pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pazopanib (Votrient) for Soft Tissue Sarcoma

November 29, 2012

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the efficacy and safety of pazopanib on patient outcomes compared to standard therapies or placebo in the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior systemic therapies or who are unsuited for such therapies. Patients diagnosed with gastrointestinal stromal tumour (GIST) or adipocytic sarcoma were excluded.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The efficacy and safety of pazopanib 800 mg (n=246) once daily, were compared to placebo (n=123) in an international, multicentre, double-blind, randomized control trial (RCT) (the PALETTE study). Patients were aged ≥18 years with advanced STS with a World Health Organization (WHO) performance status 0 or 1. All patients had received prior chemotherapy, 93% for advanced disease and 25% as (neo)adjuvant therapy. This included anthracyclines in 99% (given for advanced disease in 82%) and 71% had been treated with ifosfamide or analogues. Patients diagnosed with GIST or adipocytic sarcoma were excluded from this study; therefore the generalizability of the study results to this subgroup is uncertain.

The primary endpoint of the trial was progression-free survival (PFS) with the median PFS being 4.6 months in the pazopanib arm versus 1.6 months in the placebo arm (HR = 0.31, 95% CI: 0.24 - 0.40, $p < 0.0001$). The difference in overall survival (OS) was not statistically significant between the two treatment arms: 12.5 months in the pazopanib group versus 10.7 months in the placebo group (hazard ratio [HR] = 0.86, 95% confidence intervals [CI]: 0.67 – 1.11, $p = 0.25$).

Quality of life (QoL) was assessed in the first 12 weeks after randomization using different scales. There were no statistically significant differences between treatments in the global health status at each time point. More patients in the pazopanib arm experienced serious adverse events (SAEs) than those in the placebo arm (41% vs. 24%). The most common SAEs in patients treated with pazopanib were dyspnea, increasing alanine aminotransferase and aspartate aminotransferase, decreasing hemoglobin, pheumothorax and venous thromboembolism. Adverse events were all more frequent in patients receiving pazopanib than in patients on placebo. Most of these were mild, while Grade 3 adverse events were reported for fatigue, diarrhoea, hypertension and anorexia. Grade 4 adverse events were rare, with one case of fatigue being reported in each group. While treatment discontinuation was common in both trial groups, more patients in the pazopanib group stopped treatment due to adverse events, while more patients in the placebo group stopped treatment due to lack of efficacy.

1.2.2 Additional Evidence

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

1.2.3 Interpretation and Guidance

STS are malignant tumours derived from mesenchymal tissue outside the skeleton. Excluding pediatric sarcomas, peak age incidence of STS is 60-80 years, but there is a significant spread to include adolescents and young adults with incidence rates ranging from 1.5-5 per 100,000 population. Median survival from diagnosis of metastases in patients requiring palliative chemotherapy is poor, in the range of 12-18 months, with less than 10% surviving 5 years.

Therapeutic options are limited for patients with advanced STS. Standard chemotherapy agents, such as doxorubicin and ifosfamide produce objective response in 20-30% of patients, with stable disease in a further 30-40%. Toxicities of these agents are often substantial. Administration require IV treatments every 3-4 weeks and ifosfamide is often given as multiday infusions with associated hydration and mesna to reduce toxicity. Pazopanib is the first oral agent to receive regulatory approval for use in advanced STS.

PALETTE is a well conducted international, multicentre, double-blind RCT comparing efficacy and safety of pazopanib to placebo. The PALETTE data supports pazopanib use as a second line (or greater) agent, rather than in chemotherapy-naïve patients. Benefit was limited to a 3-month improvement in median PFS for patients treated with pazopanib versus placebo. OS did not differ significantly between the treatment arms.

To be eligible for PALETTE, patients were required to have WHO performance status (PS) 0 or 1. In addition, a multivariate analysis in PALETTE showed that good PS was a favourable prognostic factor overall.

Most common adverse events were fatigue, diarrhea, weight loss and hypertension, all more frequent on pazopanib. Grade 3/4 toxicities were uncommon and more patients experienced SAEs in pazopanib versus placebo arms. Global measures of health/quality of life (QoL) did not differ between the arms.

1.3 Conclusions

The pCODR Sarcoma Clinical guidance Panel concluded that there is a net overall clinical benefit to pazopanib in the treatment of advanced and metastatic non-adipocytic STS, based on data from one high quality randomized trial (PALETTE) that demonstrated a clinically and statistically significant 3-month improvement in median PFS for patients receiving pazopanib compared with those receiving placebo. Pazopanib was well tolerated. Fatigue, diarrhea, nausea and vomiting were the most common toxicities, but were rarely severe. Over the initial 12-week treatment period, global QoL did not differ between the arms.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Although there was only a small 1.8 month non-significant improvement in OS, this is consistent with data from several randomized trials evaluating standard palliative chemotherapy for advanced STS.
- Patients with adipocytic sarcomas and GIST were excluded from the PALETTE trial. There are insufficient data to recommend its use in these subtypes of sarcoma.
- In PALETTE, pazopanib was evaluated as a second line (or greater) systemic therapy, and 99% of patients had received previous chemotherapy.
- In studies of palliative chemotherapy for advanced STS, patients with high PS usually have improved outcomes. PS 0 or 1 was an eligibility requirement of the PALETTE study, and multivariate analysis across both groups showed that PS 0 (vs 1) was associated with improved PFS (HR 0.73, p=0.045).
- Important patient concerns with currently available chemotherapy options are addressed by the convenience of oral administration, and the relatively mild toxicities associated with pazopanib therapy.

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 (Votrient) for STS. 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 STS conducted by the Sarcoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Health Canada has recently approved the use of pazopanib in the treatment of adult patients with selective subtypes of advanced STS who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy.[1] Patients were required to have diseasee progression on or after, or be intolerant to, an anthracyline-based regimen in the pivotal pahse III study in STS. The recommended dose of pazopanib is 800 mg administered orally once daily as monotherapy. It is a multi-target tyrosine kinase inhibitor (TKI), and targets vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor, and stem cell factor receptor.[2] The action of pazopanib at these receptors reduces the proliferation of cancer cells through inhibition of angiogenesis pathways. For patients who fail first line therapy, the current standard of care is chemotherapy, such as gemcitabine with or without docetaxel, dacarbazine, or trabectedin. Surgery is also an option for metastatic STS.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the efficacy and safety of pazopanib on patient outcomes compared to standard therapies or placebo in the treatment of patients with advanced STS who have received prior systemic therapies or who are unsuited for such therapies.

2.1.3 Highlights of Evidence in the Systematic Review

The efficacy and safety of pazopanib 800 mg (n=246) once daily, were compared to placebo (n=123) in an international, multicentre, double-blind, RCT (the PALETTE study).[3-6] The study recruited patients aged ≥18 years with advanced STS, with a World Health Organization (WHO) performance status 0 or 1, and who had received prior systemic therapy or unsuited for such therapy. The median age was 55 years (range 19 to 84 years), and patients were predominately Caucasian (72%). Patients diagnosed with GIST or

adipocytic sarcoma were excluded from this study; therefore the generalizability of the study results to this subgroup is uncertain.

As of the clinical cut-off date of October 24, 2011, 77% of patients had died. The difference in overall survival (OS) was not statistically significant between the two treatment arms: 12.5 months in the pazopanib group versus 10.7 months in the placebo group (hazard ratio [HR] = 0.86, 95% confidence intervals [CI]: 0.67 – 1.11, p = 0.25). Progression-free survival (PFS) – the primary endpoint of the trial – was assessed over a median follow-up period of 15 months, with a clinical cut-off date of November 22, 2010. The median PFS was 4.6 months in the pazopanib arm versus 1.6 months in the placebo arm (HR = 0.31, 95% CI: 0.24 - 0.40, p < 0.0001). Results of OS and PFS in subgroups were consistent with those reported in the whole population.

Quality of life (QoL) was assessed in the first 12 weeks after randomization using different scales: Global Health Status/quality-of-life scores, European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) (version 3), and European Quality of Life-5 Dimensions (EQ-5D) Scales. There were no statistically significant differences between treatments in the global health status at each time point; however, patients in the pazopanib arm reported worse symptoms of diarrhea, loss of appetite, nausea/vomiting and fatigue than those treated with placebo. The tumour response rates (partial response) were higher in patients treated with pazopanib than placebo.

The most common adverse events observed were: fatigue, diarrhea, nausea, weight loss, and hypertension. They were all more frequent in patients receiving pazopanib than in patients on placebo. Most of these adverse events were graded 1 or 2. Dose reduction of study drug was reported in 92 patients (39%) in the pazopanib arm and in five patients (4%) in the placebo arm. Treatment discontinuation was common in both trial groups. The main reasons for early discontinuation were disease progression (67.9% versus 95.9%) and adverse events (15.0% versus 2.4%). Compared to the placebo group, more patients in the pazopanib group stopped treatment due to adverse events, while more patients in the placebo group stopped treatment due to lack of efficacy.

