



pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Sunitinib malate (Sutent) for pancreatic neuroendocrine tumours

May 3, 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, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

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

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

FUNDING

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

INQUIRIES

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

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

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

TABLE OF CONTENTS

DISCLAIMER & FUNDING.....	ii
INQUIRIES.....	iii
TABLE OF CONTENTS.....	iv
1. GUIDANCE IN BRIEF.....	1
1.1. Background.....	1
1.2. Key Results and Interpretation.....	1
1.3. Conclusions.....	3
2. CLINICAL GUIDANCE.....	4
2.1. Context for the Clinical Guidance.....	4
2.2. Interpretation and Guidance.....	7
2.3. Conclusions.....	8
3. BACKGROUND CLINICAL INFORMATION.....	10
4. SUMMARY OF PATIENT ADVOCACY GROUP INPUT.....	14
5. SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT.....	17
6. SYSTEMATIC REVIEW.....	20
6.1. Objectives.....	20
6.2. Methods.....	20
6.3. Results.....	23
6.4. Ongoing Trials.....	36
7. SUPPLEMENTAL QUESTIONS.....	37
8. ABOUT THIS DOCUMENT.....	38
APPENDIX A: LITERATURE SEARCH STRATEGY.....	39
REFERENCES.....	44

1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of sunitinib malate on patient outcomes including progression free survival (PFS), overall survival, and harms compared to standard treatment or placebo in patients with unresectable locally advanced or metastatic well differentiated pancreatic neuroendocrine tumours and progressive disease.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One double-blind, placebo-controlled, randomized controlled trial, Study A6181111, met the inclusion criteria for the pCODR systematic review.¹⁻³ Study A6181111 compared sunitinib 37.5mg (n=86) orally once daily with matching placebo (n=85) in 171 patients with pathologically confirmed, well-differentiated, advanced or metastatic pancreatic neuroendocrine tumours (NETs) not eligible for surgery. Study A6181111 originally intended to have an enrolment of approximately 340 patients, but an assessment by the Data and Safety Monitoring Committee (DSMC) recommended early discontinuation of the trial due to a greater number of deaths and serious adverse events reported in the placebo group as well as a difference in progression-free survival (PFS) in favour of the treatment group. Trial discontinuation occurred prior to the planned interim analysis; the objective of this interim analysis was to provide recommendations on whether to continue the trial as planned, to adjust the sample size, or to discontinue the trial.³

Efficacy

- The primary endpoint of Study A6181111 was PFS, defined as the time from randomization to the first evidence of objective tumour progression or death from any cause. At the time of trial termination, investigators reported that patients treated with sunitinib had an improvement in median PFS compared with placebo (11.4 months for sunitinib versus 5.5 months for placebo; HR=0.42; 95% CI: 0.26 to 0.66; p<0.001). However, due to the early termination of the trial, a post-hoc analysis of the data indicated that the test statistic did not cross the efficacy boundary. Therefore, the efficacy of sunitinib in improving PFS should be assessed and interpreted with caution.
- Overall survival was a secondary endpoint of the study, defined as the time interval from randomization until death due to any cause. In the absence of death, the data was censored at the last date the patient was known to be alive. At the time of the trial termination, the median overall survival could not be estimated due to data censoring.
- Quality of life data was captured using the self-administered European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) version 3.0. Data was available for 85% (n=73) of patients in the sunitinib group and 84% (n=71) of patients in the placebo arm. Compared to placebo, patients in the sunitinib group had statistically significant (based on a difference of 10 points or more) worsening diarrhea, worsening insomnia and reduction in constipation. For other outcomes, there were no statistically significant differences between treatment arms in global health related quality of life, functional scales (cognitive, emotional, physical,

role and social functioning) or in other symptoms (appetite loss, dyspnea, fatigue, nausea, vomiting, and pain).

Harms

- A total of 27% (n=22) of patients in the sunitinib group experienced a severe adverse event compared to 42% (n=34) in the placebo arm. The most frequently reported serious adverse events with sunitinib were disease progression, cardiac failure, abdominal pain, nausea, vomiting, and renal failure.
- The majority of patients in the trial experienced at least one adverse event, with 99% (n=82) of patients in the sunitinib group experiencing an adverse event compared with 95% (n=78) in the placebo arm. Patients in the sunitinib group experienced a greater incidence of diarrhea (59% for sunitinib versus 39% for placebo) and nausea (45% for sunitinib versus 29% for placebo).
- Grade 3 / 4 adverse events occurred more frequently in the sunitinib group (49%) compared with placebo (44%) and included a greater incidence of neutropenia, hypertension, leukopenia and hand-foot syndrome.
- Adverse events leading to withdrawal or discontinuation were reported for 22% (n=18) of sunitinib patients compared with 17% (n=14) of patients in the placebo group. The most common adverse events leading to treatment discontinuation were fatigue, diarrhea and cardiac failure.

1.2.2 Additional Evidence

pCODR received input on sunitinib from one patient advocacy group, Carcinoid-NeuroEndocrine Tumour Society Canada (CNETS Canada). Provincial Advisory Group input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

1.2.3 Interpretation and Guidance

- Pancreatic NETs are a subset of NETs arising from the neuroendocrine cells of the pancreas. Most patients diagnosed with pancreatic NETs are not candidates for curative intent treatment.
- The management of advanced pancreatic NETs is challenging. Presently available therapies for patients with pancreatic NETs can help to manage symptoms and maintain quality of life. These treatment options may have an impact on survival, although controlled trials evaluating impact on survival have not been conducted.
- Systemic chemotherapy with approved agents including streptozocin, adriamycin, and 5-fluorouracil in patients with pancreatic NETs has produced disappointing results in clinical trials, with responses in a small minority of patients.
- The burden of illness associated with these cancers is significant as patients with advanced NETs have a median survival of 28 months and many patients may live for years with symptoms associated with a progressive terminal illness and the associated impacts on physical health, functional, emotional and social well being.⁴⁻⁶
- The interpretation of results from Study A6181111 is challenging. The trial was appropriately discontinued early on the advice of the DSMC due to a greater number of adverse events and deaths in the placebo arm of the study. However, this occurred prior to the pre-specified interim analysis for stopping and may result in an over

estimation of the benefit of sunitinib in this setting. Indeed, it was observed that the PFS findings were not statistically significant at all data looks for PFS, which occurred prior to the pre-specified interim analysis, although there was a trend towards statistical significance. Despite the uncertainty in the statistical significance of the results, a clinically meaningful doubling of median PFS was observed.

- Patients randomized to placebo were, appropriately, offered the opportunity to cross over to sunitinib upon progression with the majority in the placebo arm subsequently receiving sunitinib. As a majority of patients in the placebo arm did crossover and subsequently received sunitinib, the ability of this study to demonstrate an overall survival benefit is limited.
- Importantly there were also no differences in health related quality of life, cognitive, emotional, physical and social functioning in patients treated with sunitinib compared to placebo.
- The side effects and toxicities observed in Study A6181111 were consistent with those seen in other treatment indications for sunitinib, are manageable, and acceptable to physicians. Data collected from two extension studies with sunitinib in this patient population has not demonstrated any additional toxicities or concerns.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to sunitinib in the treatment of pancreatic NETs. This conclusion was based on one, randomized controlled trial comparing sunitinib with placebo. The Clinical Guidance Panel was limited in their ability to interpret progression-free survival and overall survival results because the trial was discontinued early before the planned interim analysis designed to evaluate stopping. However, the Panel considered that the magnitude of difference in PFS between the two treatment groups was clinically significant, suggesting that there is very likely a benefit associated with sunitinib.

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

- Sunitinib is administered orally and does not require hospitalization or administration in a tertiary care setting, resulting in significant advantages for patients.
- Systemic chemotherapy with existing approved agents provides minimal benefit to patients with advanced pancreatic NETs and is associated with significant toxicities and inconvenience to patients and their families. There is a need for more effective, easily administered systemic treatments for patients with pancreatic NETs. The side effects and toxicities observed with sunitinib were consistent with those seen in other treatment indications for sunitinib, are manageable, and acceptable to physicians and patients.
- Pancreatic NETs are uncommon neoplasms that often present when disease is locally advanced or metastatic and are not amenable to curative intent treatment. Although uncommon, the incidence of this disease is increasing and effective treatment options are needed.

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 sunitinib malate (Sutent) for pancreatic NETs. 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 sunitinib malate (Sutent) for pancreatic neuroendocrine tumours conducted by the pCODR Gastrointestinal Clinical Guidance Panel 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 Clinical Guidance Panel, a summary of submitted Patient Advocacy Group Input on sunitinib for pancreatic NETs and a summary of submitted Provincial Advisory Group Input on sunitinib for pancreatic NETs are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Sunitinib malate has a Health Canada approved indication for use in patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours whose disease is progressive. The Product Monograph notes that regulatory approval was based on progression free survival in patients with good performance status, i.e., Eastern Cooperative Oncology Group score ≤ 1 . The recommended dose is 37.5 mg administered orally once daily.

Sunitinib is a multi-targeted tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptors, platelet derived growth factor receptors, stem cell factor receptors, colony stimulating factor receptors and others. It has direct anti-tumour and anti-angiogenic effects.

