011[14]
FDA reports [45,46]
pCODR Submission[44]

Note: Additional data related to the included study were also obtained through requests to the Submitter by pCODR[57]

6.3.1 Summary of Included Studies

6.3.1.1 Detailed Trial Characteristics

Table 2: Summary of Included Study[1]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes

Study VEG105192
 	
80 centres in Europe, Asia, South America, North Africa, Australia and New Zealand
 	
April 2006 to May 2008
 	
n= 435 enrolled;
n= 435 randomized;
n= 435 completed;
 	
• DB, placebo-controlled, RCT
• Randomization was stratified on the basis of :
 	
a) ECOG PS (0 vs. 1),
b) prior nephrectomy (yes vs. no),
c) prior systemic treatment for advanced RCC(treatment naive vs. cytokine pre-treated)
	Age ≥18 years;
	
	A diagnosis of advanced and/or metastatic RCC (clear cell) with no prior systemic therapies or cytokine-pre-treated;
	
	ECOG PS≤1;
	
	Adequate renal, hepatic, and hematologic function
		Pazopanib 800 mg once daily administered orally 1 hour before or 2 hours after meals
		
		Targeted therapies for advanced RCC (i.e., VEGF inhibitors, mTOR inhibitors)
		• Sunitinib
		• Sorafenib
		• Bevacizumab + interferon
		• Temsirolimus
		• Everolimus
		
		Immunotherapy (i.e., interferon-alpha, interleukin-2)
		
		Placebo
			<u>Primary</u>
			• Progression-free survival
			<u>Secondary</u>
			• Overall survival
			• Response rate [complete response + partial response]
			• QoL

DB=double blind; **ECOG PS**=Eastern Cooperative Oncology Group Performance Status; **QoL**=quality of life; **RCC**=renal cell carcinoma; **RCT**=randomized controlled trial; **VEGF**=vascular endothelial growth factor; **mTOR**=mammalian target of rapamycin			

a) Trials

One double-blind, placebo-controlled RCT (Study VEG105192) was included in this review (see Table 2).[1,14] The study was conducted in 80 centres in Europe, Asia, South America, North Africa, Australia and New Zealand (no North American sites). The study was manufacturer-sponsored.

The study compared pazopanib 800 mg once daily with placebo in 435 patients aged ≥18 years with advanced and/or metastatic RCC who were treatment naïve or who received one prior cytokine-based systemic therapy. Additional eligibility criteria included a diagnosis of clear cell or predominantly clear-cell histology and an ECOG performance status of either 0 or 1. Patients were randomized 2:1 to receive either pazopanib or placebo. Randomization was stratified on the basis of ECOG performance status (0 vs. 1), prior nephrectomy (yes vs. no), and prior systemic treatment for advanced RCC (treatment naive vs. cytokine pre-treated).

Trial procedures for allocation concealment, randomization, and blinding were considered adequate to maintain the internal validity of the study. All participants were followed up and assessed at the completion of the study according to the treatment arm to which they were randomized.

b) Populations

Of the total 435 patients enrolled and randomized in this study, 290 patients were assigned to pazopanib and 145 patients were assigned to placebo. Baseline demographic and disease characteristics were balanced between the two treatment arms. Eighty-six percent of patients were white, 14% were Asian, and <1% were of other races. The median age was 60 years (range 25 to 85 years). The proportion of males was somewhat higher in the placebo group (75%) than in the pazopanib group (68%). More than 80% of patients had metastasis with ≥ 2 organs involved and more than 50% had ≥ 3 organs involved (lung, lymph nodes, bone or liver).

All patients had clear cell (90%) or predominantly clear-cell histology (10%). 233 patients had received no prior systemic therapy (54%) and 202 had received at least one prior cytokine-based therapy (46%). The majority of cytokine pre-treated patients (75%) had received interferon-based treatment. ECOG status was balanced between the 2 arms; overall, 42% patients were ECOG 0 and 58% were ECOG 1. Prior nephrectomy was conducted in 88% of all participants. MSKCC prognostic risk scores were balanced between the 2 treatment arms: overall, 55% were intermediate risk, 39% favourable risk, and 3% poor risk.

c) Interventions

Patients received either 800 mg pazopanib once daily or matching placebo. Study medications were administered orally one hour before or two hours after meals. Dose modifications were in 200 mg increments in a stepwise fashion based on individual tolerability. The maximum daily dose was 800 mg. Patients received continuous treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any reason. All patients also received best supportive care; no concomitant therapy was provided. A definition of best supportive care was not provided. Subsequent anticancer therapy for patients with progressive disease was at the discretion of the patient and treating physician. Patients who progressed were unblinded; if patients were found to be on placebo, they had the option of receiving pazopanib via an open-label study provided they met predefined eligibility criteria.

d) Patient Disposition

As of the clinical cut-off date of 23 May 2008, 419 (94%) patients had either died (n = 176, 40%) or were ongoing (n = 233, 54%) in the study. The percentage of patients ongoing was similar in both treatment arms (pazopanib: 56%; placebo: 50%). Twenty-two percent of patients in the pazopanib arm and 10% in the placebo arm were on treatment as of the cut-off date. Rates of early termination from study were 7% in the pazopanib arm and 4% in the placebo arm. No significant protocol violations were observed in either treatment arms.

The median duration of follow-up, defined as date of randomization to date of last contact with patient or death, was similar for both treatment arms (14.4 months for pazopanib [range 0.4 to 24.5 months] and 13.5 months for placebo [range 0.9 to 22.6 months]. As shown in Table 3 below, the majority of patients had discontinued the study treatment (pazopanib: 78%; placebo: 90%) at the cut-off date. The main reason for discontinuation of treatment was disease progression (pazopanib: 51%; placebo: 77%). Compared to the placebo arm, a higher proportion of patients in the pazopanib arm discontinued treatment for reasons other than disease progression or death: 14% vs. 3% discontinued due to adverse events, and 10% vs. 3% discontinued for other reasons.