Table 1. Key Results from PALETTE:

Efficacy				
OS	Pazopanib, n=246 Placebo, n=123	**Median (months)** 12.5 10.7	**HR (95% CI)** 0.86 (0.67, 1.11)	**P-value** 0.25
PFS	Pazopanib, n=246 Placebo, n=123	4.6 1.6	0.31 (0.24, 0.40)	<0.0001
Harms				
	Pazopanib (N = 239)	**Placebo (N = 123)**		
Deaths, n (%)	185 (77.4)	95 (77.2)		
Patients with ≥ 1 AE, n (%)	237 (99)	110 (89)		
SAEs	99 (41)	29 (24)		
AE leading to discontinuation of treatment,* n (%)	37 (15.5)	3 (2.4)		
AE=adverse event; **CI**=confidence interval; **HR**=hazard ratio; **OS**=overall survival; **PFS**=progression-free survival; **SAE**=serious adverse event				

* As of November 22, 2010

At present, a randomized, double blind, crossover, phase II study that compares gemcitabine + pazopanib with gemcitabine + placebo is ongoing in patients with refractory STS. It planned to enroll 80 patients.(NCT01532687).[7]

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.

There are no drug class reviews, systematic reviews, health technology assessments or other randomized controlled trials available at present to provide more comprehensive insights on the effectiveness and safety of pazopanib on advanced STS.

A single-arm, open-label phase II study was conducted to examine the effectiveness and safety profile of pazopanib in advanced STS.[8] One hundred forty-two patients were recruited. The median age in this population was 51.4 years. The investigated histological subtypes included adipocytic STS (13.3%), leiomyosarcomas (29.6%), synovial sarcomas (26.8%), and other STS types (30.3%). Most of the patients were with high- or intermediate-grade advanced disease. The primary endpoint was progression-free survival at week 12 ($PFS_{12\ weeks}$), and the secondary endpoints were overall PFS, response rate (RR), duration of response, OS and safety. The recruitment of adipocytic STS was terminated when fewer than 20% of these patients achieved treatment success (defined as surviving without disease progression) in the first stage of the study. The results showed that $PFS_{12\ weeks}$ was 26% in the adipocytic sarcoma cohort, 44% in the leiomyosarcomas cohort, 49% in the synovial sarcomas cohort, and 39% in the other eligible sarcomas. When comparing the mixed study population (excluding adipocytic STS) with historical controls treated with other active regimens, pazopanib was associated with prolonged PFS and OS (data were presented graphically; thus it was difficult to determine if the differences were significant).

The most frequently reported adverse events included leukopenia, anemia, elevating AST and ALT, and proteinuria. Hypertension, fatigue, hypopigmentation and nausea were considered common treatment-related adverse events.

The authors indicated that pazopanib met the predefined criteria for antitumour activity that allow additional investigation in certain groups of STS.

Quality of this study was compromised by its study design. Unlike a phase III study, the objective of this phase II study was to explore whether pazopanib warrants further exploration in STS and to establish a safety profile of pazopanib in the study population. This was a open-label, single-arm study without comparing pazopanib simultaneously to an active or inactive agent. Sample size calculation was not reported and the number of patients in each histologic subgroup was small.

Compared with this phase II study, subjects enrolled in the PALETTE study had different patient characteristics and received more intensive anti-cancer treatment. A direct comparison on the results between PALETTE and the phase II study is challenging. However, the phase II study suggested an unsatisfied treatment effect for pazopanib on adipocytic STS; in addition, it indicated a potential favourable survival benefit for other advanced STSs, despite the corresponding drug-related adverse events.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

Patient Advocacy Group Input

From a patient perspective, extending life expectancy and reducing adverse effects are important aspects when consideration is given to treatment. Currently available treatment options in Canada for soft tissue sarcoma are limited, time consuming, and are typically associated with significant adverse effects. Patients would like to see new treatment options, such as pazopanib, available to treat soft tissue sarcoma so that patients and physicians have more choice to design a treatment protocol. Patients indicated that they are willing to try treatments associated with side effects if there is the potential to prolong life or to have a reduced side effect profile as compared to current treatments.

PAG Input

Input on the pazopanib (Votrient) review was obtained from seven of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, pazopanib was noted to be a new and novel therapy for the treatment of advanced soft tissue sarcoma. Although PAG estimated that there would only be small patient populations accessing pazopanib for this indication as it is a relatively uncommon cancer, they noted that there was potential for pazopanib to be used in other treatment settings where it has not specifically been studied. As pazopanib is orally administered, PAG recognized that it may be a convenient option for patients, and there may be cost avoidance as chemotherapy clinics would not have to be utilized.

Other

Studies on pazopanib for the treatment of other tumours, such as non-small cell lung cancer, renal cell carcinoma, myeloma, breast cancer, and gynaecologic malignancies are ongoing.

2.2 Interpretation and Guidance

Burden of Metastatic Soft Tissue Sarcoma (STS)

STS are malignant tumours derived from mesenchymal tissue outside the skeleton. As this tissue is ubiquitous, STS are not organ specific and can arise in any site. Excluding pediatric sarcomas, peak age incidence of STS is 60-80 years, but there is a significant spread to include adolescents and young adults. Misclassification within organ sites may occur and thus accurate information about disease burden is difficult to obtain. Textbooks and reviews give incidence rates ranging from 1.5-5 per 100,000 population. The latest statistics from the Canadian Cancer Society are 1,116 new cases (2007) and 430 deaths (2008). The majority of deaths occur as a result of distant metastases, the most common sites being lung (for extremity/trunk STS) and liver/intraabdominal (for abdominal/pelvic STS). Median survival from diagnosis of metastases in patients requiring palliative chemotherapy is poor, in the range of 12-18 months, with less than 10% surviving 5 years.[9,10]

Effectiveness of Pazopanib

PALETTE[3] is an international, multicentre, double-blind RCT comparing efficacy and safety of pazopanib, 800 mg once daily, to placebo. It was led by the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), which held the database, and was sponsored by GSK. A 2:1 randomization scheme resulted in 246 patients assigned to pazopanib and 123 to placebo. Patients with adipocytic sarcomas and GIST were excluded. All patients had received prior chemotherapy, 93% for advanced disease and 25% as (neo)adjuvant therapy. This included anthracyclines in 99% (given for advanced disease in 82%) and 71% had been treated with ifosfamide or analogues. The protocol did not permit cross-over to pazopanib after progression on placebo, but 14% in the pazopanib group and 10% on placebo received subsequent targeted therapies. In addition, more patients progressing on placebo (62%) received further chemotherapy, compared with 45% on pazopanib.

The primary endpoint was PFS, and analysis was event-driven requiring at least 274 patients with disease progression and 195 deaths. At the analysis cut-off (October 2011), median follow-up was 15 months and 77% of patients had died. Median PFS was 4.6 months in the pazopanib arm versus 1.6 months in the placebo arm (HR 0.31, 95% CI 0.24-0.40, $p<0.0001$). OS did not differ significantly between the treatment arms, at 12.5 months for pazopanib versus 10.7 months for placebo (HR 0.86, 95% CI 0.67-1.11, $p=0.25$).

Safety of Pazopanib

The most common adverse events were fatigue, diarrhea, weight loss and hypertension, all more frequent on pazopanib. Grade 3/4 toxicities were uncommon, all less than 10% except for a 14% incidence of fatigue on pazopanib. More patients experienced SAEs in pazopanib vs placebo arms, 99 (41%) versus 29 (24%). Fatal SAEs did not differ between arms, 8 (3%) versus 6 (5%) respectively. Venous thromboembolic events occurred in 13 (5%) on pazopanib versus 3 (2%) on placebo. Pneumothorax, an unusual complication of lung metastases from STS was more frequent in the pazopanib arm, 8 (3%) versus 1 (1%), perhaps a marker of drug efficacy.

QoL was assessed in the first 12 weeks on study. At week 12, more patients in the placebo arm compared with pazopanib, 91 (74%) versus 118 (48%), had dropped out of the study and did not complete QoL data. Global measures of health/QoL did not differ between the arms, but on the QLQ-C30 subscale there were statistically significant differences, with worse

scores for pazopanib in the domains of diarrhea, anorexia, nausea and vomiting, fatigue at most timepoints.

Limitations of Evidence

Limitations of the evidence include:

- Evidence is only available from a single RCT. However, this was a well-conducted study, placebo controlled, and the database was held and analysed by a credible organization (EORTC STBSG) independent of the sponsoring pharmaceutical company.

- The median PFS of 4.6 months in patients receiving pazopanib, and 3-month improvement compared with placebo should be viewed in the context of the limited efficacy of second-line therapies in STS. For example, in the only randomized placebo-controlled study[11] in this setting, ridaforolimus administered as maintenance therapy produced a statistically significant improvement in PFS (HR 0.72, p=0.0001), but the difference in median PFS was only 3.1 weeks (17.7 versus 14.6 weeks). Similarly, in two randomized phase II trials comparing combination docetaxel/gemcitabine with gemcitabine alone, median PFS for the combination ranged from 4.2-6.3 months, and improvements compared with single agent therapy ranged from 1.2-2.5 months[12,13].

- The median OS difference of 1.8 months was not statistically significant despite a design that prohibited cross-over of therapies. PFS was chosen as the primary endpoint based on a published analysis (Van Glabbeke 2002[14]) of a large EORTC STBSG database of phase II trials in STS that linked a PFS at 12 weeks of >40% with agents accepted as clinically active in STS. Data from a phase II trial (Sleijfer 2009[8]) of 142 patients with advanced STS in which pazopanib showed 12 weeks PFS >40% in several major histological subtypes of STS, with the exception of adipocytic sarcomas, provided the rationale for proceeding with a phase III trial. In advanced STS, it has rarely been shown that improvements in response rate or PFS translate into OS benefit, even for agents such as doxorubicin and ifosfamide that are the accepted standard of care. Thus, in a meta-analysis of studies comparing single agent doxorubicin to doxorubicin-based combination chemotherapy,[15] there was no significant improvement in OS for combination chemotherapy, despite higher response rates and better PFS in most studies.