It also has a Health Canada approved indication for the treatments of gastrointestinal stromal tumour and metastatic renal cell carcinoma. For both of these indications, sunitinib is administered in repeated 6-week cycles at doses of 50 mg daily for 4 weeks followed by 2 weeks off treatment.

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect of sunitinib on patient outcomes including progression free survival, overall survival, and harms compared to standard treatment or placebo in patients with unresectable locally advanced or metastatic well-differentiated pancreatic neuroendocrine tumours and progressive disease.

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 sunitinib 37.5 mg administered daily (n=86) were compared to placebo (n=85) in an international multicentre double-blind randomized controlled trial (Study A6181111).^{1,2}

The study recruited patients with pathologically confirmed, well differentiated advanced or metastatic pancreatic endocrine tumours not eligible for surgery, who had documented disease progression within the last 12 months, who had one or more measurable target lesions, and who had an Eastern Cooperative Oncology Group performance status of 0 or 1. The median age of the patients was 56.5 years (range 25 years to 84 years). The groups were equally distributed between males and females. The majority of patients had hepatic metastases (>95%) and >89% had received prior surgery. All received best supportive care (analgesics, anti-diarrheal agents, beta blockers, emollients or protective).⁷ Before enrolling in the trial¹ under review, more than 65% of trial patients had received prior systemic chemotherapy, therefore, the findings of the trial may not be generalizable to chemotherapy-naive patients.

It was pre-determined that an interim analysis would be conducted after 130 PFS events and the trial would end when 260 PFS events had occurred. The objective of the interim analysis was to provide recommendations on whether to continue the trial as planned, to adjust the sample size, or to discontinue the trial.³ The Data and Safety Monitoring Committee conducted three data looks before the scheduled interim analysis. The Committee recommended that the trial be terminated after the third data check. At trial termination, 81 PFS events (31% of the planned events) had been reported. There was no pre-specified statistical plan for the pre-interim analyses.

Based on the analysis conducted after the third data check and prior to the planned interim analysis, patients treated with sunitinib had an improvement in PFS compared to placebo (HR=0.42; 95% CI: 0.26 to 0.66, p=0.000118). The median PFS time was greater in the sunitinib group compared to placebo (11.4 months vs. 5.5 months). Despite having no pre-specified statistical plan, the statistical significance of the data obtained was measured to account for multiple data looks. The final PFS analysis had an observed test statistic (Z value) of 3.8506. This value did not exceed the adjusted Z value of 3.8809. Hence, the test statistic was close but did not cross the efficacy boundary. Therefore, the efficacy of sunitinib in improving PFS should be assessed and interpreted with caution.

The observed hazard ratio for death was in favour of sunitinib but the statistical significance is uncertain as the expected threshold for significance is unknown. The median overall survival time could not be determined because of the number of patients with data censoring. At trial termination, nine patients on sunitinib and 21 placebo patients had died. This meant that for the analysis of overall survival, data for 77/86 (90%) sunitinib and 64/85 (75%) placebo patients were censored. The low event rate and the high number of censored events make challenging the interpretation of overall survival.

Patient reported outcomes were measured using the self-administered European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) version 3.0. There were no statistically significant differences between the treatment arms in global health related quality of life, cognitive, emotional, physical, role and social functioning, or in other symptoms and scales at baseline or at other times.

Compared to placebo, the sunitinib group had statistically significantly worsening diarrhea ($p < 0.001$) at all assessment points, statistically significantly worsening insomnia ($p = 0.04$) in cycles 2 to 7, and a statistically significant reduction in constipation at cycles 2, 3 and 4 (p value not reported).

Adverse events commonly seen in this trial (occurring $>15\%$ in either group) included hair colour changes, neutropenia, hypertension, hand-foot syndrome, stomatitis, dysgeusia, epistaxis, rash, and thrombocytopenia, with greater incidence in the sunitinib group than the placebo group. Patients in the sunitinib group also experienced a greater incidence of diarrhea and nausea. Grades 3/4 neutropenia, hypertension, leukopenia, diarrhea, and hand-foot syndrome occurred more frequently in sunitinib patients. Adverse events leading to treatment discontinuation included fatigue, diarrhea, and cardiac failure.

A dose reduction to 25 mg occurred in 31% sunitinib patients and in 11% of placebo patients whereas a dose increase to 50 mg occurred in 10% sunitinib patients and in 24% of placebo patients.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in 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

pCODR received input on sunitinib from one patient advocacy group, Carcinoid-NeuroEndocrine Tumour Society Canada (CNETS Canada). From a patient perspective, stabilization of the pancreatic NETs, as well as preventing the further spread of the cancer to other areas of the body, is an important aspect when consideration is given to treatment. Patients are looking for a therapy that will help to improve their quality of life but are also willing to tolerate certain side effects if this means stabilization or regression of the tumour.

Provincial Advisory Group (PAG) Input

Input was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that everolimus is also expected to receive Health Canada approval for the treatment of locally advanced/metastatic pancreatic NETs in the near future and as such, PAG felt it would be important to be aware of any differences between sunitinib and everolimus with respect to treatment outcomes, side effect profile and overall costs. In addition, PAG identified that information on the sequential use of sunitinib and everolimus would be helpful.

Other

There are no randomized clinical trials directly comparing sunitinib and everolimus or evaluating combination or sequential therapy with these two drugs. However, one randomized controlled trial has been published, evaluating everolimus compared with placebo in patients with low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumour, whose disease is progressive.⁶ Everolimus does not yet have a Health Canada indication for treatment of patients with pancreatic NETs.

Two ongoing uncontrolled open-label extension studies (Study A6181078 and Study A6181114) enrolled 103 patients who had previously participated in the one randomized controlled trial included in this review. Placebo patients were considered for inclusion if they had documented evidence of disease progression. Patients from the sunitinib or the placebo group were also considered for inclusion upon termination of the phase 3 trial. As of 01 June 2010, no new safety concerns were reported based on these data.

2.2 Interpretation and Guidance

Burden of Illness and Therapeutic Options for Pancreatic NETs

Pancreatic neuroendocrine tumours are uncommon neoplasms that most often present when disease is locally advanced or metastatic. Most patients diagnosed with pancreatic NETs are not candidates for curative intent treatment. The management of advanced pancreatic NETs is challenging, in part because of the limited number of systemic treatment options available for the treatment of these tumours. Patients live with the symptoms associated with local growth of tumour and invasion into surrounding structures as well as symptoms secondary to hormone production by these tumours. The impact of the diagnosis of pancreatic NETs and the symptoms associated with these malignancies on patients and their families is significant. A diagnosis of pancreatic NETs impacts physical well being, functional status, and ability for gainful employment and social interactions for patients and their families.

Registry data suggest that patients diagnosed since the mid 1980's may be surviving longer due to advances in medical imaging, aggressive surgical management and the availability of other local ablative and non chemotherapy based systemic treatments.⁴ Patients with advanced NETs have a median survival of 28 months with many patients living for years with symptoms associated with a progressive terminal illness and the associated impacts on physical health, functional, emotional and social well being.⁴⁻⁶ The burden of illness associated with these cancers is significant.

Presently available therapies for patients with pancreatic NETs can help to manage symptoms and maintain quality of life. These treatment options may have an impact on survival, although controlled trials evaluating impact on survival have not been conducted. Treatments require hospitalization, often repeatedly, for invasive procedures in highly specialized treatment facilities in tertiary referral centers. This requires a patient to travel to the treating facility, necessitating time away from family (and the patient's support system) and work, which may result in loss of income and increased isolation and distress.

Systemic chemotherapy with approved agents including streptozocin, adriamycin, and 5-fluoruracil (FU) in patients with pancreatic NETs has produced disappointing results in clinical trials, with responses in a small minority of patients. Such treatment requires repeated IV

administration in centers experienced with the use and administration of these agents and is associated with significant side effects and potential toxicity.

Study A6181111 and the Effectiveness and Safety of Sunitinib for Pancreatic NETs

Sunitinib, a multi targeted tyrosine kinase inhibitor administered orally, was compared appropriately, to placebo in Study A6181111, the one study included in this pCODR systematic review.

The interpretation of these results from this single trial is challenging. The trial was appropriately discontinued early on the advice of the DSMC due to a greater number of adverse events and deaths in the placebo arm of the study. However, this occurred prior to the pre-specified interim analysis for stopping and may result in an over estimation of the benefit of sunitinib in this setting. Indeed, it was observed that the PFS findings were not statistically significant at all data looks for PFS, which occurred prior to the pre-specified interim analysis, although there was a trend towards statistical significance. Despite the uncertainty in the statistical significance of the results, a clinically meaningful doubling of median PFS was observed. Patients randomized to placebo were, appropriately, offered the opportunity to cross over to sunitinib upon progression with the majority in the placebo arm subsequently receiving sunitinib which also limits the ability of this study to demonstrate an overall survival benefit. Early termination of the trial, crossover of patients and the high proportion of censored data limits the ability to measure clinically meaningful endpoints such as overall survival and may result in an over estimation of the benefit of treatment with sunitinib. Importantly there were also no differences in health related quality of life, cognitive, emotional, physical and social functioning in patients treated with sunitinib compared to placebo.