Table 3: Patient Disposition in Study VEG105192

	Pazopanib N=290	Placebo N=145
Randomized	290	145
On treatment, n(%)	63 (22)	14 (10)
Discontinued treatment, n (%)*	227 (78)	131 (90)
Disease progression, n(%)	147 (51)	112 (77)
Adverse event, n(%)	41 (14)	5 (3)
Death, n(%)	11 (4)	9 (6)
Protocol violation, n(%)	2 (<1)	0
Investigator decision, n(%)	8 (3)	1 (<1)
Lost to follow-up, withdrew consent and other, n(%)	18 (6)	4 (3)

*Reasons for study discontinuation were based on investigator's assessment.

e) Potential Limitations/Sources of Bias

- 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 a retrospective data analysis by Heng et al.[7]
- At the assessment of progression-free survival, seventy (48%) of 145 placebo patients experiencing progression in study VEG105192 subsequently enrolled in an open-label study of pazopanib. Due to the high rate of crossover to active therapy, results for overall survival are likely to be biased against pazopanib. Likewise, safety assessments are likely to be biased against pazopanib due to the longer median duration on pazopanib compared with placebo.
- The primary analysis of PFS in study VEG105192 only adjusted for ECOG (0 or 1) and prior treatment. Other measures of disease status (e.g., number of metastatic sites of disease, prior nephrectomy) and MSKCC prognostic score were not accounted for in the multiple regression analysis.
- Patients were assigned to treatment groups in study VEG105192 by central randomization without stratification by centre/country site, leading to an imbalance in the numbers assigned to each treatment group within some

centres/country sites. The impact of such imbalances on the internal validity of the study is uncertain.

- Compared with independent review committee-assessed PFS, investigator-assessed PFS may be more reflective of 'real-world' effectiveness. Overall agreement between the independent review committee and investigators was 68.3% of subjects in each of the pazopanib and placebo arms. However, median PFS results were similar for both independent review committee and investigator-assessed PFS, indicating that the observed disagreement did not impact the interpretation of the primary outcome.
- The Health Canada approved indication for pazopanib is for the treatment of metastatic clear cell RCC, while study VEG105192 included both locally advanced RCC and metastatic RCC.
- Study VEG105192 excluded patients with ECOG > 1, thus the majority of patients (94%) had MSKCC prognostic risk of 'favourable' or 'intermediate' (3% had a risk score of 'poor' and 3% unknown). The Submitter stated that the exclusion of patients with ECOG > 1 from the study was to ensure that patients could stay in the study for a sufficient period to allow detection of the treatment effect.[57]
- Study VEG105192 did not include any study sites in North America. The apparent reason for this is that the availability in North America of sunitinib for patients with renal cell carcinoma would have made placebo an inappropriate treatment[45]; sunitinib was approved by the FDA in January 2006, while study VEG105192 began enrolling patients in April 2006. Health Canada determined that the extrapolation of these study results to the Canadian population was appropriate based on the fact that the response rates observed in a Phase II study of pazopanib in North American patients were consistent with those obtained in non-North American patients in that same study, as well as in pazopanib-treated patients in study VEG105192.[29]
- Sunitinib, sorafenib, and pazopanib work through the same pathway (VEGF receptor inhibition) to inhibit angiogenesis. It is unknown whether resistance to sunitinib or sorafenib will confer similar resistance to pazopanib. No information is available on the use of pazopanib in patients with advanced RCC who have received first-line targeted therapies such as sunitinib or temsirolimus.

6.3.1.2 Detailed Outcome Data and Summary of Outcomes

The primary efficacy analysis was based on the intent-to-treat population, comprising of all randomized subjects. The safety population comprised all subjects who received at least one dose of investigational product. All safety and efficacy outcomes reported in this review were summarized per the clinical cut-off date of 23 May, 2008. Patients who discontinued study treatment before disease progression were followed up until progression or initiation of alternate anti-cancer treatment. Follow-up for overall survival was performed every three months after disease progression until death or study withdrawal.

Table 4: Summary of Key Trial Outcomes from Study VEG105192

Efficacy				
PFS Total ITT population	 Pazopanib, n=290 Placebo, n=145	**Median (months)** 9.2 4.2	**HR (95% CI)** 0.46 (0.34, 0.62)	**p-value** <0.0001†
Treatment-naïve	Pazopanib, n=155 Placebo, n=78	11.1 2.8	0.40 (0.27, 0.60)	<0.0001‡
Cytokine-pre-treated	Pazopanib, n=135 Placebo, n=67	7.4 4.2	0.54 (0.35, 0.84)	<0.001‡
Overall survival (final data)	Pazopanib, n=290 Placebo, n=145	22.9 20.5	0.91 (0.71, 1.16)	0.224†
Response rate (CR+PR)	 Pazopanib, n=290 Placebo, n=145	**n/N** 88/290 5/145	**% (95% CI)** 30 (25.1, 35.6) 3 (0.5, 6.4)	**p-value** <0.001**
Harms				
	Pazopanib (N = 290)	**Placebo (N = 145)**		
Deaths, n (%)	109 (38)	67 (46)		
SAE, n (%)	69 (24)	27 (19)		
Any AE, n (%)	268 (92)	107 (74)		
AE with causality suggested by INV, n (%)	257 (89)	56 (39)		
AE leading to discontinuation of treatment or early withdrawal, n (%)	44 (15.2)	8 (5.5)		
AE leading to changes in medication: -dose interruption, n (%) -dose reduction, n (%)	 96 (33) 69 (24)	 13 (9) 5 (3)		

AE=adverse event; **CI**=confidence interval, **CR**=complete response; **HR**=hazard ratio; **ITT**=intention-to-treat; **PFS**=progression-free survival; **PR**=partial response; **SAE**=serious adverse event

Note: All efficacy outcome measures including PFS, overall survival and tumour responses were based on independent review committee assessment. Quality of life results were statistically non-significant for each of the EQ-5D and EORTC (QLQ-C30) global health status/quality of life scales. Hazard ratios were calculated using Pike estimator as stratified by ECOG performance status and prior therapy; †based on log-rank test (one sided) stratified by ECOG performance status and prior therapy; ‡unadjusted estimate; **based on Fisher's exact test

Efficacy Outcomes

a) Progression-free Survival

The primary endpoint in study VEG105192 was PFS, defined as the time interval between the date of randomization and the date of documented disease progression or death due to any cause as evaluated by an independent review committee. The ascertainment of progression required a documented radiological progression determined by the independent review committee, or death prior to documentation of radiological progression. Disease assessments were performed every 6 weeks until Week 24, and every eight weeks thereafter until disease progression.