- Adipocytic sarcomas were excluded from the PALETTE study, based on phase II results (Sleijfer 2009[8]). As only 19 patients with this histological type were evaluated, with a 12 week PFS of 26%, it can be concluded that there are insufficient data for the efficacy of pazopanib in this histological subtype. Thus, based on current information, pazopanib should not be used in adipocytic sarcomas.

- The data support pazopanib use as a second line (or greater) agent, rather than in chemotherapy-naïve patients. In PALETTE, 93% of patients had received previous chemotherapy, with 99% of those treated with anthracyclines. As pazopanib is an oral agent, convenient to administer, with mild toxicity compared to standard drugs (doxorubicin, ifosfamide) given as palliative first line chemotherapy for STS, there will be pressure from patients and physicians to access pazopanib as first line treatment, particularly for those deemed unfit for chemotherapy, or with specific contraindications, but also based on patient and physician preference. There is no *a priori* reason to suspect that pazopanib will be less active in this setting, and indeed it could have greater efficacy/benefit, although there is no evidence as yet and such use would have cost implications above estimates using trial-eligible patients.

- To be eligible for PALETTE, patients were required to have WHO performance status (PS) 0 or 1. In addition, a multivariate analysis in PALETTE[3] showed that good PS (HR for 0 versus 1 was 0.73, 95% CI 0.54-0.99, p=0.045) was a favourable prognostic factor overall, and this has been shown in other studies of chemotherapy in advanced STS.

- Although toxicities of pazopanib (fatigue, diarrhea, weight loss, hypertension) were mild (<15% grade 3/4) compared with standard IV chemotherapies, they were not insignificant. It is disappointing that global QoL during the first 12 weeks of therapy did not differ between the arms, as the desired effect of palliative chemotherapy is that tumour shrinkage or delay in progression will improve patients' activity or wellbeing, and this was not definitively shown.

There are also limited data to suggest that the activity of pazopanib is associated with specific anti-angiogenesis mechanisms in STS. Unlike the action of imatinib, which is known to specifically target the cKit gene and its protein product that drive tumour growth in GIST, data are conflicting on the contribution of angiogenesis in STS progression, as most have complex molecular alterations that may drive growth. In the phase II study of pazopanib (Sleijfer 2009[8]), a number of cytokines and angiogenic factors were measured at baseline (85 patients) and during treatment (32 patients) with pazopanib (Sleijfer 2012[16]). Low soluble vascular endothelial growth factor receptor-2 ($sVEGFR_{2)}$ and high placental-derived growth factor (PlGF) at week 12 were associated with several pazopanib-specific toxicities. If confirmed in a larger cohort, this could provide evidence for a targeted effect of pazopanib and allow better patient selection.

Need and Therapeutic Options

Therapeutic options are limited for patients with advanced STS. Standard chemotherapy agents, such as doxorubicin and ifosfamide produce objective response (CR + PR) in 20-30% of patients, with stable disease in a further 30-40%. These responses are thought to equate with patient benefit and may extend survival, but this has not been proven in placebo controlled trials. Toxicities of these agents are often substantial, with alopecia occurring in all patients, nausea/vomiting/anorexia being common, and there is significant risk (10-20%) of hospitalization due to neutropenic fever. Most chemotherapies used in STS require IV treatments every 3-4 weeks, and ifosfamide is often given as multiday infusions with associated hydration and mesna to reduce toxicity. Similar issues related to IV administration and toxicities occur with common second-line agents such as docetaxel, gemcitabine, trabectedin.

For patients failing first-line chemotherapy, current treatment options include other IV chemotherapies or palliative/supportive care (or rarely palliative surgery or radiotherapy). Patients with rapidly progressive disease causing deterioration in performance status, or those with significant comorbidities, may not tolerate further IV chemotherapy. Younger fitter patients are likely to be considered for sequential single agent treatments such as standard dose ifosfamide(if not given first-line), high dose ifosfamide, gemcitabine, trabectedin or dacarbazine, all of which are given IV and have significant toxicities. Patients with leiomyosarcoma may be offered combination chemotherapy with gemcitabine/docetaxel. If available, pazopanib is likely to be offered somewhere in this sequence, and may substitute for one line of IV chemotherapy, it could also represent an additional option in this group of patients.

The evidence for benefit of these second-line chemotherapies is of poor quality (Level 3). Most have been evaluated in phase II studies, documenting highly variable response rates and survival outcomes, probably due to differences in patient selection. The outcomes of the only three randomized trials (Level 2 evidence) conducted in this setting are presented earlier in bullet 2 of the section on Limitations of Evidence, and illustrate small effect of second-line treatments on PFS.

Pazopanib is the first oral agent to be approved for use in advanced STS. The convenience of oral administration and its mild toxicities, associated with a modest delay in disease progression, align well with patient values, even though improvements in QoL have not been demonstrated.

2.3 Conclusions

The pCODR Sarcoma Clinical guidance Panel concluded that there is a net overall clinical benefit to pazopanib in the treatment of advanced and metastatic non-adipocytic STS, based on data from one high quality randomized trial (PALETTE) that demonstrated a clinically and statistically significant 3-month improvement in median PFS for patients receiving pazopanib compared with those receiving placebo. Pazopanib was well tolerated. Fatigue, diarrhea, nausea and vomiting were the most common toxicities, but were rarely severe. Over the initial 12-week treatment period, global QoL did not differ between the arms.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Although there was only a small 1.8 month non-significant improvement in OS, this is consistent with data from several randomized trials evaluating standard palliative chemotherapy for advanced STS.
- Patients with adipocytic sarcomas and GIST were excluded from the PALETTE trial. There are insufficient data to recommend its use in these subtypes of sarcoma.
- In PALETTE, pazopanib was evaluated as a second line (or greater) systemic therapy, and 99% of patients had received previous chemotherapy.
- In studies of palliative chemotherapy for advanced STS, patients with high PS usually have improved outcomes. PS 0 or 1 was an eligibility requirement of the PALETTE study, and multivariate analysis across both groups showed that PS 0 (vs 1) was associated with improved PFS (HR 0.73, p=0.045).

Important patient concerns with currently available chemotherapy options are addressed by the convenience of oral administration, and the relatively mild toxicities associated with pazopanib therapy.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Soft tissue sarcomas (STS) are malignant tumours derived from mesenchymal tissue outside the skeleton. As this tissue is ubiquitous throughout the body, STS are not organ specific and can arise in any site. Commonest primary locations are lower limb, 29%, particularly the thigh, and intra-abdominal, 36%, including 15% retroperitoneal and 21% visceral.[17] The median age at diagnosis is 65 years. Pathological classification is complex, and conventionally is based on features of histological differentiation characteristic of normal mesenchymal tissues such as striated/smooth muscle, fat, nerve sheath, blood vessels, etc. (Table 2)

Table 2. Common histologic subtypes of soft tissue sarcoma

Common histologic subtypes of soft tissue sarcoma
• malignant fibrous histiocytoma • liposarcoma (well diff, myxoid, round cell, pleomorphic) • leiomyosarcoma • fibrosarcoma • rhabdomyosarcoma (embryonal, alveolar, pleomorphic) • synovial (monophasic, biphasic) • malignant peripheral nerve sheath tumor (MPNST) • angiosarcoma (hemangiopericytoma, lymphangiosarcoma) • undifferentiated • unclassified

Rare miscellaneous: alveolar soft parts, clear cell, epithelioid, malignant mesenchymoma, malignant granular cell, carcinosarcoma, mixed mesodermal (uterine), endometrial stromal (uterine).

Immunohistochemical markers are used to distinguish STS from carcinomas, melanomas, lymphomas and other malignancies, and may assist in characterization of subtypes. Increasing knowledge of molecular biology has allowed the identification of some rare types of sarcoma that are associated with specific types of chromosomal translocation (e.g., Ewing's sarcoma, synovial sarcoma, myxoid liposarcoma, alveolar rhabdomyosarcoma), although understanding of the molecular changes that drive growth is still imperfect.[18,19] Our knowledge improved with the discovery that growth of gastrointestinal stromal tumours (GIST), previously known as leiomyosarcomas of bowel, is frequently driven by mutations of the KIT gene, and targeted therapy with imatinib is highly effective in producing durable remissions in recurrent and metastatic GIST.[20] Unfortunately, similar successes in other adult STS are rare, as tumour growth is usually driven by complex molecular alterations.[18,19]

As many cancer registries collect organ specific data, it is difficult to find accurate information on incidence and mortality. Many textbooks and reviews give vague figures, e.g.,

STS are <1% of all cancers, incidence rates range from 1.5 - 5 per 100,000 population.[17] The American Cancer Society[21] estimates that in 2012 there will be 11,280 cases of STS with 3,900 deaths. The latest statistics from the Canadian Cancer Society[22] are 1,116 new cases (2007) and 430 deaths (2008). Most deaths occur as a result of distant metastases which develop in approximately one-third of patients. Extremity STS have a predilection for metastasis to lung and, except for a few subtypes (e.g., epithiliod, synovial, rhabdomyosarcomas) rarely spread to lymph nodes. Intra-abdominal sarcomas often metastasize to liver.[17]

Although some patients with metastatic STS may have prolonged survival, particularly if they present with small volume disease amenable to surgery, those for whom palliative chemotherapy is the only option generally do poorly with median survivals in the range of 12-18 months. For example, in a study evaluating prognostic and predictive factors for outcome after first-line ifosfamide containing chemotherapy in adult STS, based on analysis of a database of 1,337 patients established by the EORTC Soft Tissue and Bone Sarcoma Group, Sleijfer et al.[9] reported an overall median survival of 54 weeks, and 5 years OS was <10%. However, there may have been modest improvements in outcome over time. Using a database of patients with metastatic STS established by the French Sarcoma Group, Italiano et al.[10] compared data from 4 successive treatment periods P1 (1987-1991, 208 patients), P2 (1992-1996, 287 patients), P3 (1997-2001, 285 patients) and P4 (2002-2006, 265 patients). With no obvious differences in clinical characteristics between groups, median OS was better (p=0.027) in the later cohorts P3 (15 months) and P4 (18 months) compared with P1 (12.4 months) and P2 (11.3 months). Two year OS rate also increased from 28.1% during P1 to 38.7% during P4.