The side effects and adverse events experienced by patients and reported in this trial were consistent with the experience with sunitinib use in patients with metastatic renal cell carcinoma and gastrointestinal stromal tumours (GIST) where this drug has an established role in treatment. The side effects and toxicities of treatment are manageable in the hands of clinicians experienced with the use of sunitinib and are generally acceptable to patients dealing with a diagnosis of pancreatic NETs. Data collected from two extension studies with sunitinib in this patient population has not demonstrated any additional toxicities or concerns.

2.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to sunitinib in the treatment of pancreatic NETs. This conclusion was based on one, randomized controlled trial comparing sunitinib with placebo. The Clinical Guidance Panel was limited in their ability to interpret progression-free survival and overall survival results because the trial was discontinued early before the planned interim analysis designed to evaluate stopping. However, the Panel considered that the magnitude of difference in PFS between the two treatment groups was clinically significant, suggesting that there is very likely a benefit associated with sunitinib.

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

- Sunitinib is administered orally and does not require hospitalization or administration in a tertiary care setting, resulting in significant advantages for patients.

- Systemic chemotherapy with existing approved agents provides minimal benefit to patients with advanced pancreatic NETs and is associated with significant toxicities and inconvenience to patients and their families. There is a need for more effective, easily administered systemic treatments for patients with pancreatic NETs. The side effects and toxicities observed with sunitinib were consistent with those seen in other treatment indications for sunitinib, are manageable, and acceptable to physicians and patients.
- Pancreatic NETs are uncommon neoplasms that often present when disease is locally advanced or metastatic and are not amenable to curative intent treatment. Although uncommon, the incidence of this disease is increasing and effective treatment options are needed.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Gastroenterohepatic NETs are a group of uncommon neoplasms arising from the neuroendocrine cells of the gastrointestinal system. The annual incidence of these tumours is between 1 to 4 per 100,000 but appears to be increasing over the last three to four decades.⁸⁻¹¹ Although uncommon, due to the prolonged natural history of these generally indolent tumours, prevalence of gastroenterohepatic NETs is second only to colorectal cancer amongst malignancies arising from the gastrointestinal system.⁴

Pancreatic NETs are a subset of NETs arising from neuroendocrine cells of the pancreas. These tumours make up 1-4% of pancreatic neoplasms.^{4,5,10,12} The incidence of this subset of NETs is estimated to be 0.2 per 100,000 but also appears to be increasing in recent decades.^{4,5,12}

Most pancreatic NETs occur sporadically, but genetic syndromes including Multiple Endocrine Neoplasia type 1, von Hippel Lindau disease, neurofibromatosis 1 and tuberous sclerosis are associated with an increased risk of pancreatic NET development.¹³

The majority of pancreatic NETs (68 - 90%) are nonfunctional and nonsymptomatic.^{5,14-16} Nonfunctional tumours cause symptoms due to progressive growth and affects on surrounding structures, or metastatic spread, most commonly to the liver. Nonfunctioning tumours are often discovered incidentally as a result of imaging studies of the abdomen done for other indications.

Functional pancreatic NETs produce excess quantities of endogenous hormones (insulin, gastrin, glucagon and others) that result in recognizable clinical syndromes, although not all hormone producing tumours cause symptoms. Tumours that produce hormones unassociated with clinical syndromes are usually thought of as non-functional by clinicians.

Unfortunately the majority of patients with PNETs present with metastatic (60%) or locally advanced (20%) disease^{5,6} and are treated with non-curative intent. Only a small minority are able to undergo curative-intent surgery.

The median overall survival for patients with metastatic pancreatic NETs is 24 to 28 months⁴⁻⁶ and 60- 65% of patients with advanced NET's will die within five years of diagnosis.^{1,5,13} Survival correlates closely with disease stage at presentation and those with early stage disease enjoy better survival times than those with locally advanced or metastatic disease.⁵ Disease grade has also been shown to be an important prognostic indicator.⁴ Often the pathological stain of ki-67 is used to assess grade. Other prognostic markers include elevated levels of chromogranin A, a common biomarker in NETs.¹⁷

3.2 Accepted Clinical Practice

The optimal clinical management for patients with pancreatic NETs involves a multidisciplinary approach to diagnosis and treatment.¹⁸ Surgery is the only potentially curative therapy for patients presenting with early stage disease.⁴ Surgery also has an important role in the management of metastatic disease, particularly when confined to the liver. While not curative, surgical debulking of the primary tumour and liver metastases can provide effective palliation lasting months to years.^{19,20} If surgical debulking of tumours is not feasible, local ablative procedures (band embolization, chemoembolization, and radiofrequency ablation), can also provide effective symptom control and reductions in tumour burden.²¹ Registry data suggest that these therapies may have an impact on overall survival outcomes,⁴ but there are no controlled trials evaluating the impact of debulking surgery or ablative procedures on survival. Most published data describes single institution experiences, often comparing outcomes to historic controls, and therefore lacks the rigor of clinical trial analytic frameworks and methodology.²¹

Peptide Receptor Radio nucleotide Therapy (PRRT) is a form of systemic therapy that capitalizes on the fact that the majority of NETs (> 80%) express somatostatin receptors or other peptide receptors, e.g. metaiodobenzylguanidine (MIBG).²² Somatostatin analogues tagged with radionucleotides (radiation source) and administered intravenously, result in the systemic delivery of radiation therapy preferentially to sites of disease due to binding of the therapeutic agent to the target tissue. Data supporting PRRT comes from European single institution phase I and II studies which often accrued patients with very late stage disease.²³⁻²⁵ Pancreatic NETs have been included in these trials although no trials have been published looking at PRRT in pancreatic NETs only. There are no randomized controlled trials comparing the various radioisotopes used in PRRT to one another or comparing PRRT to other therapeutic modalities utilized in management of pancreatic NETs. PRRT is costly, usually requires repeated hospitalization for administration (typically every 2-4 months) and is only available in 2 to 3 centers in Canada (Edmonton and London or Halifax for MIBG) and is, therefore, not easily accessible for the majority of the Canadian pancreatic NETs patient population.

Somatostatin analogues (Octreotide, Lanreotide) are effective in managing symptoms and improving quality of life for the majority of patients with neuroendocrine functional disease.^{22,26} There remains controversy as to whether these agents also exert an antiproliferative effect in pancreatic NETs. Data from older clinical series suggest that tumour shrinkage is observed in approximately 8% of NETs patients treated with somatostatin analogues.^{27,28} More recent data from the PROMID study suggest that these agents may prolong disease stabilization and improve progression-free survival regardless of functional status, for patients with metastatic NETs of midgut (non-pancreatic origin).²⁹ There is no direct evidence that somatostatin analogues have any anti-proliferative effects in pancreatic NETs. Presently in Canada, somatostatin analogues are approved for symptom control in functional pancreatic NETs but not as an anti proliferative (anti-cancer) therapy.

Systemic chemotherapy has a limited role in the management of pancreatic NETs. Streptozocin combined with 5-fluorouracil or adriamycin is approved for the treatment of patients with advanced pancreatic NETs based upon small trials published between 1980 and 2004, which were not conducted using modern day clinical trial standards such as RECIST criteria to evaluate response.^{30,31} More recent publications challenge the results of earlier trials and raise questions about the utility of these chemotherapy treatment protocols in this patient population.³² Streptozocin is challenging for most patients due to

toxicities associated with treatment and many patients with advanced pancreatic NETs are not candidates for this therapy. These chemotherapy protocols require intravenous administration in a facility with appropriate expertise and supportive care personnel (e.g., chemotherapy nursing staff, chemotherapy unit pharmacies), requiring patients to travel to treatment centers. Streptozocin is only available in Canada now through a special access program.

Alpha-interferon alone, or in combination with somatostatin analogues, can improve symptom control for patients with advanced, functional midgut (non-pancreatic) NETs and has been associated with stabilization and/or partial regression of disease in some patients in some series.^{33,34} The use of interferon is associated with many side effects and is rarely used in Canada for the treatment of this disease.

Most patients with high grade, poorly-differentiated NETs (not the subject of this review) benefit from Cis-platinum based chemotherapy protocols with high response rates but relatively short durations of response. This patient subset is typically excluded from clinical trials of well differentiated disease due to significant differences in both natural history and clinical behaviour.

Small non-randomized trials published since 2006 suggest a potential benefit for patients with advanced pancreatic NETs treated with chemotherapy doublets combining temozolamide with capecitabine, thalidomide, or bevacizumab.^{35,36} Access to these agents for the treatment of pancreatic NETs is variable across Canada as they are not approved by Health Canada or funded by provinces for this indication.

Two randomized phase III placebo-controlled trials have examined novel targeted agents for patients with progressive, metastatic, well differentiated pancreatic NETs. Two agents were evaluated in separate trials: sunitinib, a multi-targeted tyrosine kinase inhibitor, and everolimus, an oral inhibitor of the mTOR (mammalian target of rapamycin) pathway.^{1,6} Both agents are oral daily dosed medications with usual better side effect profiles than systemic chemotherapy. Because of the variability with which these diseases can behave over time, it was also appropriate to restrict accrual to patients with documented progression of their disease within 12 months of study entry with advanced metastatic disease. The patient population included both pre-treated and chemotherapy naive patients. Both trials demonstrated similar results in an elongation of PFS of approximately six months. Given the paucity of randomized controlled trial evidence in support of the previously described systemic therapeutic options for patients with advanced pancreatic NETs, a placebo comparator was appropriate for both these phase III trials designed to assess the efficacy of targeted therapies (sunitinib, and everolimus) in advanced disease.