Kaplan-Meier methods were used by the Submitter to analyze PFS with comparisons between the arms being made using a log-rank test (one-sided) adjusted for ECOG performance status (0 vs. 1) and prior therapy (yes or no). Hazard ratios were

calculated using a Pike estimator adjusted for ECOG performance status (0 vs. 1) and prior therapy (yes or no). Comparison of PFS between treatment arms was also performed in predefined subgroup analyses based on prior treatment, age, sex, MSKCC risk group[9] and ECOG performance status.

Based on assessment of disease progression by the independent review committee, 148 out of 290 (51%) patients in the pazopanib arm were identified as 'progressed' or 'died' as of the cut-off date (May 23, 2008), compared with 98 out of 145 (68%) patients in the placebo arm (Table 5). Patients treated with pazopanib demonstrated a statistically significant improvement in PFS [HR 0.46 (95% CI: 0.34 to 0.62; P < 0.001)]. Median PFS was more than double in the pazopanib arm versus placebo (9.2 vs. 4.2 months). A similar degree of improvement in overall PFS was observed based on investigator assessment of progression [HR 0.44 (95% CI: 0.34 to 0.57, P < 0.0001)]. As shown in Figure 1, the difference in risk between the two arms was evident between 6 weeks and 15 months. After 15 months, six patients remained progression-free in the pazopanib arm while all patients had progressed in the placebo arm.

The treatment-naive subpopulation had a median PFS (IRC assessed) of 11.1 vs. 2.8 months in the pazopanib and placebo arms, respectively [HR 0.40 (95% CI: 0.27 to 0.60, P < 0.0001)], while the cytokine-pre-treated subpopulation had a median PFS of 7.4 vs. 4.2 months [HR 0.54 (95% CI: 0.35 to 0.84, P < 0.001)].

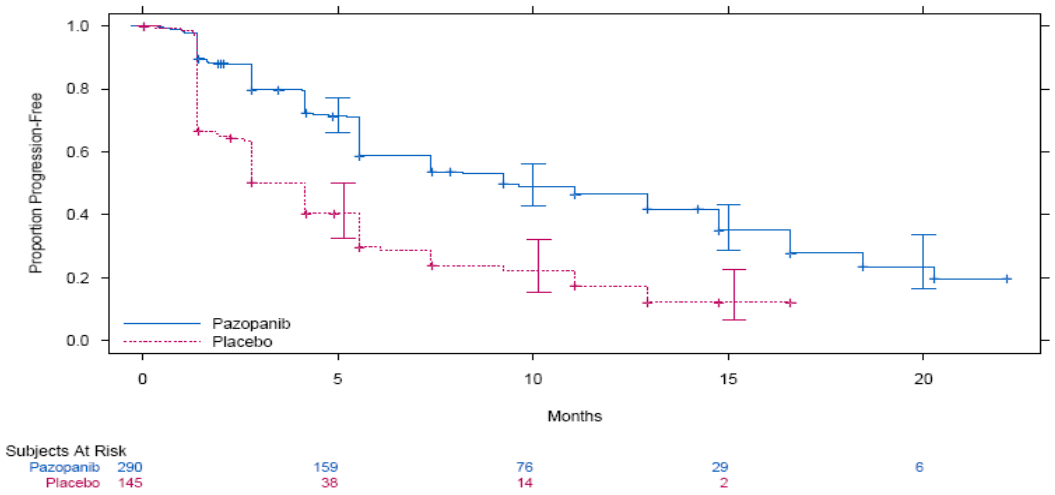
Table 5: PFS in Study VEG105192 – Independent Review Committee Assessment, Intention-to-Treat Population

	Pazopanib (N=290)	**Placebo (N=145)**
Subject status, n (%)		
Progressed or died (event)	148 (51)	98 (68)
Censored	142 (49)	47 (32)
Censored, follow-up ended	90 (31)	42 (29)
Censored, follow-up ongoing	52 (18)	5 (3)
Kaplan-Meier Estimates for PFS (months)		
1st Quartile (95% CI)	4.2 (2.8, 5.6)	1.4 (NC, NC)
Median (95% CI)	9.2 (7.4, 12.9)	4.2 (2.8, 4.2)
3rd Quartile (95% CI)	18.4 (16.6, NC)	7.4 (5.6, 12.9)
Adjusted Hazard Ratio (95% CI)	0.46 (0.34, 0.62)	P<0.0000001

CI=confidence interval; **ITT**=intent-to-treat; **NC**=not calculable; **PFS**=progression-free survival