3.2 Accepted Clinical Practice

Primary STS are treated by surgery alone, surgery plus radiotherapy with or without (neo)adjuvant chemotherapy. Locally recurrent tumours are managed in a similar way. In a highly selected group of patients, resection of metastases (usually in lung or liver) may be curative.[17]

Most patients who develop metastases are not suitable for surgery, and if medically fit will receive palliative chemotherapy. Standard first-line regimens include doxorubicin (DOX) alone, DOX combinations such as mesna/adriamycin/ifosfamide/dacarbazine (MAID), DOX + ifosfamide (IFOS) and adriamycin + dacarbazine (ADIC) with/without cyclophosphamide (CYVADIC).[10,23] A meta-analysis of randomized trials of DOX versus DOX combinations formed the basis for a Cancer Care Ontario, Program in Evidence-Based Care, Practice Guideline 11.2.[15] This was first published in 1999, with updated literature searches in 2004 and 2010. Eight randomized trials including 2,281 patients were reviewed. Objective response rates ranged from 16-27% for DOX and 14-34% for DOX combinations. There was a trend for improved response rates with combination chemotherapy, but this did not reach statistical significance (OR 0.79; 95% CI 0.60-1.05; p=0.10). Survival data could only be abstracted from 6 studies involving 2,097 patients, and showed no significant advantage for DOX combination therapy (OR 0.84; 95% CI 0.67-1.06; p=0.13). Nausea, vomiting and myelosuppression were more frequent with combination chemotherapy. Other common toxicities occurring with DOX alone or in combination include alopecia, mucositis and the risk of cardiotoxicity with cumulative doses of DOX >550 mg/m^2. A randomized phase III trial of DOX versus DOX + high dose IFOS, conducted by the Soft Tissue and Bone Sarcoma Group of the EORTC, completed accrual in 2010 and results should be reported soon.

IFOS combinations may also be associated with bladder and renal toxicity, and rarely confusion/coma. Mesna and extensive hydration reduce those risks. A phase III clinical trial of palifosfamide,[24] an analogue of ifosfamide with significantly reduced toxicity, in combination with DOX versus DOX alone has just completed accrual, with early results expected by late 2012. If similar/better efficacy with reduced toxicity can be demonstrated, it may eventually replace ifosfamide.

More recently, based on promising phase II data,[25,26] use of a combination of docetaxel /gemcitabine has been advocated for treatment of leiomyosarcomas (particularly those in the uterus). In an early study[25] of 34 patients with leiomyosarcoma (29 uterine), an objective response rate of 53% was reported (3 complete remissions, 15 partial remissions). In a later study[26] of 44 patients (23 uterine), the results of first-line gemcitabine/docetaxel were more modest, with a partial response rate of 27%. However, the results of this combination, in a randomized trial (versus gemcitabine alone) in an unselected group of STS, were disappointing.[12] Based on 122 randomized patients who had received 0-3 prior chemotherapy regimens, objective response rates were 16% for docetaxel /gemcitabine and 8% for gemcitabine alone. Despite numerical differences in median progression free survival (PFS), 6.2 versus 3.0 months, these were not significantly different. Important toxicities were myelosuppression, but also grade 3/4 pulmonary toxicity, fatigue and myalgias in 2-16% of cases.

The benefits of second-line chemotherapy are even more limited, and few randomized trials have been performed in this setting. The most commonly used agents in Canada are IFOS (if not used first line), dacarbazine[27] and gemcitabine +/- docetaxel. In selected patients, high dose (12-14 g/cycle) ifosfamide may be used in patients who have failed conventional doses of the drug. Objective response rates are usually in the range 10-20% with PFS in the range of 3-6 months. Dacarbazine is associated with significant nausea, vomiting and myelosuppression. Trabectedin is a novel agent that has been approved in Europe for some time for treatment of STS.[28] In July 2011 it was also approved by Health Canada, but not yet by the FDA. It has been available in some Canadian Centres through a compassionate release program. Response rates and survival outcomes are in a similar range to other second-line agents. It is quite well-tolerated, but nausea, vomiting, myelosuppresion and hepatotoxicity may occur.

There are some data to suggest that certain chemotherapy agents are more active in specific histologic types of STS, e.g., ifosfamide in synovial sarcoma, gemcitabine (± docetaxel in leiomyosarcomas, paclitaxel in angiosarcomas, trabectedin in myxoid liposarcomas and leiomyosarcomas). However, this is low level evidence from phase II studies, and usually these associations lack a "targeted" mechanism of action.[29]

Oral targeted agents such as imatinib, sunitinib and sorafenib have produced low objective response rates and modest prolongations in PFS, based on limited phase II data. These agents, which are marketed in the US and Canada for other indications, are used in STS and included as treatment options in NCCN guidelines.[30] They are not approved by Health Canada for STS, and in most provincial cancer drug plans they are not funded options. Thus they are used infrequently, mainly in patients with private drug plans, or in those individuals willing to pay.

Another targeted agent, the oral mTOR inhibitor ridaforolimus, has been evaluated as maintenance therapy for STS in the SUCCEED trial.[11] A total of 711 patients, who achieved stable disease or better response to standard chemotherapy, were randomized to

ridaforolimus versus placebo as maintenance treatment. The study met its primary end-point of improved PFS (HR 0.72, p=0.0001). Median PFS was 17.7 weeks on ridaforolimus versus 14.6 weeks on placebo. Follow-up for OS is ongoing. Ridaforolimus is not presently approved in either US or Canada for marketing.

3.3 Evidence-Based Considerations for a Funding Population

Pazopanib, if approved, is likely to be used as second- or third-line chemotherapy after DOX ± IFOS in patients with metastatic (Stage IV) STS. In the PALETTE study,[3] 26% of patients had received prior (neo)adjuvant systemic therapy, 93% had received prior systemic therapy for advanced disease, 99% (82% for advanced disease) with anthracyclines and 71% with IFOS or analogs. Absolute numbers of patients eligible for treatment annually are more difficult to estimate. Most patients dying of STS are likely to be candidates for palliative chemotherapy, i.e., 430 in Canada in 2008, but factors such as advanced age and/or comorbidity, as well as patient interest and referral patterns may reduce that number. In addition, patients with adipocytic sarcomas, which represent up to 20% of cases, were excluded from the PALETTE trial, and should not receive pazopanib treatment. A reasonable estimate is 250-320 patients/year may be eligible for treatment with pazopanib.

Eligibility would be determined by the pathological diagnosis of a non-adipocytic STS by a local pathologist and evidence of metastatic or unresectable local disease. Many centres routinely obtain a review by an expert sarcoma pathologist. Specific marker studies would not be required.

3.4 Other Patient Populations in Whom the Drug May Be Used

Pazopanib is currently approved in Canada for renal cell cancer. The FDA has approved pazopanib for use in STS, and similar applications are ongoing in Europe. It is possible that, without strict criteria in provincial drug formularies, pazopanib may be used for adipocytic sarcomas, GIST and bone sarcomas (there are no available studies in these settings, and low patient numbers would preclude randomized trials).

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Sarcoma Cancer Foundation of Canada, provided input on pazopanib for soft tissue sarcoma; their input is summarized below.

The Sarcoma Cancer Foundation of Canada gathered qualitative data through input provided by the organization's board of directors, patients and families affected by sarcoma, and from physicians involved in the sarcoma community across Canada. The number of people interviewed by the Sarcoma Cancer Foundation was not provided.

From a patient perspective, extending life expectancy and reducing adverse effects are important aspects when consideration is given to treatment. Currently available treatment options in Canada for soft tissue sarcoma are limited, time consuming, and are typically associated with significant adverse effects. Patients would like to see new treatment options, such as pazopanib, available to treat soft tissue sarcoma so that patients and physicians have more choice to design a treatment protocol. Patients indicated that they are willing to try treatments associated with side effects if there is the potential to prolong life or to have a reduced side effect profile as compared to current treatments.

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 Soft Tissue Sarcoma

Patients with soft tissue sarcoma often have a number of symptoms that vary depending on the location of the tumour. Symptoms usually include, pain, discomfort, sleeplessness, shortness of breath, cough, and gastrointestinal issues. These typically translate to an interference with regular daily activities. The disease is difficult to diagnose, and is often diagnosed at a later stage.