3.3 Evidence-Based Considerations for a Funding Population

Based upon the available data from a single randomized controlled trial, there now exists randomized controlled trial evidence that patients with advanced pancreatic NETs with evidence of progressive disease and good performance status (Eastern Co-operative Oncology Group score of 0 or 1) would be appropriate candidates for treatment with sunitinib. Based on the inclusion and exclusion criteria of this trial, patients who have received previous systemic therapy with streptozocin, anthracyclines, or fluoropyrimidines (5-fluorouracil or capecitabine) or those who are chemotherapy naive may have the potential for similar benefit. As well, previous or concomitant treatment with somatostatin analogues should not exclude patients from sunitinib. The goal of treatment

would be to prolong progression free survival for those with progressing, metastatic disease.

Given these cancers are uncommon, the number of Canadian patients who would potentially receive this treatment is small. Because 80% of patients diagnosed with pancreatic NETs have locally advanced or metastatic disease at the time of diagnosis,^{5,6} and given the fact that patients with localized disease treated with curative intent surgery remain at risk for systemic recurrence of disease however, most patients diagnosed with pancreatic NETs would be potential candidates for treatment with sunitinib at some point.

At the present time there is no established role for adjuvant systemic treatment of pancreatic NETs in patients treated surgically with curative intent.

3.4 Other Patient Populations in Whom the Drug May Be Used

Most NETs are gastroenterohepatic in origin however NETs also can arise in the lung, thymus, thyroid gland (medullary thyroid cancer), skin (Merkel's cell carcinoma) and can also present as rare subtypes including pheochromocytomas and paragangliomas as well as arising in the kidney and other sites in the body. Clinical trials conducted to date have included small numbers of patients with NETs arising from sites other than the gastrointestinal tract. Trials with other tyrosine kinase inhibitors in medullary thyroid cancer are demonstrating similar benefits to those defined by the trials discussed in this review. Clinical trials designed to assess the efficacy of targeted therapies in NETs arising from sites other than the gastrointestinal tract are enrolling patients or are in planning stages presently. The similarities shared by NETs arising from different anatomic sites suggest that patients with advanced well differentiated NETs, regardless of site of origin, could benefit from targeted therapies. Currently however no evidence exists for patients with non pancreatic NETs cancers to derive any benefit from sunitinib. Definitive data derived from clinical trials in these other NET patient populations will be challenging given these tumours are uncommon.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on sunitinib for pancreatic NETs and their input is summarized below: Carcinoid-NeuroEndocrine Tumour Society Canada (CNETS Canada)

CNETS Canada conducted a qualitative study using responses obtained through telephone and email responses from respondents to gather information about the patient and caregiver experience with the medical condition and drug under review. Response was solicited via a letter posted on the CNETS website as well as emails to group leaders and online support groups. A small number of responses were received by CNETS Canada.

From a patient perspective, stabilization of the pancreatic NETs, as well as preventing the further spread of the cancer to other areas of the body, is an important aspect when consideration is given to treatment. Although there are side effects associated with sunitinib therapy, patients indicated that they are willing to tolerate certain side effects if this means stabilization or regression of the tumour. Patients are also looking for a therapy that will help to improve their quality of life and enable them to continue to work and maintain a normal life. In addition, patients desire more knowledge in the medical community concerning pancreatic NETs.

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 Pancreatic NETs

Patients with pancreatic NETs may experience a number of different symptoms depending upon the hormone most strongly secreted by their particular NET. For many of these patients, the symptoms of the pancreatic NETs have a severe impact on their day-to-day living, from the anorexia and fatigue experienced by patients with glucagonoma to continuous diarrhea experienced by patients with VIPoma.

Due to the non-specific nature of the symptoms that patients experience, many are misdiagnosed as having a different medical condition which can be frustrating. Oftentimes, these patients may be sent to see psychiatrists as it is felt that “it is all in [their] minds”.

Many patients with pancreatic NETs are of the opinion that they are alone and need to advocate for themselves due to a lack of connectedness in the medical community with respect to neuroendocrine cancers.

Patient advocacy group input indicated that some of these patients become debilitated and as a result, cannot continue to work. This can cause immense financial implications for the patient. They may be unable to afford to travel to treatment centers or even pay for medications.

Slowing the growth of the tumour to prevent blockages and metastases to the liver and other locations is very important to these patients.

4.1.2 Patients' Experiences with Current Therapy for Pancreatic NETs

Patient advocacy group input noted that pancreatic NETs are not currently considered curable, except in the few cases where smaller tumours can be completely removed through surgery. Current treatments for pancreatic NETs include surgery, embolization, chemotherapy, biotherapy and nuclear medicine. Surgery and somatostatin analogues can extend life for many years in the view of patients. Nuclear medicine treatments are also effective and can extend life and also create a quality of life for some patients.

Patients in the survey indicated there is a high tolerance for side effects from treatment if there is a possibility it will result in a reduction of their tumour size.

Some patients are not able to access all available treatment options in their community, which may be due to a lack of knowledge that such resources exist. A patient navigator for pancreatic NET patients is needed to help guide patients through the health care system and act as a link between patients and the health care system.

4.1.3 Impact of Pancreatic NETs and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of this cancer on caregivers can be profound. Caregivers spend a great deal of time in managing medical aspects for the patient (i.e. picking up and delivering scans and ensuring all medical professionals are informed of the patients medical history) and taking care of the patients. Being a caregiver can be a challenging role and many report being overstressed.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Sunitinib

Patient advocacy group input indicated that patients with pancreatic NETs are seeking drug therapies which would help to stabilize their condition. Treatments which result in tumour shrinkage and treatments which lead to an improvement in a patient's quality of life would be considered an additional benefit. Overall, patients deem that the benefits of therapy outweigh the risks for patients who are able to achieve stable disease.

In addition, patients seek a treatment that will enable them to continue to work and maintain a normal life. They also consider fewer visits to the emergency room would be a benefit of treatment as well.

Patients with direct experience with sunitinib indicated that it has controlled tumour growth better than existing therapies. They feel that sunitinib can extend the life of a patient pancreatic NETs and in some cases; the survival advantage can be significant. In addition, patients state that sunitinib is easier to use than other therapies for the treatment of pancreatic NETs and patients can remain at home while receiving this treatment.

With respect to side effects, patient input indicated that that some patients experienced hand and foot disease, fatigue, diarrhea and hair color change with sunitinib, whereas some patients did not experience any side effects at all. However, as previously noted,

many patients are willing to tolerate certain side effects with sunitinib if it means that their disease is kept under control.

4.3 Additional Information

CNETS Canada indicated that locating patient members in the community has been a challenge. No other comments within the scope of the input requested by pCODR were received.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for sunitinib malate for pancreatic neuroendocrine tumours. 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).

Input on the sunitinib (Sutent) review was obtained from eight of the nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that everolimus is also expected to receive Health Canada approval for the treatment of locally advanced/metastatic pNET in the near future and as such, PAG felt it would be important to be aware of any differences between sunitinib and everolimus with respect to treatment outcomes, side effect profile and overall costs. In addition, PAG identified that information on the sequential use of sunitinib and everolimus would be helpful.

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

5.1 Factors Related to Comparators

PAG identified that there are relatively few treatment options available for patients with locally advanced/metastatic pNET. Sunitinib would represent a new standard of care for this indication where there are limited treatment choices.

Streptozocin, an antineoplastic agent that is used for this indication, it is no longer available in Canada and can only be accessed through Health Canada's Special Access Program. Since access to streptozocin requires authorization through the Special Access Program, having an alternative option for treatment, such as sunitinib, would be favourable to jurisdictions.

PAG noted that another new agent, everolimus, is also under review by Health Canada for this indication. PAG felt that comparative data between sunitinib and everolimus would be valuable to identify any differences between the two agents with respect to effectiveness or side effects. In addition, it would be useful if the difference in costs between these two agents is factored into the economic analysis.

While some of the currently available treatment agents for pNET require IV administration and take up chemo chair time, PAG noted that sunitinib is an oral medication which could be easily administered to patients in an outpatient setting, which would be an enabler for sunitinib therapy.

PAG also identified that there would not be any impact on the use of somatostatin analogues in these patients.

5.2 Factors Related to Patient Population

As locally advanced or metastatic pancreatic NETs affect a relatively small patient population, PAG recognized that there may only be a small number of patients accessing sunitinib for this indication when considering budget impact, which may be an enabler for jurisdictions if implementing a funding recommendation.

PAG identified that the proposed indication for sunitinib is specific to patients with Eastern Co-operative Oncology Group status 0 or 1, which could potentially further limit the number of patients eligible for sunitinib.

PAG noted that there was potential for sunitinib to be used in other clinical settings, such as the adjuvant treatment of pancreatic NETs. Therefore, evidence to support use of sunitinib in this setting would be needed to help determine if funding could be provided for this population.