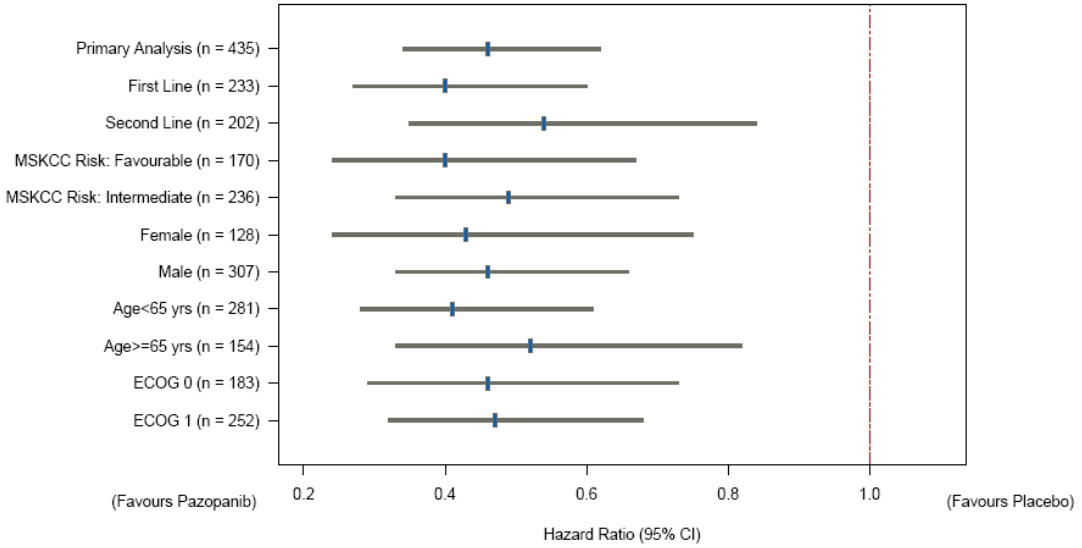
Note: Subjects were classified as censored with follow-up ended if their progression event occurred after a period of extended inadequate assessment or if they withdrew from the study prior to disease progression. Subjects were classified as censored with follow-up ongoing if the subjects were still on-study and progression free at their last disease assessment. The hazard ratio and p-value from the stratified log-rank test were adjusted for ECOG performance status (0 vs. 1) and cytokine-pre-treated (yes or no).

Figure 1 Kaplan-Meier Curves of PFS in Study VEG105192 – Independent Review Committee Assessment, Intention-to-Treat Population



As shown in Figure 2, the PFS benefit associated with pazopanib was maintained in pre-specified subgroups: age (<65 vs. ≥65 years of age); gender; ECOG performance status (0 vs1); and MSKCC risk category (favourable vs. intermediate). The hazard ratio in each of these subgroups was consistent with the primary analysis and statistically significant. In all subgroup analyses, the P-value for the log rank test comparing pazopanib to placebo was less than 0.001.

Figure 2: Forest Plot of Subgroup Analyses on PFS in Study VEG105192 - IRC Assessment, Intention-to-Treat Population



b) Overall Survival

The secondary endpoint was overall survival, defined as the time interval from randomization to death from any cause. Kaplan-Meier methods were used by the Submitter to analyze overall survival with comparisons between the arms being made using a log-rank test (one-sided) adjusted for ECOG performance status (0 vs. 1) and prior therapy (yes or no).

Final analysis results for overall survival showed a statistically non-significant difference between pazopanib and placebo; median 22.9 versus 20.5 months, HR = 0.91 (95% CI: 0.71 to 1.16; P = 0.224).[10] It is noteworthy that 54% of patients in the placebo arm had crossed over to pazopanib in the final analysis of overall survival.[10]

An interim analysis of overall survival was planned at the time of final PFS analysis. A pre-specified O'Brien-Fleming boundary of P < 0.004 was required for rejecting the null hypothesis for either superiority or futility of pazopanib. In the pre-planned interim analysis, median OS was 21.1 vs. 18.7 months in the pazopanib and placebo arms, respectively [HR = 0.73 (95% CI: 0.53 to 1.00; P = 0.020)]. The result was statistically non-significant as it did not cross the pre-specified O'Brien-Fleming boundary of P < 0.004 required for rejecting the null hypothesis for either superiority or futility of pazopanib. The interim analysis was based on 176 death events (109 in the pazopanib arm and 67 in the placebo arm), representing 60% of the total death events (n = 287) required for the final overall survival analysis. The subgroup analyses of overall survival in the treatment-naive and cytokine-pre-treated patients were statistically non-significant for both the interim and final analyses.

c) Response Rate

Response rate was defined as the percentage of patients who achieved either a confirmed complete response or partial response per RECIST criteria.[58] The duration of response was defined as the time from first documented evidence of partial response or complete response until the first documented sign of disease progression or death due to RCC. Tumour response evaluations were performed both by the investigators and independent review committee.

The overall response rate (complete plus partial) for patients on pazopanib as assessed by the independent review committee was 30% (95% CI: 25.1 to 35.6) with a median duration of response of 58.7 weeks. In comparison, the overall response rate in the placebo arm was 3% (95% CI: 0.5 to 6.4); P<0.001 based on Fisher's exact test. A similar response rate for patients on pazopanib was observed in the treatment-naive (32%) and cytokine-pre-treated (29%) subgroups.

The investigator-assessed response rate in the overall population was consistent with the independent review committee-assessed response rate, 36% (95% CI: 30.0 to 41.0); median duration of response 62.4 weeks.

d) Quality of Life

Quality of life was assessed using EORTC QLQ-C30 global health status/quality of life scale[12] and EQ-5D questionnaires[11] at baseline and at six, 12, 18, 24, and 48 weeks. The following minimal important differences (MID) for these questionnaires have been reported in the literature: five to 10 for EORTC QLQ-C30, 0.08 for EQ-5D Index, and seven for EQ-5D visual analog scale.[59,60]

Data were analyzed by a mixed-model repeated-measures analysis of change from baseline for each of EORTC QLQ-C30, EQ-5D Index, and EQ-5D (visual analog scale). There were no statistically significant changes in quality of life scores from baseline at any time point in either treatment arm, and no statistically significant differences between pazopanib and placebo.

A subsequent *post-hoc* analysis assessed the effect of pazopanib on time to 20% or greater reduction from baseline in EORTC QLQ-Global Health Status/quality of life score.[14] This analysis was based on patients with non-missing values at baseline and with at least one post-baseline quality of life assessment (267 out of 290 in the pazopanib arm and 131 out of 145 in the placebo arm). The main rationale for the *post hoc* analysis was that 20% deterioration corresponded to an absolute change from baseline of greater than the minimal important difference (five to 10 points) for most patients.[57] There was a statistically non-significant trend for pazopanib-treated patients to have a lower likelihood than placebo patients to have ≥20% decline from baseline in EORTC QLQ-C30 global health status/quality of life scale (HR = 0.77, 95% CI: 0.57 to 1.03). The results were consistent across treatment-naïve (HR = 0.75, 95% CI: 0.50 to 1.13) and cytokine-pre-treated subgroups (HR = 0.75, 95% CI: 0.48 to 1.18).