Patient input indicated that because of the variability in location of tumour presentation, the impact on quality of life varies from patient to patient. For example, surgical interventions to remove tumours can lead to loss of or restricted mobility (if for example a limb has to be amputated) or alter a patient's future plans for a family (if for example a hysterectomy is performed). Furthermore, the Sarcoma Cancer Foundation noted that many children and young individuals are affected by this disease and it impairs their ability to pursue their education or careers.

4.1.2 Patients' Experiences with Current Therapy for Soft Tissue Sarcoma

Current therapies for soft tissue sarcoma include surgery often in conjunction with radiation and chemotherapy administered in a hospital setting. There are limited treatment centres in Canada.

Patient input highlighted that many of the treatments, although able to prolong life for patients, are associated with significant side effects that impair the ability to lead a productive life. It was also noted that remission is possible with surgical intervention however, other existing therapies offer low survival rates.

Furthermore, patient input indicated that access to currently available treatment options can be difficult for some patients who are in remote or smaller communities. It was noted that a large proportion of patients are required to travel hours from home in order to receive treatment that is only available in the hospital setting. It was expressed that this incurs a significant cost to patients in terms of time that could be spent working or with family.

Although patients are aware of and have had direct experience with significant side effects of currently available therapies, patient input notes that some patients are willing to try new treatments associated with side effects if there is a potential to extend life or reduce tumour size.

It was also noted that some patients who were previously in remission, and subsequently experienced a relapse, are either unable to receive further treatment due to previous chemotherapy use or fail further therapies. This patient population is often desperate for new therapies in order to help increase the odds for longer term treatment success.

4.1.3 Impact of Soft Tissue Sarcoma and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of this cancer on caregivers and families is significant. Caregivers must often uproot their lives in order to provide for the patient. There are reports that some caregivers, especially ones looking after children or young adults, leave their jobs, re-mortgage homes or take on substantial loans in order to continue to support ongoing treatment; resulting in families going into debt. Additionally, family life and marriages suffer as a result of the strain put on relationships. The challenges of being a caregiver are also compounded by the fact that there is typically a bleak outlook on long term survival.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Pazopanib

Input from patients without direct experience with pazopanib highlighted that there are few treatment options available in Canada for soft tissue sarcoma and that many of the available treatments are being used off-label. Any new effective treatment option would be welcomed by patients and their families and provide an additional tool for physicians to use.

As this cancer affects so many children and individuals in the prime of their lives, patients expressed that even months added to life can be extremely significant. A new treatment option will provide hope for patients who often feel isolated, suffering from a cancer that has limited resources allocated to fund research globally. Furthermore, treatments that reduce suffering related to symptoms of the disease and adverse effects of current therapies are needed.

There were no patients with direct experience with pazopanib interviewed by the advocacy group.

4.3 Additional Information

No additional comments were received.

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 (Votrient) for the treatment of advanced soft tissue sarcoma (STS). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the pazopanib (Votrient) review was obtained from seven of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, pazopanib was noted to be a new and novel therapy for the treatment of advanced soft tissue sarcoma. Although PAG estimated that there would only be small patient populations accessing pazopanib for this indication as it is a relatively uncommon cancer, they noted that there was potential for pazopanib to be used in other treatment settings where it has not specifically been studied. As pazopanib is orally administered, PAG recognized that it may be a convenient option for patients, and there may be cost avoidance as chemotherapy clinics would not have to be utilized.

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

5.1 Factors Related to Comparators

PAG recognized that there have not been any new or novel chemotherapy agents recently approved by Health Canada for the treatment of advanced soft tissue sarcoma, which would be an enabler when implementing a funding decision for pazopanib in this indication.

5.2 Factors Related to Patient Population

PAG noted that there would likely be a small patient population accessing pazopanib for this indication, as soft tissue sarcoma is a relatively uncommon cancer.

PAG recognized that there was potential for indication creep with pazopanib into other treatment settings, such as earlier stages of the disease, or in GIST and adipocytic soft tissue sarcomas, two tumour types that were excluded from the pivotal trial. However, PAG also noted that the use of pazopanib in the treatment of GIST and adipocytic soft tissue sarcomas would likely be mitigated if the Health Canada approved indication specifically states that pazopanib should not be used for these tumour types.

Furthermore, PAG noted that the manufacturers funding request is for patients who have failed previous chemotherapy, as well as, those who are unsuited for such therapy. However, PAG also noted that the majority of patients in the pivotal trial had received prior chemotherapy and therefore, they note that the evidence to support the use of pazopanib in patients unsuited for previous chemotherapy may be lacking.

5.3 Factors Related to Accessibility

PAG noted that pazopanib is an oral medication, and in some jurisdictions, oral medications are not covered in the same way as intravenous cancer medications, which may limit accessibility For these jurisdictions, patients would first require an application to their pharmacare program, and these programs can be associated with co-payments and deductibles,which may cause financial burden on patients. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of- pocket expenditure.

5.4 Factors Related to Dosing

As pazopanib is an orally administered medication, PAG identified that this would likely be a more convenient option for patients, which would be an enabler to pazopanib therapy.

However, PAG also noted that since pazopanib is only available as 200mg tablets, the recommended dosing of pazopanib at 800mg once daily would require the administration of four 200mg tablets. Patients may consider having to take four tablets a significant pill burden, and it could have an impact on patient compliance.

5.5 Factors Related to Implementation Costs

As pazopanib is an orally administered therapy, PAG identified that utilization of chemotherapy clinics would be reduced, which may result in decreased costs, and would be considered an enabler for pazopanib therapy.

PAG also noted that the addition of pazopanib after failure of previous chemotherapy may introduce an additional workload, as in the past, certain patients who failed chemotherapy would have previously only received best supportive care.

5.6 Other Factors

PAG noted that there were no Canadian trial sites in the pivotal study for pazopanib in the setting of advanced soft tissue sarcoma and as a result, there may be less familiarity with pazopanib in this treatment setting.

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 Soft Tissue Sarcoma who have received prior chemotherapy or who are unsuited for such therapy (see Table 3 in Section 6.2.1 for outcomes of interest and comparators).

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCT	Patients with advanced Soft Tissue Sarcoma (STS) who have received prior chemotherapy, or who are unsuited for such therapy. Patients with GIST and adipocytic STS are excluded.	Pazopanib (oral) as monotherapy at recommended 800 mg once daily	Chemotherapy agents for STS: -Ifosfamide -Paclitaxel -Gemcitabine -Dacarbazine -Trabectedin -Ifosfamide + Doxorubicin -Gemcitabine + Docetaxel Surgery and/or radiotherapy Placebo	• Overall survival • Progression-free survival • QoL • ORR (CR + PR) • SAE • AE • WDAE

AE=adverse events; **CR**=complete response; **GIST**=gastrointestinal stromal tumor; **ORR**=overall response rate; **PR**=partial response; **QoL**=quality of life; **RCT**=randomized controlled trial; **SAE**=serious adverse events; **STS**=soft tissue sarcoma; **WDAE**=withdrawal due to adverse events

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

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 (1974-) with daily updates via Ovid; The Cochrane Central Register of Controlled Trials (2012, Issue 9) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pazopanib and Votrient.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The search is considered up to date as of September 7, 2012.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – 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 the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for 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 protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

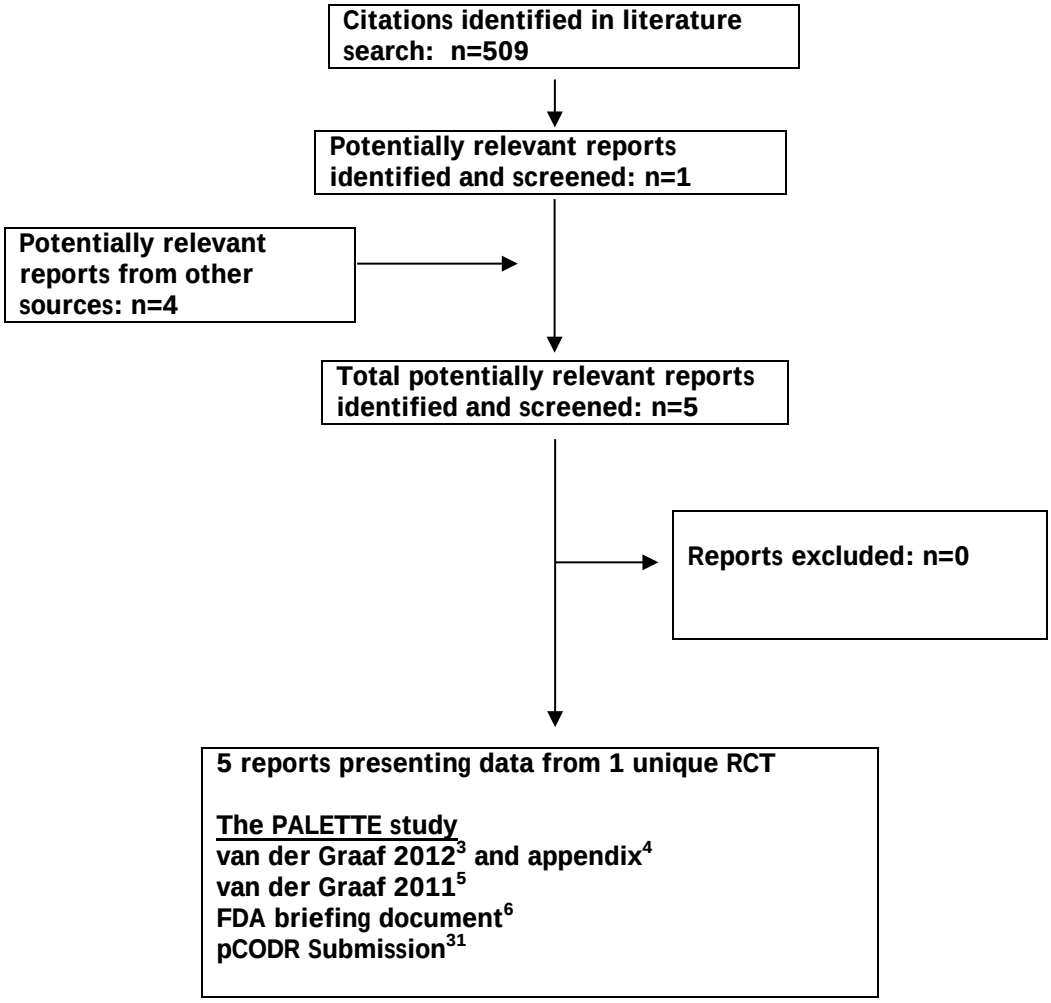
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the five potentially relevant reports identified, five reports relating to one unique study were included in the pCODR systematic review[3-6,31] and no study was excluded.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of the PALETTE Study[3-6]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes

72 centres in Europe, Asia, North America and Australia
 	
October 2008 to February 2010
 	
n= 372 enrolled;
n= 369 randomized;
n= 369 analyzed
 	
• DB, placebo-controlled, RCT
• Randomization was stratified on the basis of :
a) number of previous lines of systemic therapy for advanced disease (0 or 1 vs. ≥2)
b) WHO PS (0 vs. 1)
	Age ≥18 years;
	
	A diagnosis of metastatic STS and progressive disease, and received prior chemotherapies;
	
	WHO PS 0 or 1;
	
	Adequate bone marrow, renal, hepatic, and cardiac function;
	
	BP <150/90 mm Hg
		Pazopanib 800 mg once daily administered orally
		
		Placebo
			Primary
			• Progression-free survival
			Secondary
			• Overall survival
			• Response rate
			• QoL
			• Safety

BP=blood pressure; **DB**=double blind; **WHO PS**= World Health Organization performance status; **QoL**=quality of life; **RCT**=randomized controlled trial; **STS**=soft tissue sarcoma

a) Trials

One double-blind, placebo-controlled RCT (PAzopanib expLorEd in SofT-Tissue Sarcoma-a phase 3 study - PALETTE) was included in this review (see Table 4).[3-6] The purpose of this study was to compare the efficacy and safety of pazopanib with placebo in the treatment of advanced STS. The study was conducted at 72 centres in Europe, Asia, North America (no Canadian site) and Australia. It was sponsored by the manufacturer, and the manufacturer played a role in study design, data collection and data analysis.

The study compared pazopanib 800 mg once daily with placebo in 369 patients aged ≥18 years with advanced STS who were treated with prior chemotherapy. Additional eligibility criteria included a WHO performance status of either 0 or 1, and adequate organ function. Patients with adipocytic sarcoma and GIST were excluded from the study. Patients were randomized 2:1 to receive either pazopanib or placebo. Randomization was stratified on the basis of number of previous lines of chemotherapy (0/1 versus 2 or more), and WHO performance status (0 versus 1). The primary outcome was PFS and the key secondary outcome was OS. More description on outcomes is provided in Section 6.3.2.2.

Trial procedures for randomization and allocation concealment were adequate to maintain the internal validity of the study. During the study, patients, investigators who gave the treatment and staff who conducted data analysis were blinded to the

treatment allocation, and the methods of blinding were appropriate. Intention-to-treat (ITT) analyses were performed, according to the treatment arm to which the patients were randomized.

b) Populations

In total, 372 patients were enrolled in PALETTE. Among the 369 patients who were randomized, 246 patients were assigned to pazopanib and 123 patients were assigned to placebo. Seventy-two percent of patients were enrolled from Europe or North American, 22% were from East Asia, and 6% were from Australia. Ninety-three percent of these patients received systemic therapy for advanced disease before the study, primarily anthracyclines. Seventy-two percent of the population were Caucasians, and 23% were Asians. Patients with pazopanib tended to be older (median 56.7 [range 20-84] years versus 51.9 [range 19-79] years), and slightly more females were randomized to this group (60% versus 56%). Other baseline demographic and disease characteristics (performance status, histological grade and organ involvement) were balanced between the two treatment arms.

c) Interventions

Patients received either 800 mg pazopanib once daily or matching placebo. Patients received continuous treatment until disease progression, unacceptable toxicity, withdrawal of consent, or death. Cross-over from placebo to pazopanib was not allowed. The dose intensity was 100% for placebo and 96% for pazopanib. The median treatment duration was 8.1 (range 1-52) weeks for placebo and 16.4 weeks (range 0-79) for pazopanib. Concomitant medications and other supportive care were not reported in the PALETTE study. Subsequent anticancer therapy for patients with progressive disease was at the discretion of the patient and treating physician. More patients in the placebo group received post progression therapy than the pazopanib group: chemotherapy, 62% versus 45%; targeted therapy, 14% versus 10%; radiotherapy, 23% versus 16%).[4]

d) Patient Disposition

Three hundred and seventy-two patients were enrolled in the study. Among them, three were not assigned to any treatment group; therefore 369 patients were randomized and comprised the ITT population. The safety population consisted of 362 patients when seven patients were excluded from safety analyses due to not receiving the assigned treatment or no treatment information was available. As of the data cut-off date for the primary analysis (November 22, 2010), 19 patients were still on treatment, with 18 (7.3%) in the pazopanib group and one (0.8%) in the placebo group. As shown in Table 5, the majority of patients had discontinued the study treatment (89.8% in pazopanib versus 99.2% in placebo) at the cut-off date. The main reason for discontinuation of treatment was disease progression (67.9% in pazopanib versus 95.9% in placebo). Compared to placebo, a higher proportion of patients in the pazopanib arm discontinued treatment due to adverse events that may or may not be treatment-related: 15.0% versus 2.4%, respectively. The percentage of deaths was lower in patients with pazopanib than with placebo (pazopanib: 137, 55.7%; placebo: 78, 63.4%). As of the cut-off date for final analysis (October 24, 2011), six patients still received treatment drugs; the number of patients in each group was not reported. The death rates were similar between the pazopanib group and the placebo group (pazopanib: 185, 77.4%; placebo: 95, 77.2%).

Table 5: Patient Disposition in the PALETTE Study (as of November 22, 2010)

	Pazopanib	Placebo
Randomized	246	123
Received assigned treatment	239	123
Still on treatment, n (%)	18 (7.3)	1 (0.8)
Discontinued treatment, n (%)	221 (89.8)	122 (99.2)
Disease progression, n (%)	167 (67.9)	118 (95.9)
Adverse event, n (%)	37 (15.0)	3 (2.4)
Refused treatment for reasons unrelated to adverse events, n (%)	12 (4.9)	0
Intercurrent death, n (%)	3 (1.2)	0
Protocol violation, n (%)	1 (0.4)	0
Discontinued for other reasons, n (%)	0	1 (0.8)

Source: Figure 1 in van der Graaf 2012[3]

e) Limitations/Sources of Bias

PALETTE was a randomized double-blind trial in which patients and investigators who gave the treatment, assessed outcomes and conducted analyses were blinded to eliminate performance and assessor biases. Central randomization was carried out to ensure allocation concealment and balanced patient characteristics at baseline. Data were evaluated independently by an external review committee, as well as by the study investigators. Results of PFS from both parties were similar. Cross-over from the placebo to pazopanib at disease progression was not allowed to avoid data contamination. Other strengths of the study included an appropriate sample size and power calculation, ITT analysis, and subgroup and sensitivity analyses to adjust for various patient/trial characteristics.

Potential limitations in the PALETTE study include:

- PFS was the primary endpoint in the study. However, OS was deemed an reliable and preferred health outcome in cancer research.[32] Guidance from the FDA[32] indicates that for a given sample size, the magnitude of effect on PFS can be larger than the effect on OS. Based on an EORTC analysis of a large database of STS clinical trials, a 3-month progression-free survival of more than 40% for second line chemotherapy indicates clinical activity of a particular agent.[14] Whether significant improvement in PFS can be translated into a benefit in OS is unclear.
- Various post-protocol/post-progression treatment modalities may bias OS. Higher percentage of patients in the placebo group received chemotherapy, other targeted therapy and radiotherapy, compared to those in the pazopanib group.[4]
- Patients were included if they had performance status of 0 or 1 with about half having a performance status of 0 (fully active, no restriction in activities). It may be unusual to see so many patients with good performance status in this study population. The effect of high

performance status scores have on the assessment of the impact of pazopanib on quality of life and symptoms remains uncertain. On the other hand, patients with performance status 2 or greater were excluded when they may benefit from the study drug. There is a lack of evidence to assess the effectiveness and safety in such patients.