As everolimus is also being reviewed by Health Canada for the same indication, PAG noted that there may be potential for sequential use of these agents, especially in light of their differing mechanisms of action. This may be a barrier to implementation as it could potentially increase costs to each jurisdiction's drug program. Therefore, PAG would be interested to know if there is evidence available to support sequential use of these two agents or any other agents in locally advanced or metastatic pancreatic NETs.

5.3 Factors Related to Accessibility

PAG recognized that sunitinib is administered as an oral therapy. This would pose as an enabler in jurisdictions as it would help save chemotherapy unit resources and patient travel time to treatment centers. However, in some jurisdictions, oral therapies are funded under provincial drug plans and not all provincial drug plans cover the entire patient population, which may be a barrier to access as these patients would have to pay 'out of pocket' for the medication.

5.4 Factors Related to Dosing

PAG noted that sunitinib is given at a continuous daily dose of 37.5 mg in the treatment of locally advanced or metastatic pancreatic NETs. PAG noted that dose de-escalations have been observed when sunitinib is used for the treatment of other cancer types (such as metastatic renal cell carcinoma) and could potentially occur in the treatment of locally advanced/metastatic pancreatic NETs. Therefore, PAG would appreciate information regarding the effectiveness of sunitinib at lower doses in this indication, if available.

PAG also noted that sunitinib is available in a variety of strengths and any dose decreases would likely result in minimal drug wastage. In addition, PAG recognized that the pricing of sunitinib is linear based on the strength of the medication, so dose de-escalations would not likely have any budget impact to the jurisdictions, which would be an enabler to sunitinib therapy.

Sunitinib is also indicated for the treatment of metastatic renal cell carcinoma but is given in four week out of six week cycles (i.e. 2 week treatment break) which differs from the

continuous dosing frequency used in pancreatic NETs. PAG noted that taking sunitinib in a continuous daily fashion without a need for treatment breaks may potentially increase patient compliance which would be an enabler to sunitinib therapy. Alternatively, it was noted that if patients are experiencing severe side effects with sunitinib, a two-week break in therapy may be welcomed by these patients.

5.5 Factors Related to Implementation Costs

PAG noted that sunitinib is an oral drug therapy and as a result, would require minimal resources with regards to implementation, which would be an enabler for jurisdictions. Although chemotherapy unit services would not be required for sunitinib administration, it was noted that there would still be costs for physician visits, pharmacy dispensing and toxicity monitoring.

PAG also recognized that everolimus may soon be approved by Health Canada for the same indication and jurisdictions would need further comparative information on these two agents with regards to efficacy, side effects and costs, as well as information regarding sequential therapy.

5.6 Other Factors

No other input was provided by PAG.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of sunitinib malate on patient outcomes compared to standard therapies or placebo in the treatment of patients with unresectable locally advanced or metastatic well differentiated pancreatic neuroendocrine tumours and progressive disease.

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 1: Selection Criteria				
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished DB RCT	Patients with unresectable locally advanced or metastatic, well differentiated pancreatic neuroendocrine tumours, whose disease is progressive	Sunitinib malate (oral) as monotherapy at a recommended dose of 37.5 mg once daily.	Placebo Streptozocin based regimen Everolimus	<ul style="list-style-type: none"> • Overall survival • Progression free survival • Tumour response • Dosage reductions • QoL • SAE (neutropenia, leukopenia, cardiac failure) • AE (hypertension, hand-foot syndrome, abdominal pain, fatigue, diarrhea) • WDAE
<p>AE=adverse events; DB=double blind; QoL=quality of life; RCT=randomized controlled trials; SAE=serious adverse events; WDAE=withdrawal due to adverse events</p>				

* 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 (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2011, Issue 4) 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 Sutent (sunitinib malate) and pancreatic neuroendocrine tumours.

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 was completed on November 14, 2011 and was updated during the review. The search is considered up to date as of February 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 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

One p value for assessing statistical significance of PFS was calculated using a z to p value calculator.³⁷

6.2.6 Writing of the Review Report

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

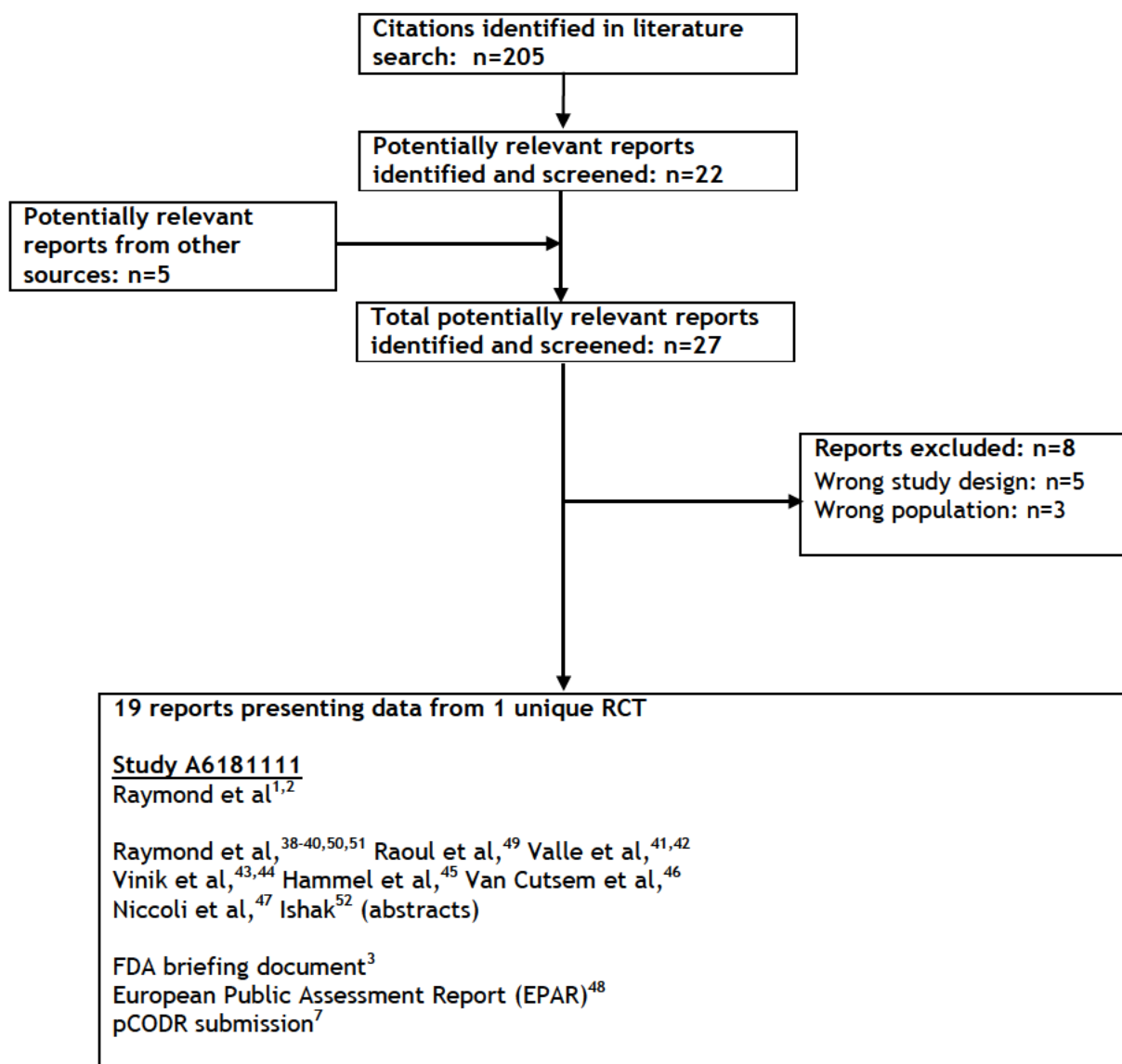
- The Methods Team wrote a systematic review of the evidence.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- 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 25 potentially relevant reports identified, 19 reports presenting data from 1 unique RCT were included in the pCODR systematic review^{1-3,7,38-52} and 8 studies were excluded. Studies were excluded because they were the wrong study design⁵³⁻⁵⁷ or wrong population.⁵⁸⁻⁶⁰

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 2: Summary of Trial Characteristics of the Included Study			
Trial Design	Inclusion Criteria	Intervention and Comparator	Outcomes
<p>A6181111^{1,2}</p> <p>42 centres in 11 countries*</p> <p>June 2007 to April 2009</p> <p>DB, PC, RCT</p> <p>n=171 randomized†</p> <p>n=165 as-treated</p> <p>Funded by Pfizer</p>	<ul style="list-style-type: none"> Patients with pathologically confirmed, well-differentiated advanced or metastatic pancreatic endocrine tumours and not eligible for surgery Documented disease progression within the previous 12 months as assessed by RECIST One or more measurable target lesions ECOG PS\leq1 	<ul style="list-style-type: none"> Sunitinib 37.5 mg orally once daily vs. matching placebo Treatment interruptions or a dose reduction to 25 mg daily permitted if AEs Increase in dose to a maximum of 50 mg permitted if no tumour response in the absence of AEs \geqgrade 2 Somatostatin analogs permitted at the investigator's discretion 	<p><u>Primary</u></p> <ul style="list-style-type: none"> Progression-free survival <p><u>Secondary</u></p> <ul style="list-style-type: none"> Overall survival Objective tumour response Time to tumour response Safety Patient reported outcomes
<p>AEs=adverse events; DB=double-blind; ECOG PS=Eastern Cooperation Oncology Group performance status; PC=placebo controlled; RECIST=Response Evaluation Criteria in Solid Tumours; RCT=randomized controlled trial</p>			

*Canada had five participating centres that enrolled 17 patients.¹

†trial terminated early by the Data and Safety Monitoring Committee

a) Trials

One randomized double-blind placebo controlled trial (study A6181111) was included in this review (Table 2).^{1,2} The study was conducted in 42 centres in 11 countries and was manufacturer-sponsored.