Harms Outcomes

Clinical assessments for safety, including physical examinations, vital signs (with blood pressure monitoring), clinical laboratory evaluations, electrocardiograms, ECOG performance status, and adverse events, were evaluated at baseline, day 8, every three weeks until week 24, and every four weeks thereafter until study treatment discontinuation.

a) Deaths

Thirty-eight percent (n = 109) of patients died in the pazopanib group compared to 46% (n = 67) in the placebo group as of the cut-off date (see Table 4). Four deaths (1.4%) in the pazopanib arm were determined by the investigator to be directly related to pazopanib and none in the placebo arm. The causes of death were abnormal hepatic function, ischemic stroke, and peritonitis.

b) Serious Adverse Events

No definition was reported for serious adverse events. A total of 69 (24%) patients in the pazopanib arm experienced a serious adverse event compared to 27 (19%) patients in the placebo arm (see Table 4). Diarrhea was the most frequently reported serious adverse event (2.1%) followed by anemia, dyspnea and vomiting.

Table 6: Serious Adverse Events reported in Study VEG105192 - Safety Population

	Pazopanib (N=290)	Placebo (N=145)
Any event, n(%) patients	69 (24)	27 (19)
Diarrhea	6 (2.1)	0
Anemia	5 (1.7)	3 (2.1)
Dyspnea	5 (1.7)	3 (2.1)
Vomiting	4 (1.4)	2 (1.4)
Hemoptysis	3 (1.0)	1 (0.7)
Hepatotoxicity	3 (1.0)	0
Dehydration	2 (0.7)	2 (1.4)
Abdominal pain	2 (0.7)	1 (0.7)
Abdominal pain upper	2 (0.7)	1 (0.7)
ALT increased	2 (0.7)	1 (0.7)
Hepatic function abnormal	2 (0.7)	1 (0.7)
Hypertension	2 (0.7)	1 (0.7)
Pleural effusion	2 (0.7)	1 (0.7)
Pneumonia	2 (0.7)	1 (0.7)
Confusional state	2 (0.7)	0
Gastric cancer	2 (0.7)	0
Hyperkalemia	2 (0.7)	0
Intestinal obstruction	2 (0.7)	0
Myocardial ischemia	2 (0.7)	0
Asthenia	0	2 (1)
Upper respiratory tract infection	0	2 (1)
Acute renal failure	0	2 (1)
Femur fracture	0	2(1)

c) Any Adverse Event

The median duration of exposure to pazopanib was 7.4 months (range 0.3 to 23.1) compared 3.8 months (range 0.3 to 22.0) in the placebo arm. More patients in the pazopanib group (n = 268, 92%) experienced at least one adverse event than in the placebo group (n = 107, 74%). Adverse events with causality suggested by the investigator occurred in 89% of patients on pazopanib compared to 39% of patients on placebo. The most common adverse events occurring in ≥ 10% patients receiving

pazopanib included diarrhea, hypertension, hair colour changes, nausea, anorexia, vomiting, fatigue, asthenia, abdominal pain and headache; all of these events were more frequent among patients on pazopanib compared with placebo (see Table 7). 40% of patients receiving pazopanib became hypertensive compared to 10% in the placebo arm. Hemorrhagic events were more frequent in patients receiving pazopanib (13%) compared to patients receiving placebo (5%). The most common hemorrhagic events in the pazopanib arm were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal haemorrhage (1%).

Known tyrosine kinase inhibitor-associated adverse events such as hand-foot syndrome, mucositis/stomatitis, proteinuria, thrombocytopenia, and hypothyroidism occurred with an incidence <10% each, with grade three and grade four events reported in <1% of patients received pazopanib.

Thirty-three percent (33%) of patients who received pazopanib required a dose interruption and 24% required a dose reduction compared to 9% and 3%, respectively in patients who received placebo (see Table 4).

Table 7: Adverse Events Reported for at least 10% of Patients in Study VEG105192 – Safety Population

	Pazopanib (N=290)			Placebo (N=145)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	268 (92)	96 (33)	20 (7)	107 (74)	21 (14)	8 (6)
Diarrhea	150 (52)	9 (3)	2 (<1)	13 (9)	1 (<1)	0
Hypertension	115 (40)	13 (4)	0	15 (10)	1 (<1)	0
Hair colour changes	109 (38)	1 (<1)	0	4 (3)	0	0
Nausea	74 (26)	2 (<1)	0	13 (9)	0	0
Anorexia	65 (22)	6 (2)	0	14 (10)	1 (<1)	0
Vomiting	61 (21)	6 (2)	1 (<1)	11 (8)	3 (2)	0
Fatigue	55 (19)	7 (2)	0	11 (8)	2 (1)	2 (1)
Asthenia	41 (14)	8 (3)	0	12 (8)	0	0
Abdominal pain	32 (11)	6 (2)	0	2 (1)	0	0
Headache	30 (10)	0	0	7 (5)	0	0

d) Dose Reduction/Interruption

Overall, 24% of patients who received pazopanib required a dose reduction due to adverse events and 33% required a dose interruption, compared to 3% and 9% respectively in patients who received placebo. The leading causes of dose reductions in >5% of patients receiving pazopanib were hypertension (7%) and diarrhea (6%). The leading causes of dose interruption in ≥5% of patients receiving pazopanib were: ALT increased (6%); diarrhea (6%); AST increased (5%); and hypertension (5%).

e) Withdrawals due Adverse Events

Adverse events leading to discontinuation of treatment or early withdrawal were reported for 44 (15%) patients in the pazopanib arm and for 8 (5.5%) patients in the placebo arm. Adverse events leading to withdrawal were varied in nature.

f) Laboratory Abnormalities

Among patients with at least one adverse events (representing 92% of pazopanib patients and 74% of placebo patients), increased levels of ALT, AST, and total bilirubin (all grades) occurred in 53%, 53%, and 36% of patients treated with pazopanib, respectively compared to 22%, 19%, and 10% in the placebo arm, respectively. ALT grade 3 or 4 elevations were observed in 12% of patients in the pazopanib arm compared to 1% of patients in the placebo arm. AST grade 3 or 4 elevations were observed in 8% of patients in the pazopanib arm compared to <1% in the placebo arm.