- Handling of some safety data may not be appropriate: 3 intercurrent deaths (defined as death not attributed to study treatment or toxicity) were reported. Causes of these cases were pneumonia related to pneumothorax for one patient, and deep venous thromboembolism for another. These may be related to the pazopanib therapy and, hence, may have been misclassified as intercurrent deaths.
- The QoL data should be interpreted with caution, due to the high drop-out rates in the two groups, especially the placebo group at week 12; in addition, QoL data were only available for the first 12 weeks of the study.
- Generalizability is restricted by the rigorous selection criteria (for example effect of excluding adipocytic disease)
- The study did not include any sites in Canada. However, it may be appropriate to extrapolate the study results to the Canadian population according to the subgroup analyses where geographical region and race were taken into account; in addition, sites in Europe and the US were likely approximated the Canadian population.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The efficacy analyses were conducted in the ITT population, comprised of all randomized patients. The safety population comprised all patients who received at least one dose of study drug. The assessments of efficacy and safety were performed at baseline, and week 4, 8, 12 and at 8-week intervals thereafter. The cut-off date for the primary analysis (PFS) was November 22, 2010, and the cut-off date for analysis on OS was October 24, 2011. Tables 6 and 7 present the key outcomes from the PALETTE study.

Table 6: Summary of Key Trial Outcomes (Efficacy) from the PALETTE Study (Pazopanib n = 246, Placebo n = 123)[3,4,6]

OS *	**Median (months)** Pazopanib 12.5 (95% CI: 10.6-14.8) Placebo 10.7 (95% CI: 8.7-12.8)	**HR (95% CI)** 0.86 (0.67, 1.11)	**P-value** 0.25
PFS **	**Median (months)** Pazopanib 4.6 (95% CI: 3.7-4.8) Placebo 1.6 (95% CI: 0.9-1.8)	**HR (95% CI)** 0.31 (0.24, 0.40)	**P-value** < 0.0001
QoL			
Global Health Status/quality-of-life †	Baseline: 1.4 Week 12: -1.6	P = 0.29	
QLQ-C30 †	Diarrhea Baseline: 1.9 Week 12: 20.9 Loss of appetite	P < 0.001 P < 0.001	

	Baseline: 0.1 Week 12: 13.2 Nausea/vomiting Baseline: -0.2 Week 12: 12.3 Fatigue Baseline: -1.0 Week 12: 4.5	 P < 0.001 P = 0.012
RR		
By external review group	Pazopanib - n (%) PR: 11 (4) SD: 134 (54) DP: 66 (27) Placebo - n (%) PR: 0 SD: 33 (27) DP: 76 (62)	P for difference in RR = 0.019
By investigators	Pazopanib - n (%) PR: 23 (9) Placebo - n (%) PR: 0	P for difference in RR < 0.001
CI=confidence interval; **DP**=disease progression; **HR**=hazard ratio; **OS**=overall survival; **PFS**=progression-free survival; **PR**=partial response; **QLQ-C30**=Quality of Life Questionnaire Core 30; **QoL**=quality of life; **RR**=response rate; **SD**=stable disease		

*As of October 24, 2011
** As of November 22, 2010
† Values are between-group differences

Table 7: Summary of Key Trial Outcomes (Safety) from the PALETTE Study[3,6]

	Pazopanib (N = 239)	Placebo (N = 123)
Deaths, n (%)	185 (77.4)	95 (77.2)
Patients with ≥ 1 AE, n (%)	237 (99)	110 (89)
SAEs	99 (41)	29 (24)
AE leading to discontinuation of treatment, n (%) **	37 (15.5)	3 (2.4)
AE=adverse event; **SAE**=serious adverse event		

** As of November 22, 2010

Efficacy Outcomes

a) Overall Survival

Overall survival (OS) was the secondary endpoint in the PALETTE study.[3] It was defined as the time interval from randomization to death from any cause. Kaplan-Meier methods were used by the submitter to plot the OS. A stratified log-rank test was performed to compare differences in OS between the treatment arms. The study was designed to provide 90% power at the 5% significance level to detect a

33% decrease in the death HR, which translated to an increase of median OS from eight months to 12 months. An interim analysis of OS was performed on November 22, 2010 - the time of the analysis of the primary endpoint (PFS), when 274 PFS events was needed to detect a 15% difference between pazopanib and placebo at six months. A final analysis of OS was conducted on October 24, 2011, when 279 deaths were required to detect the targeted 33% decrease in the death HR.

Interim analysis results for OS showed a statistically nonsignificant difference between pazopanib and placebo: median 11.9 months (95% CI: 10.4 – 14.7) versus 10.4 months (95% CI: 8.1 - 12.7), HR = 0.83 (95% CI: 0.62 - 1.09, p = 0.18). In the final analysis of OS as of October 24, 2011, the difference between treatment arms remained statistically nonsignificant: median 12.5 months (95% CI: 10.6 – 14.8) versus 10.7 months (95% CI: 8.7 - 12.8), HR = 0.86 (95% CI: 0.67 - 1.11, p = 0.25).

The interim analysis was based on 215 death events (137 in the pazopanib arm and 78 in the placebo arm), representing 77% of the required 279 death events for the final OS analysis.

Subgroup analyses were performed to assess the impact of age (< 65 years versus ≥ 65 years), race (white versus Asian/other), prior lines of treatment (0/1 versus ≥ 2), WHO performance status (0 versus 1), geographical region (Europe/Australia versus Japan/South Korea versus the United States), histology type (leimoyosarcoma versus synovial sarcoma versus other STS histology) and tumour grade (high versus low/intermediate) on OS. The results of OS in each subgroup were consistent with that in the whole population, indicating nonsignificant difference in OS between the two treatment arms.[6]

b) Progression-free Survival

The primary endpoint in PALETTE was progression-free survival (PFS), defined as the time interval between randomization and either the first disease progression as evaluated by an independent radiology review of image or death due to any cause.[3] Kaplan-Meier methods were used by the submitter to plot PFS. A stratified log-rank test was performed to assess differences in PFS between the treatment arms. The study was designed to provide 95% power at a 5% significance level to detect a 15% increase in PFS at 6 months in the pazopanib group from 15% in the placebo group, which translated to an HR of 0.63. A multivariable Cox regression model was developed to identify the prognostic factors for PFS, where variables with significance value of $p < 0.05$ in a univariate Cox model were taken into account.

As of October 24, 2011, the cut-off date for primary analysis of PFS, 274 events had occurred (disease progression or death from any cause): 168 in the pazopanib group compared with 106 in the control group. Median PFS was significantly longer in the pazopanib group than in the placebo group: 4.6 months (95% CI: 3.7 – 4.8) versus 1.6 months (95% CI: 0.9 – 1.8), HR = 0.31 (95% CI: 0.24 – 0.40, p < 0.0001).

Results from the multivariable Cox model indicated that prognostic factors for favourable PFS outcome were good performance status (0 versus 1) and low to intermediate tumour grade (I to II versus III), where histology subtype of STS was not a significant factor for disease prognosis, in patients treated with pazopanib.