The study included patients with pathologically confirmed well-differentiated advanced or metastatic pancreatic endocrine tumours not eligible for surgery. Additional eligibility criteria included documented disease progression within the previous 12 months as assessed by the Response Evaluation Criteria in Solid Tumours (RECIST), one or more measurable target lesions, an Eastern Cooperation Oncology Group performance status of 0 or 1, and adequate hematologic, hepatic, and renal functions. Exclusion criteria included: patients with poorly differentiated pancreatic neuroendocrine tumours, previous tyrosine kinase or VEGFR inhibitor treatment,

cardiac events or pulmonary embolism in the previous year, ongoing cardiac dysrhythmias or prolonged QT interval, symptomatic brain metastases, or a left ventricular ejection fraction $\leq 50\%$.

The trial started in June 2007. An estimated 340 patients (260 events) were to be enrolled in the study based on 90% power to detect a 50% improvement in progression free survival (PFS) with sunitinib from an estimated median PFS of 5.1 months with placebo, with the use of a two-sided, unstratified log-rank test adjusted for one interim analysis (130 events). The objective of the interim analysis was to provide recommendations on whether to continue the trial as planned, to adjust the sample size, or to discontinue the trial.³ However, in February 2009, prior to the planned interim analysis, the Data and Safety Monitoring Committee assessed data on 154 patients (73 events). It recommended early discontinuation of the trial due to a greater number of deaths and serious adverse events reported in the placebo group as well as a difference in progression-free survival in favour of the treated group. The trial ended on April 15, 2009 (81 events reported).

Trial procedures for randomization and allocation concealment were considered adequate. Allocation to treatment was done randomly using a centralized registration system. Blinding may have been more difficult to maintain due to adverse events, mainly diarrhea, reported with sunitinib.

b) Population

A total of 86 patients received sunitinib and 85 patients were assigned to placebo. Randomization was balanced by country/ region. Median age was 56.5 years (range 25 years to 84 years). The groups were equally distributed between males and females. Patients were predominantly caucasian. More patients in the placebo group had extrahepatic metastases (40% vs. 24%), and had ≥ 3 disease sites (41% vs. 28%). Placebo patients also had a longer median time since diagnosis (3.2 years vs. 2.4 years). Placebo patients had worse ECOG performance status, with 48% having a performance status of 0 (vs. 62%) and with 51% having a performance status of 1 (vs. 38%). More than 65% of trial patients had received prior systemic chemotherapy. A post hoc analysis using Fisher's exact test determined that there were no statistically significant differences in baseline characteristics between the two study groups.

c) Interventions

Patients received sunitinib 37.5 mg administered orally once daily for a median duration of 4.6 months (range 0.4 to 17.5) or matching placebo for a median duration of 3.7 months (range 0.03 to 20.2). Both treatment arms received best supportive care (analgesics, antidiarrheal agents, beta blockers, emollients or protective).⁷ Treatment interruption or a dose reduction to 25 mg per day were permitted in patients experiencing an adverse event. Subsequently, these patients were permitted an increase in dose if toxicity grade 2 or higher did not recur. In patients without an objective treatment response and no treatment-related adverse events during the first 8 weeks of treatment, an increase in dose to 50 mg per day was permitted. Patients continued treatment until progression was documented (using RECIST), until unacceptable adverse events occurred, or until death.

A total of 30/86 (35%) sunitinib patients and 32/85 (38%) placebo patients received a somatostatin analogue prior to enrollment. Of these, 22 sunitinib patients and 20 placebo patients continued somatostatin therapy during trial. One sunitinib patient initiated somatostatin therapy during the trial compared to the five placebo patients.

d) Patient Disposition

The intention to treat population included 171 patients who were randomized to one of the two study groups regardless of whether or not they had received a study drug or a drug different from the original assignment. The as-treated population included 165 patients who had received at least one dose of study treatment.

The most common reasons for treatment discontinuation were disease progression (22% and 55% of sunitinib and placebo patients respectively), termination of trial (48% and 19% of sunitinib and placebo patients respectively), and adverse events (17% and 8% sunitinib and placebo patients respectively).

	Sunitinib	Placebo
Randomized	86	85
As-treated	83	82
Intention to treat analysis	86	85
Safety analysis (%)	83	82
• Did not receive treatment due to early trial termination	3 (3%)	2 (2%)
• Did not receive treatment due to protocol violation	0	1 (1%)
Discontinued treatment (%)	83	82
• Study terminated by sponsor	41 (48%)	16 (19%)
• Objective progression or relapse	19 (22%)	47 (55%)
• Adverse event*	15 (17%)	7 (8%)
• Protocol violation	2 (2%)	1 (1%)
• Patient discontinued treatment (not due to adverse events)	2 (2%)	1 (1%)
• Global deterioration of health status	1 (1%)	5 (6%)
• Death	1 (1%)	3 (4%)
• Pregnancy	1 (1%)	0
• Lost to follow-up	0	1 (1%)
• Other	1 (1%)	1 (1%)

*based on investigator assessment

e) Limitations/Sources of Bias

- As reported in an FDA report, an independent Data and Safety Monitoring Committee was installed eight months after the accrual of patients to the study began. Their role was to monitor the safety of patients and conduct an interim analysis of efficacy. The objective of the interim analysis was to provide recommendations on whether to continue the trial as planned, to adjust the sample size, or to discontinue the trial.³ The interim analysis was scheduled when 130 PFS events had occurred and data analysis was to take into consideration the Lan-DeMets methodology (allocates a fraction of the pre-specified overall significance level at the interim and final analyses).¹ The Data and Safety Monitoring Committee met three times, before the planned interim analysis, to review safety data (May 2008, November 2008, and February 2009).³ At the same time, PFS data were also reviewed (20 events, 50 events and 73 events respectively).³ At the third data assessment, a decision was made to terminate the trial early because of an increase in events in the placebo group compared to the treated group (a total of 73 events which represented 28% of the planned number of events).^{3,7} The analyses of the early PFS data

were not based on a pre-specified statistical plan (no alpha spending and statistical stopping boundaries were implemented).³ According to the FDA, the protocol amendment did not state that the Data and Safety Monitoring Committee would review efficacy data before the planned interim analysis.³

- An early trial termination due to a positive result may be a random result and the difference between treatments may be overestimated. Furthermore, a trial that is stopped early will include a small number of patients and the estimated differences will be large. Finally, on the Kaplan-Meier curve, the results will represent the early part of the curve and long-term results may be different.⁶¹
- At trial termination, nine patients on sunitinib and 21 placebo patients had died. This meant that for the analysis of overall survival, data for 77/86 (90%) sunitinib and 64/85 (75%) placebo patients were censored. The low event rate and the high number of censored events make challenging the interpretation of overall survival.
- PFS may be a surrogate outcome for overall survival but it has not been determined if benefits of PFS translates into overall survival benefits in patients with pancreatic NETs.
- Patients in the sunitinib group experienced statistically more diarrhea than the placebo group, and blinding may have been difficult to maintain. This may have led to detection bias (investigator becomes aware to which treatment the patient is assigned) which may have impacted the way tumour response was assessed, in favour of the treated group.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The efficacy analysis was based on intention to treat which included all randomized patients. The safety analysis included patients who had received at least one dose of study treatment. Data was collected at screening, every four weeks (defined as one cycle), and at the end of treatment or at withdrawal from study. Tumour imaging was performed at screening, at week 5, at week 9, and every 8 weeks thereafter. Additional scans were performed if disease progression was suspected, to confirm tumour response, or when a patient withdrew from the study.

The analyses were conducted based on data obtained as of April 15, 2009, which included 81 events (progression or death).