Table 8: Selected† Clinical Laboratory Abnormalities among Patients with at least one adverse event in Study VEG105192 – Safety Population

	Pazopanib (N=290)			Placebo (N=145)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Clinical Chemistry						
ALT increase	152 (53)	30 (10)	5 (2)	32 (22)	2 (1)	0
AST increase	152 (53)	21 (7)	2 (<1)	27 (19)	1 (<1)	0
Total bilirubin increase	102 (36)	7 (3)	2 (<1)	15 (10)	2 (1)	1 (<1)
Hypophosphatemia	95 (34)	11(4)	0	16(11)	0	0
Hyponatremia	86 (31)	11 (4)	4 (1)	35 (24)	6 (4)	0
Hypomagnesemia	31 (11)	9 (3)	0	13 (9)	3 (2)	0
Hematologic Outcomes						
Leukopenia	103 (37)	0	0	9 (6)	0	0
Neutropenia	94 (34)	3 (1)	1 (<1)	9 (6)	0	0
Thrombocytopenia	89 (32)	2 (<1)	1 (<1)	7 (5)	0	0
ALT=alanine aminotransferase; **AST**=aspartate aminotransferase						

†Clinical laboratory abnormalities with an incidence of >=30% in the pazopanib arm or with a 5% increase in incidence in the pazopanib arm compared with the placebo arm are displayed.

6.4 Ongoing Trials

Three ongoing studies of pazopanib identified through trial registries and materials provided by the Submitter met the inclusion criteria for this review: VEG108844 (COMPARZ), VEG113046 (PISCES), and VEG113387.[2-4] The Submitter indicated that no outcomes data were currently available for these trials.[57] Key design aspects of these studies are reported in the following tables.

Table 9: Study VEG108844 (COMPARZ) - Pazopanib vs. sunitinib in the treatment of locally advanced and/or metastatic renal cell carcinoma[2]

Trial Design	Inclusion Criteria	Interventions and Comparators	Key Outcome Measures
NCT00720941 Phase III, open-label, randomized (1:1), active controlled trial Start date: August 2008 Expected completion date: December 2011 Estimated enrolment: 876	Age ≥18 years; Diagnosis of advanced and/or mRCC (clear cell) with no prior systemic therapy (interleukin-2, interferon-alpha, chemotherapy, bevacizumab, mTOR inhibitor, sunitinib, sorafenib or other VEGF TKI)	Pazopanib 800 mg administered orally once daily Sunitinib 50 mg administered in 6-week cycles: 50 mg orally daily for 4 weeks followed by 2 weeks off treatment	Primary • Progression-free survival Secondary • Overall survival • Time to response (partial or complete) • Duration of response • Safety • Health outcomes
mRCC=metastatic renal cell carcinoma; **mTOR**=mammalian target of rapamycin; **VEGF**=vascular endothelial growth factor; **TKI**= tyrosine kinase inhibitors			

Table 10: Study VEG113046 (PISCES) - Patient preference study of pazopanib versus sunitinib in advanced or metastatic kidney cancer[3]

Trial Design	Inclusion Criteria	Interventions and Comparators	Key Outcome Measures
NCT01064310 Phase III, randomized, double-blinded, crossover trial Start date: May 2010 Expected completion date: October 2011 Estimated enrolment: 161	Age ≥18 years; Diagnosis of locally advanced or mRCC with no prior systemic therapy (including interleukin-2, interferon-alpha, chemotherapy, bevacizumab, mTOR inhibitor, sunitinib, sorafenib or other VEGF TKI) ECOG performance status '0 or 1'	Pazopanib 800 mg daily administered orally for 10 wks followed by 50 mg sunitinib orally for 10 wks Sunitinib 50 mg daily administered orally for 10 wks followed by pazopanib 800 mg daily for 10 wks	• Patient preference pazopanib vs. sunitinib as assessed by a patient preference questionnaire • Fatigue as assessed by FACIT-Fatigue and quality of life as assessed by EuroQoL EQ-5D • Dose modifications and time to dose modification • Safety and tolerability
mRCC=metastatic renal cell carcinoma; **mTOR**=mammalian target of rapamycin; **VEGF**=vascular endothelial growth factor; **TKI**= tyrosine kinase inhibitors; **ECOG**=Eastern Cooperative Oncology Group; **wks**=weeks			

Table 11: Study VEG113387 - A study to evaluate pazopanib as an adjuvant treatment for localized renal cell carcinoma[4]

Trial Design	Inclusion Criteria	Interventions and Comparators	Key Outcome Measures
NCT01235962 Phase III, double-blind RCT Start date: November 2010 Expected completion date: August 2017 Estimated enrolment: 1500	Age ≥18 years; A diagnosis of RCC (clear cell) No prior adjuvant or neo-adjuvant treatment for RCC	Pazopanib 800 mg daily administered orally Placebo matching pazopanib 200 mg tablets, 800 mg daily	• Disease-free survival • Overall survival • Health outcome • Safety
RCC=Renal cell carcinoma; **RCT**=randomized controlled trial			

7. SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

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 on pazopanib for the treatment of advanced RCC. 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). 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*. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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 revisions were made in between posting of the Initial and Final Clinical Guidance Reports.

The Genitourinary Clinical Guidance Panel for this review is comprised of three 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. All members of the pCODR Clinical Guidance Panel must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are required on an annual basis and panel members have an obligation to disclose conflicts on an ongoing basis.

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 (emez) Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (R) (pmez)

#	Searches	Results
1	(votrient* or pazopanib* or GW786034* or GW-786034* or GW780604 or GW-780604).ti,ab.	423
2	*pazopanib/	161
3	or/1-2	437
4	3 use emez	277
5	(votrient* or pazopanib* or GW786034* or GW-786034* or GW780604 or GW-780604).ti,ab,ot,sh,hw,rn,nm.	1260
6	444731-52-6.rn.	965
7	or/5-6	1260
8	7 use pmez	181
9	4 or 8	458
10	remove duplicates from 9	312

Note: Human filter not used.