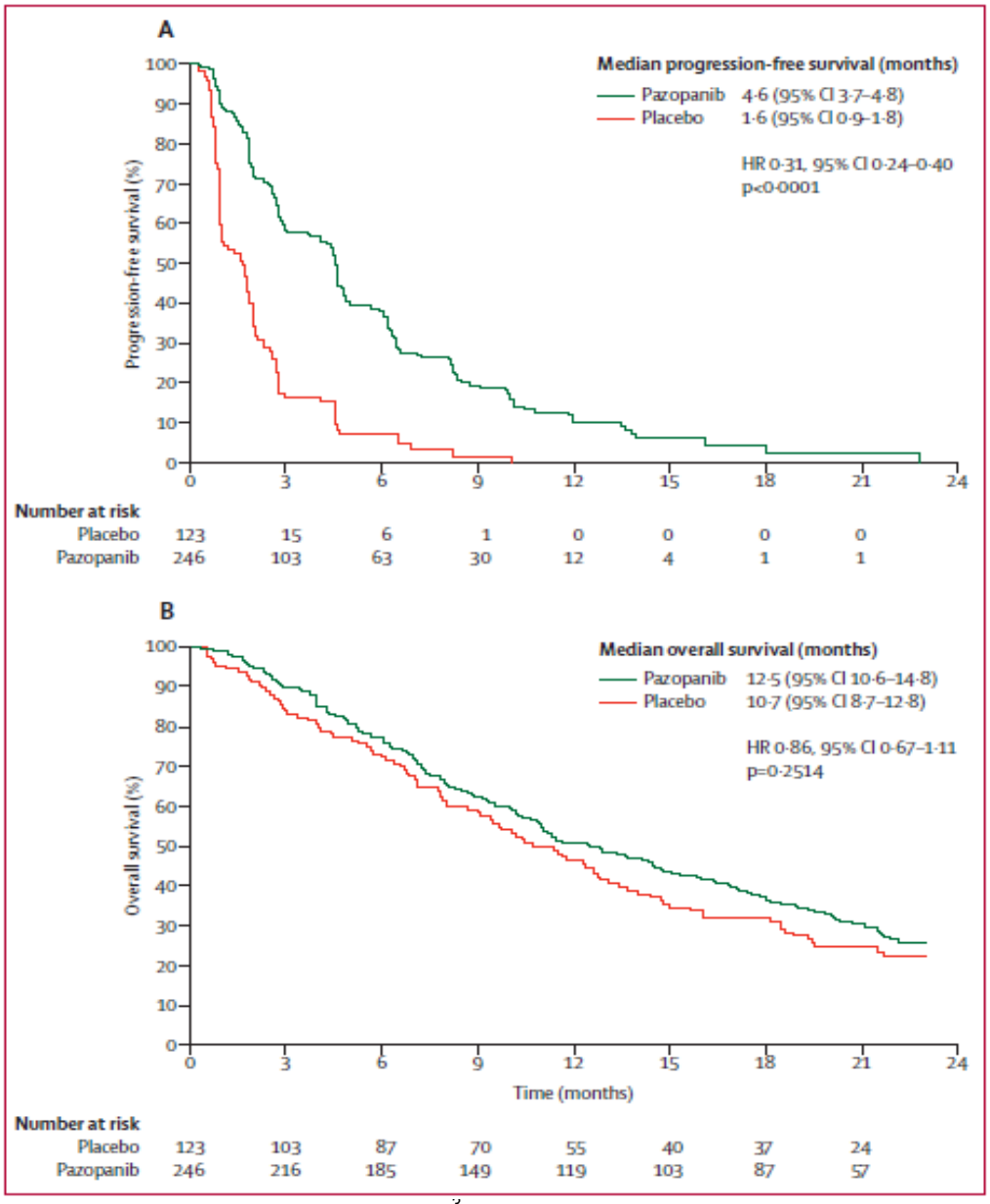


Figure 1 (copied from the PALETTE study[3])
Kaplan-Meier curves for progression-free (A) and overall (B) survival. 168 patients in the pazopanib group died or had disease progression, 106 in the placebo group (cutoff Nov 22, 2010). 185 patients died in the pazopanib group, 95 in the placebo group (cutoff Oct 24, 2011).

Subgroup analyses were performed to assess the impact of age, race, prior lines of treatment, WHO performance status, geographical region, histology type and tumour grade on PFS. The results of PFS in each subgroup were consistent with that in the overall population, indicating significantly longer PFS in the pazopanib arm compared with the placebo arm.[6]

c) Quality of Life

Health-related quality of life (QoL) in the study population was assessed with the global health status/quality-of-life score, EORTC QLQ-C30 (version 3) questionnaire, and EQ-5D, at baseline, week 4, 8, and 12. QoL data were not collected after week 12. Data were analysed by fitting a linear mixed model with treatment and time effect being taken into account. The minimum clinically meaningful difference in QLQ-C30 was pre-determined as at least 10 points in a QoL parameter on a 0-100 scale (the raw scores have been transformed to standardized scores from 0 to 100). Sensitivity analyses were performed to examine the potential impacts of missing data.

At week 12, more patients in the placebo group dropped out of the study compared with the pazopanib group (91, 74% versus 118, 48%); therefore QoL data were unavailable from these patients.[6] The baseline QoL scores were balanced between the two groups. The global health and quality-of-life scores were the primary QoL scale in the PALETTE study. The scores were not significantly different between groups at any time points. Results of QLQ-C30 found statistically significant differences in the domains of diarrhea, loss of appetite, nausea or vomiting, and fatigue, where patients with pazopanib experienced more worse symptoms than those in the placebo group, at almost all follow-up timepoints. The differences in diarrhea and loss of appetite were clinically meaningful according to the predetermined criteria.[4] The authors indicated that a full assessment on QoL will be provided in a separate report.

d) Response rates

Responses were assessed by masked independent radiology review or investigators at the primary data cut-off date on November 22, 2010. Based on the external review group assessment, higher response rates were observed in the pazopanib group (only partial responses in 11 patients, 4%) compared with the control group (0); 95%CI for difference in response rates: 1.9-7.1, p = 0.019. More patients treated with pazopanib had stable disease: 134 patients (54%) versus 33 patients (27%). Disease progression was reported in fewer patients with pazopanib when compared with placebo: 66 (27%) versus 76 (62%). The investigator-assessed response rate was consistent with those assessed by the independent review group: partial response occurred in 23 patients (9%) in the pazopanib group, while no response to placebo was observed; 95%CI for difference in response rates: 5.7-13.0, $p < 0.001$.[6]

Harms Outcomes

The safety population consisted of 362 patients, 239 in the pazopanib group and 123 in the placebo group. Six patients from the ITT population never started the assigned treatment, and information for one other patient was not available; therefore seven patients were excluded from safety analysis. Toxicities were evaluated using National Cancer Institute Common Toxicity Criteria (version 3.0). Clinical assessments for safety, including physical examinations and clinical laboratory evaluations were conducted at baseline, week 4, 8, 12 and at 8-week intervals thereafter.

a) Deaths

One hundred and eighty-five patients (77.4%) died in the pazopanib group compared to 95 (77.2%) in the placebo group as of October 24, 2011 (see Table 7). There was no statistically significant difference between the two groups for death from any cause. No data were reported with regard to the reasons of death.

b) Serious Adverse Events

More patients in the pazopanib arm (99, 41%) experienced serious adverse events (SAEs) than those in the placebo arm (29, 24%). The most common SAEs in patients treated with pazopanib were dyspnea, increasing alanine aminotransferase and aspartate aminotransferase, decreasing hemoglobin, pheumothorax and venous thromboembolism.[6]

Eight (3%) fatal SAEs occurred in the pazopanib group versus six (5%) in the placebo group. The primary causes of death for these patients in the pazopanib group were multi-organ failure, pulmonary embolism, disease progression, cardio-respiratory arrest, malignant pericardial effusion with cardiac tamponade, and inhalation pneumonitis.[6]

c) Any Adverse Event

The median duration of exposure to pazopanib was 16.4 weeks (range 0 to 79) compared with 8.1 weeks (range 1 to 52) in the placebo arm. More patients in the pazopanib group experienced at least one adverse event than the placebo group (237, 99% versus 110, 89%; Table 8).[6] The most common reported adverse events in the study were fatigue, diarrhoea, nausea, weight loss, and hypertension. Most of these were mild, while Grade 3 adverse events were reported for fatigue, diarrhoea, hypertension and anorexia. Grade 4 adverse events were rare, with one case of fatigue being reported in each group.

Table 8: Common Adverse Events Reported for Patients in the PALETTE Study - Safety Population[3,6]

	Pazopanib (N=239)			Placebo (N=123)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any event	237 (99)			110 (89)		
Fatigue	155 (65)	30 (13)	1 (<1)	60 (49)	6 (5)	1 (1)
Diarrhea	138 (58)	11 (5)	0	20 (16)	1 (1)	0
Nausea	129 (54)	8 (3)	0	34 (28)	2 (2)	0
Weight loss	115 (48)	0	0	25 (20)	0	0
Hypertension	99 (41)	16 (7)	0	8 (7)	4 (3)	0

d) Dose Reduction/Interruption

Overall, the dose intensity was 100% for placebo, while dose reduction was required for patients treated with pazopanib so that the relative dose intensity was 96%. Ninety-two patients (39%) who received pazopanib required a dose reduction compared to five patients (4%) who received placebo.

e) Withdrawals due to Adverse Events

Treatment discontinuation was common in both treatment groups (Table 5). The main reasons for early discontinuation were disease progression (67.9% versus 95.9%) and adverse events (15.0% versus 2.4%) (Tables 5 and 7). In the pazopanib group, more patients stopped treatment due to adverse events when compared to the placebo group. Conversely, more patients in the placebo group stopped treatment because of lack of efficacy.

6.4 Ongoing Trials

At present, a randomized, double blind, crossover, phase II study that compares gemcitabine + pazopanib with gemcitabine + placebo is ongoing in patients with refractory STS. It planned to enroll 80 patients (NCT01532687).[7]

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Sarcoma 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 (Votrient) for STS. 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 revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Embase 1974 to 2012 September 06 (oemezd), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present (pmez)

#	Searches	Results
1	(Votrient* or pazopanib* or patorma* or armala* or GW78603 or GW-78603 or GW786034 or (GW7 adj '86034*') or GW-786034 or GW786034B* or GW-786034B* or GW780604* or GW-780604*).ti,ab,ot,sh,hw,rn,nm.	2010
2	(444731-52-6 or 790713-33-6 or 635702-64-6).rn.	1484
3	1 or 2	2010
4	3 use pmez	319
5	*pazopanib/	264
6	(Votrient* or pazopanib* or patorma* or armala* or GW78603 or GW-78603 or GW786034 or (GW7 adj '86034*') or GW-786034 or GW786034B* or GW-786034B* or GW780604* or GW-780604*).ti,ab.	767
7	5 or 6	789
8	7 use oemezd	500
9	or/4,8	819
10	remove duplicates from 9	543
11	limit 10 to english language	499

2. Literature search via PubMed

Search	Query	Items found
#3	Search (#2) AND #1	17
#2	Search publisher [sb]	415420
#1	Search Votrient* OR pazopanib* or patorma* or Armala* OR GW78603 OR GW-78603 OR GW786034 OR "GW7 86034" OR GW-786034 OR GW786034B* OR GW-786034B* OR GW780604* OR GW-780604* OR 444731-52-6[rn] OR 790713-33-6[rn] OR 635702-64-6[rn]	314

3. Cochrane Central Register of Controlled Trials(Central)

Search for trials. Issue 8, Sept 2012

Current Search History

ID	Search	Hits
#1	(Votrient* OR pazopanib* OR patorma OR Armala OR GW78603 OR GW-78603 OR GW786034* OR GW-786034* OR GW780604* OR GW-780604* OR GW786034):ti,ab,kw in Trials	15

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) AND (sarcoma OR soft tissue)

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) AND (sarcoma OR soft tissue)

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) AND (sarcoma OR soft tissue) / last 5 years

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