Table 4: Summary of Key Outcomes ^{1,2,7}				
EFFICACY (ITT; investigator assessed)				
Outcome	Study group	Median Months (95%CI)	HR (95% CI)	P value
progression free survival*	Sunitinib	11.4 (7.4, 19.8)	0.42 (0.26, 0.66)	0.000118
	Placebo	5.5 (3.6, 7.4)		
overall survival†	Sunitinib	NE	0.41 (0.19, 0.89)	0.02
	Placebo	NE		
Outcome	Study group	n/N	% (95%CI)	P value
Response rate (CR + PR)	Sunitinib	8/ 86	9.3 (3.2, 15.4)	0.007
	Placebo	0/ 85	0	
QUALITY OF LIFE (Patient Reported Outcomes)‡				
Outcome	Study group	Number of patients in analysis	Between group difference ^ψ	P value
Diarrhea	Sunitinib	N=73	21.4	P<0.001
	Placebo	N=71		
Insomnia	Sunitinib	N=73	7.8	P=0.04
	Placebo	N=71		
HARM ^Δ				
Outcome	Study group	n/N	%	P value
Death	Sunitinib	9/86	10.5	0.02
	Placebo	21/85	24.7	
SAE	Sunitinib	22/83	26.5	NR
	Placebo	34/82	41.5	
Any AE	Sunitinib	82/83	98.9	NR
	Placebo	78/82	95.1	
WDAE	Sunitinib	18/83	21.7	NR
	Placebo	14/82	17.1	
AE=adverse events; CI=confidence interval; CR=complete response; HR=hazard ratio; ITT=intention to treat; NE=not estimable; NR=not reported; PR=partial response; SAE=serious adverse events WDAE=withdrawal due to adverse events;				

*hazard ratio for progression or death; † hazard ratio for death; ‡ obtained from the European Organization for Research and Treatment Cancer Quality of Life Questionnaire Core 30 version 3.0; ^ψ higher score represents a worsening of symptoms in sunitinib group; ^Δ all causalities

Statistical tests: Kaplan-Meier methods used to calculate median PFS; Fischer's exact test used to compare objective response rate between study groups; Cox proportional-hazards model used to calculate hazard ratios; repeated-measures mixed effects model used for patient-reported outcomes assessment

Efficacy Outcomes

a) Overall survival

Overall survival was a secondary end-point defined as the time interval from randomization until death due to any cause. In the absence of death, the data was censored at the last date the patient was known to be alive.

The overall survival analysis was performed at trial termination (15 April 2009). The hazard ratio for death was 0.41 (95% CI: 0.19 to 0.89; p=0.02) (Table 5). A pre-specified threshold for determining statistical significance of these results is unknown and the median overall survival time could not be estimated due to data censoring.

	Sunitinib (n=86)	Placebo (n=85)	P value
Deaths, n (%)	9 (10)	21 (25)	
Patients with censored data, n (%)	77 (90)	64 (75)	
Overall survival <ul style="list-style-type: none">• Estimated median• HR for death (95% CI)	NE 0.41 (0.19, 0.89)	NE	0.02

CI=confidence interval; HR=hazard ratio; ITT=intention to treat; NE=not estimable; PFS=progression free survival

b) Progression-free survival

Progression free survival was the primary end point and was defined as the time from randomization to the first evidence of objective tumour progression or death from any cause. PFS data were censored for patients who did not experience disease progression or did not die during the trial, who started a new anti-cancer therapy prior to documented progression, or who missed two consecutive tumour assessments before documented progression.

The determination of disease progression was made by the investigator and was based on objective tumour assessment done according to RECIST. Two other analyses were presented by the submitter: derived tumour assessment and blinded independent central review assessment.⁷ Irrespective of the analysis used, sunitinib improved PFS compared to placebo.

At trial termination, 30/86 (35%) sunitinib patients and 51/85 (60%) placebo patients had progression of their disease or had died (Table 6). The investigators reported that patients treated with sunitinib had an improvement in PFS compared to placebo (HR=0.42; 95% CI: 0.26 to 0.66). The median PFS doubled in the sunitinib group compared to placebo (11.4 months vs. 5.5 months).

Table 6: Progression free survival (ITT, investigator assessed) ¹			
	Sunitinib (n=86)	Placebo (n=85)	P value
Patient with events, n (%)	30 (35)	51 (60)	
Type of event, n (%)			
• Progression	27 (31)	48 (56)	
• Death without progression	3 (3)	3 (4)	
Patients with data censored, n (%)	56 (65)	34 (40)	
Estimated median PFS			
• months (95% CI)	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	0.000118 ³
• HR for progression or death (95% CI)	0.42 (0.26, 0.66)		
CI=confidence interval; HR=hazard ratio; ITT=intention to treat; PFS=progression free survival			

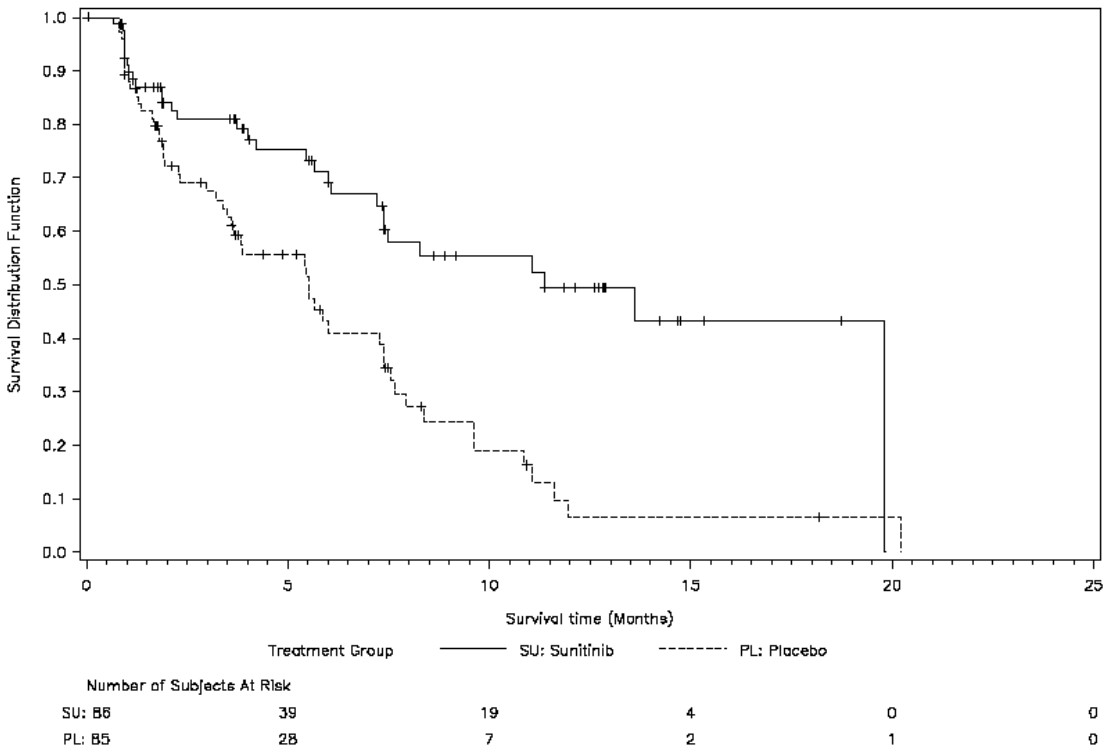
With no *a priori* statistical plan formulated for early data checks, the statistical significance of the PFS data obtained at the three unplanned analyses was measured using the Lan-DeMets procedure and O'Brien- Fleming stopping boundary. The final PFS analysis was based on 81 PFS events (31% of the planned events) and the observed test statistic (Z value) was 3.8506. This value did not exceed the Z value of 3.8809 adjusted for multiple data looks.¹ Hence, the test statistic did not cross the efficacy boundary, and the findings were not statistically significant.

Table 7: Results of the statistical analysis for PFS		
	Z scale ¹	P value
Observed test statistic	3.8506	0.000118 ³
Adjusted efficacy boundary	3.8809	0.000104*

*computed by pCODR using software obtained from the internet

The Kaplan-Meier curve showed a treatment effect early in the study (at approximately 3 months) and the effect persisted until trial termination (Figure 1).

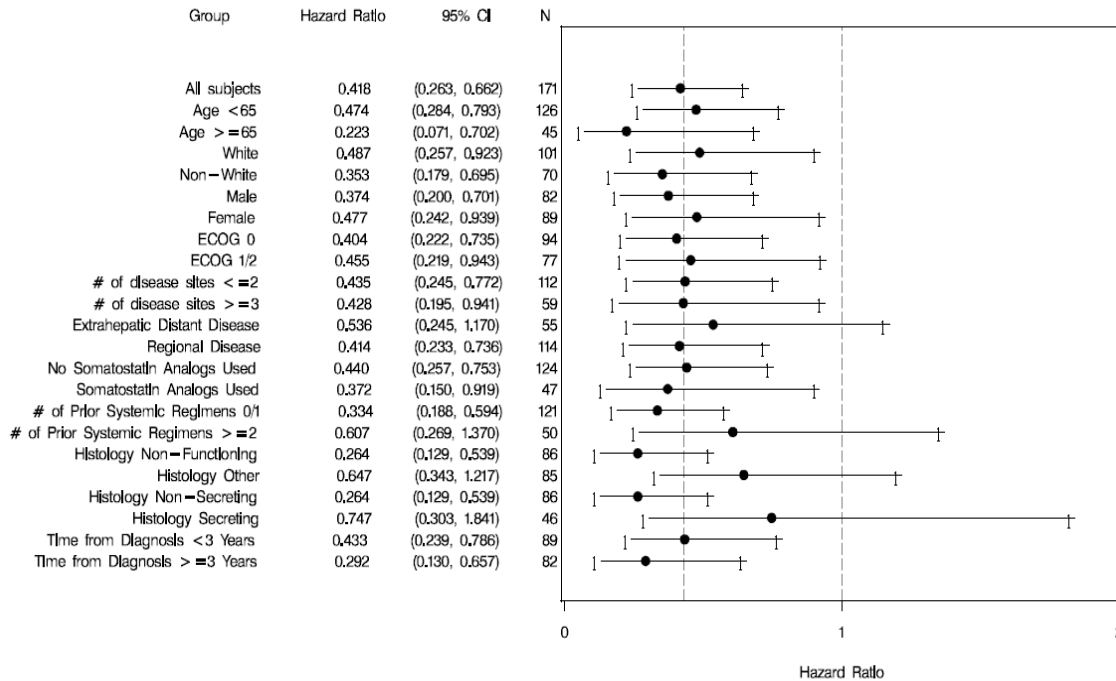
Figure 1. Kaplan-Meier Curve of Progression-Free Survival (ITT, investigator assessed)¹



Sub-group analyses for progression-free survival

The relative effectiveness of sunitinib and placebo for PFS was explored in a number of pre-specified sub-groups. (Figure 2) The hazard ratios obtained were consistent with that of the primary analysis. Median PFS times were not calculated.