2. Literature search via PubMed

Search History

Search	Most Recent Queries	Result
#3	Search **#1 AND #2**	15
#2	Search **publisher [sb]**	399546
#1	Search **votrient* or pazopanib* or GW786034* or GW-786034* or GW780604 or GW-780604**	189

3. Cochrane Central Register of Controlled Trials (Central)
Search for trials. Issue 3 of 4, Jul 2011

There are **9** results out of **651035 records** for: "**votrient* or pazopanib* or GW786034* or GW-786034* or GW780604 or GW-780604** in **Cochrane Central Register of Controlled Trials**" Bottom of Form

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: "votrient or pazopanib" / closed studies only

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: "votrient or pazopanib"

Conference abstracts:

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

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

Search terms: "votrient OR pazopanib" / last 5 years

REFERENCES

1. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol [Internet]. 2010 Feb 20 [cited 2011 Jul 27];28(6):1061-8. Available from: http://jco.ascopubs.org/content/28/6/1061.full.pdf+html

2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT00720941, Pazopanib versus sunitinib in the treatment of locally advanced and/or metastatic renal cell carcinoma (COMPARZ); 2011 Sep 8 [cited 2011 Sep 12]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00720941

3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01064310, Patient preference study of pazopanib versus sunitinib in advanced or metastatic kidney cancer (PISCES); 2011 Sep 8 [cited 2011 Sep 12]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01064310

4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29 -. Identifier NCT01235962, A study to evaluate pazopanib as an adjuvant treatment for localized renal cell carcinoma (RCC) (PROTECT); 2011 Sep 8 [cited 2011 Sep 12]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01235962

5. Kilonzo M, Hislop J, Elders A, Fraser C, Bissett D, McClinton S, et al. Pazopanib for the first line treatment of patients with advanced and/or metastatic renal cell carcinoma: a single technology appraisal. Aberdeen, UK: University of Aberdeen; 2010.

6. Canadian Cancer Society. Canadian cancer statistics 2011 [Internet]. Toronto: Canadian Cancer Society; 2011. [cited 2011 Sep 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%202011%20-%20English.ashx

7. 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.

8. 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.

9. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol [Internet]. 1999 Aug [cited 2011 Aug 4];17(8):2530-40. Available from: http://www.jco.org/cgi/reprint/17/8/2530

10. Sternberg CN, Hawkins RE, Szczylik C, Davis ID, Wagstaff J, McCann L, et al. Randomized, double-blind phase III study of pazopanib in patients with advanced/metastatic renal cell carcinoma (mRCC): final overall survival (OS) results [abstract]. Ann Oncol. 2010 Oct;21 Suppl 8:viii10. (Presented at 35th ESMO Congress Milan Italy;20101008;- 20101012).

11. Rabin R. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul;33(5):337-43.

12. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

13. Pickard AS, Cella D, Duh A, Guerin A, Mishagina N, Antràs L, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomized phase III trial [abstract]. J Clin Oncol. 2011;29(15 Suppl):9096.

14. Cella D, Pickard AS, Duh MS, Guerin A, Mishagina N, Antras L, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. Eur J Cancer. 2011 Jun 18. Epub ahead of print.

15. 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 2011 Sep 7];27(22):3584-90. Available from: http://jco.ascopubs.org/content/27/22/3584.full.pdf+html

16. Hancock B, Griffin CL, Ritchie A, Gore M, Mead G. Updated results of the MRC randomised controlled trial of alpha interferon vs MPA in patients with metastatic renal carcinoma [abstract]. Proc Am Soc Clin Oncol. 2000;19 Suppl:1336.

17. Kriegmair M, Oberneder R, Hofstetter A. Interferon alfa and vinblastine versus medroxyprogesterone acetate in the treatment of metastatic renal cell carcinoma. Urology. 1995 May;45(5):758-62.

18. 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.

19. Steineck G, Strander H, Carbin BE, Borgstrom E, Wallin L, Achtnich U, et al. Recombinant leukocyte interferon alpha-2a and medroxyprogesterone in advanced renal cell carcinoma. A randomized trial. Acta Oncol. 1990;29(2):155-62.

20. Pyrhonen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. J Clin Oncol. 1999 Sep;17(9):2859-67.

21. Negrier S, Figlin R, Hutson TE, Tomczak P, Michaelson MD. Overall survival with sunitinib versus interferon (IFN)-alpha as first-line treatment of metastatic renal cell carcinoma (MRCC) [abstract]. Ann Oncol. 2008;19 Suppl:588.

22. Hutson TE. Targeted therapies for the treatment of metastatic renal cell carcinoma: clinical evidence. Oncologist [Internet]. 2011 [cited 2011 Jul 25];16 Suppl 2:14-22. Available from: http://theoncologist.alphamedpress.org/content/16/suppl_2/14.full.pdf+html

23. 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 2011 Sep 1];356(2):115-24. Available from: http://content.nejm.org/cgi/reprint/356/2/115.pdf

24. Patard JJ, Pignot G, Escudier B, Eisen T, Bex A, Sternberg C, et al. ICUD-EAU International Consultation on Kidney Cancer 2010: Treatment of Metastatic Disease. Eur Urol. 2011 Jun 24. Epub ahead of print.

25. Cowey CL, Sonpavde G, Hutson TE. New advancements and developments in treatment of renal cell carcinoma: focus on pazopanib. OncoTargets and therapy [Internet]. 2010 [cited 2011 Jul 25];3:147-55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2962303/pdf/ott-3-147.pdf

26. Powles T, Chowdhury S, Jones R, Mantle M, Nathan P, Bex A, et al. Sunitinib and other targeted therapies for renal cell carcinoma. Br J Cancer [Internet]. 2011 Mar 1 [cited 2011 Aug 31];104(5):741-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3048200

27. Ljungberg B, Cowan N, Handbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. Guidelines on renal cell carcinoma [Internet]. Arnhem (NL): European Association of Urology; 2010. [cited 2011 Aug 24]. Available from: http://www.uroweb.org/gls/pdf/09_Renal_Cell_Carcinoma%202010.pdf

28. Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009 Mar 10;27(8):1280-9.

29. Health Canada. Summary basis of decision (SBD) for Votrient™. Pazopanib hydrochloride, 200 mg and 400 mg tablets. GlaxoSmithKline Inc. Submission Control Number: 128332 [Internet]. Ottawa: Health Canada, Health Products and Food Branch; 2010 Jul 12. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/sbd-smd/phase1-decision/drug-med/sbd_smd_2010_votrient_128332-eng.pdf

30. 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.

31. 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.

32. 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.

33. French KJ, Coatney RW, Renninger JP, Hu CX, Gales TL, Zhao S, et al. Differences in effects on myocardium and mitochondria by angiogenic inhibitors suggest separate mechanisms of cardiotoxicity. Toxicologic pathology. 2010;38(5):691-702.

34. 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.

35. 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.

36. 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 2011 Aug 30];23(4):832-41. Available from: http://www.jco.org/cgi/reprint/23/4/832

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

38. Jewett MA, Knox JJ, Kollmansberger C, Basiuk J. Canadian kidney cancer forum 2008. Can Urol Assoc J [Internet]. 2008 Jun [cited 2011 Aug 31];2(3):183. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2494888

39. 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. 2010 Sep 15;116(18):4256-65.

40. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol [Internet]. 2010 May 1 [cited 2011 Aug 31];28(13):2137-43. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2860433

41. Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010 May 1;28(13):2144-50.

42. Kollmannsberger C, Bjarnason G, Burnett P, Creel P, Davis M, Dawson N, et al. Sunitinib in metastatic renal cell carcinoma: recommendations for management of noncardiovascular toxicities. Oncologist. 2011;16(5):543-53.

43. Hainsworth J, Spigel DR, Webb C, Daniel D, Friedman E, Burris H. Second-line treatment with pazopanib following first-line sunitinib or bevacizumab in advanced renal cell carcinoma: Preliminary results of a phase II trial [abstract]. Ann Oncol. 2010 Oct;21 Suppl 8:viii285. (Presented at 35th ESMO Congress Milan Italy;20101008;- 20101012).

44. pan-Canadian Oncology Drug Review Manufacturer Submission: Votrient™ (pazopanib hydrochloride) 200 mg tablets; Company: GlaxoSmithKline. Mississauga (ON): GlaxoSmithKline; 2011 Jul.

45. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Votrient (pazopanib hydrochloride) tablets. Company: GlaxoSmithKline. Application No.: 022465. Approval Date: 10/19/2009. Rockville (MD): The Center; 2009 [cited 2011 Aug 31]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000TOC.cfm.

46. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Votrient (pazopanib hydrochloride) tablets. Company: GlaxoSmithKline. Application No.: 022465. Approval Date: 10/19/2009. Rockville (MD): The Center; 2009 [cited 2011 Aug 31]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000TOC.cfm.

47. Hutson TE, Davis ID, Machiels JP, De Souza PL, Rottey S, Hong BF, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2010 Jan 20;28(3):475-80.

48. Hutson T, Davis I, Machiels J, DeSouza PL, Baker K, Pandite L, et al. Predictive and prognostic factors in phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor [abstract]. Ann Oncol. 2008 Sep;19(S8):viii187. (Presented at 34th Congress of the European Society for Medical Oncology (ESMO) Stockholm Sweden;20080912;- 20080916).

49. Gore ME, Larkin JMG. Challenges and opportunities for converting renal cell carcinoma into a chronic disease with targeted therapies. Br J Cancer. 2011 Feb 1;104(3):399-406.

50. Escudier B, Albiges L. Vascular endothelial growth factor-targeted therapy for the treatment of renal cell carcinoma. Drugs. 2011 Jun 18;71(9):1179-91.

51. Keisner SV, Shah SR. Pazopanib: the newest tyrosine kinase inhibitor for the treatment of advanced or metastatic renal cell carcinoma. Drugs. 2011 Mar 5;71(4):443-54.

52. Clark PE. Rationale for targeted therapies and potential role of pazopanib in advanced renal cell carcinoma. Biologics [Internet]. 2010 [cited 2011 Jul 25];4:187-97. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921256/pdf/btt-4-187.pdf

53. Facchini G, Perri F, Caraglia M, Pisano C, Striano S, Marra L, et al. New treatment approaches in renal cell carcinoma. Anticancer Drugs. 2009 Nov;20(10):893-900.

54. Leung HW, Chan AL. Multikinase inhibitors in metastatic renal cell carcinoma: indirect comparison meta-analysis. Clin Ther. 2011 Jun;33(6):708-16.

55. Mickisch GHJ, Schwander B, Escudier B, Bellmunt J, Maroto JP, Porta C, et al. Indirect treatment comparison of bevacizumab + interferon-alpha-2a vs tyrosine kinase inhibitors in first-line metastatic renal cell carcinoma therapy. ClinicoEconomics and Outcomes Research. 2011;3(1):19-27.

56. McCann L, Amit O, Pandite L, Amado RG. An indirect comparison analysis of pazopanib versus other agents in metastatic renal cell carcinoma (mRCC) [abstract]. J Clin Oncol. 2010 May 20;28(15 Suppl 1). (Presented at 2010 Annual Meeting of the American Society of Clinical Oncology, ASCO Chicago, IL United States;20100604;- 20100608).

57. GlaxoSmithKline response to checkpoint meeting questions [internal report]. Mississauga (ON): GlaxoSmithKline, Inc.;

58. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst [Internet]. 2000 Feb 2 [cited 2011 Aug 4];92(3):205-16. Available from: http://jnci.oxfordjournals.org/cgi/reprint/92/3/205

59. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes [Internet]. 2007 [cited 2011 Aug 4];5:70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2248572/pdf/1477-7525-5-70.pdf

60. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.