Figure 2. Cox Proportional Hazards Analysis of Progression-Free Survival (ITT, investigator assessed)¹



c) Tumour response

Tumour response was a secondary end point. Objective response rate was defined as the percentage of patients experiencing a confirmed complete or partial response according to RECIST. Confirmed responses were those that persisted on tumour imaging 4 weeks or more after initial documentation of tumour response.

A total of 8/86 sunitinib patients (9%) had a complete or partial response to treatment. None of the placebo patients were reported to have had a response (p=0.007 for between group difference).

d) Quality of life (Patient reported outcomes)

Patient reported outcomes were measured every four weeks for 10 cycles and at the end of treatment or withdrawal using the self-administered European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) version 3.0. The patient reported outcome analysis was based on patients who completed baseline and one or more EORTC QLQ-C30 assessments. Between treatment comparisons of estimated mean differences in change from baseline were analyzed using repeated measures mixed-effects models.

Data were available for 85% (73/86) of sunitinib patients and 84% (71/85) of placebo patients. Data was limited to the first 10 cycles. Compared to placebo, patients in the sunitinib group had statistically significantly worsening diarrhea (21.4 points difference, p<0.001), statistically significantly worsening insomnia (7.8 points difference, p=0.04 cycles 2 to 7), and a statistically significant reduction in constipation⁷ (cycles 2 to 4; data not reported). A difference of 10 points or more was determined by the investigators to be clinically significant based on a previous study⁶² of breast and small-cell lung cancer patients.

For other outcomes, there were no statistically significant differences between the treatment arms in global health related quality of life, functional scales (cognitive, emotional, physical, role and social functioning), or in other symptoms (appetite loss, dyspnea, fatigue, nausea, vomiting, and pain) at baseline or at other times.

e) Dosing Regimen Modifications

One or more dose interruptions (of seven days or more) occurred in 30% of sunitinib patients and in 12% of placebo patients. These dose interruptions were due to adverse events. For the patients receiving sunitinib, the interruptions were due to neutropenia (12% of patients), diarrhea (10%), asthenia (7%), erythrodysesthesia (7%), hypertension (7%), and thrombocytopenia (6%). For the placebo patients, dose interruptions were due to abdominal pain (3% of patients), vomiting (3%), and asthenia (3%).

A dose reduction to 25 mg occurred in 31% sunitinib patients and in 11% of placebo patients whereas a dose increase to 50 mg occurred in 10% sunitinib patients and in 24% of placebo patients.

No evidence is available on the effectiveness of sunitinib at lower doses than the recommended 37.5 mg.

Harms Outcomes

a) Deaths and other serious adverse events

Serious adverse events that occurred in $\geq 2\%$ of patients are listed in Table 8. Serious adverse events were defined as those that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, or resulted in congenital abnormalities or birth defects.

Table 8: Serious adverse events in $\geq 2\%$ of patients, safety population ²		
Serious adverse events, n (%)	Sunitinib (n=83)	Placebo (n=82)
Total	22 (27)	34 (42)
Disease progression	3 (4)	2 (2)
Cardiac failure	2 (2)	0
Abdominal pain	2 (2)	4 (5)
Upper abdominal pain	2 (2)	0
Nausea	2 (2)	1 (1)
Vomiting	2 (2)	3 (4)
Renal failure	2 (2)	0
General physical health deterioration	1 (1)	2 (2)
Hepatic pain	1 (1)	2 (2)
pyrexia	1 (1)	2 (2)
Back pain	0	2 (2)
hematemesis	0	2 (2)

Table 8: Serious adverse events in ≥2% of patients, safety population ²		
Serious adverse events, n (%)	Sunitinib (n=83)	Placebo (n=82)
Hepatic failure	0	2 (2)
hypoglycemia	0	2 (2)
hypotension	0	2 (2)
melena	0	2 (2)
Pulmonary embolism	0	2 (2)

Five (6%) and nine (11%) sunitinib and placebo patients respectively died during the trial and up to 28 days after the last dose. All deaths were attributed to the disease except in two cases, with one sunitinib patient dying of cardiac failure and one placebo patient dying of dehydration. During follow-up (more than 28 days after the last dose of study medication), four (5%) and 12 (14%) sunitinib and placebo patients died respectively.

b) Any adverse event

Adverse events were collected from the first day of treatment to 28 days after the last study dose. The Data and Safety Monitoring Committee supervised the occurrence of adverse events in the trial patients (Table 9).

Table 9: Most common adverse events* (safety population)¹

Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	<i>number of patients (percent)</i>					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar-plantar erythro- dysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)

*Based on the National Cancer Institute Common Terminology Criteria for Adverse Events - events listed are those occurring in >15% of patients in either group.

Grade 1= mild adverse events; grade 2=moderate adverse events; grade 3=severe adverse events; grade 4=life-threatening or disabling adverse events

The majority of patients experienced treatment-emergent all causality adverse events: [sunitinib 82/83 (99%) vs. placebo 78/82 (95%)].⁷ Patients in the sunitinib group experienced a greater incidence of diarrhea (59% vs. 39%) and nausea (45% vs. 29%). Other common adverse events (occurring >15% in either group) included hair colour changes, neutropenia, hypertension, palmar-plantar erythro-dysaesthesia syndrome (also called hand-foot syndrome), stomatitis, dysgeusia, epistaxis, rash, and thrombocytopenia, with greater incidence in the sunitinib group than the placebo group.

Grades 3/4 adverse events occurred more frequently in sunitinib patients (49%) compared to placebo patients (44%), including a greater incidence of grade 3/4 neutropenia (12% vs. 0%), hypertension (10% vs. 1%), leukopenia (6% vs. 0%), and hand-foot syndrome (6% vs. 0) in sunitinib patients. Grade 3/4 diarrhea occurred in 5% of sunitinib patients and in 2% of placebo patients.

c) Withdrawals due to adverse events

A total of 22% (18/83) of sunitinib patients and 17% (14/82) of placebo patients discontinued treatment due to adverse events.⁷ The most common adverse events leading to treatment discontinuation were fatigue (4%), diarrhea (2%), and cardiac failure (2%).

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal 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 sunitinib for the treatment of unresectable locally advanced or metastatic well differentiated pancreatic neuroendocrine tumours and progressive disease. 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 Gastrointestinal 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.

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	(Sutent* or Sunitinib* or SU-011248 or SU011248 or SU010398 or SU-010398 or PHA-290940AD or PHA290940AD or SU-11248 or SU11248 or SU-10398 or SU10398).ti,ab,ot,sh,hw,rn,nm.	9521
2	(341031-54-7 or 557795-19-4).rn.	6527
3	or/1-2	9521
4	exp Neuroendocrine Tumors/ or exp Pancreatic Neoplasms/	269834
5	(insulinoma* or gastrinoma* or PNET or PNETs or GPNET or GPNETs or NET or NETs or panNET).ti,ab,ot,sh,hw.	171565
6	((neuroendocrine or pancreas or pancreatic or gastroenteropancreatic or gastro-entero-pancreatic or enteropancreatic or islet cell*) and (Neoplasm or neoplasms or tumour or tumours or tumor or tumors or cancer or cancers or cancerous or carcinoma or carcinomas or adenocarcinoma* or carcinoid or carcinoids or metastases or metastasis or metastatic or malignan*)).ti,ab,ot,sh,hw.	179334
7	or/4-6	483992
8	3 and 7	983
9	8 use pmez	129
10	*sunitinib/	1591
11	(Sutent* or Sunitinib* or SU-011248 or SU011248 or SU010398 or SU-010398 or PHA-290940AD or PHA290940AD or SU-11248 or SU11248 or SU-10398 or SU10398).ti,ab.	4502

12	or/10-11	4710
13	exp *Neuroendocrine Tumors/ or exp *pancreas tumor/	164786
14	(insulinoma* or gastrinoma* or PNET or PNETs or GPNET or GPNETs or NET or NETs or panNET).ti,ab.	151902
15	((neuroendocrine or pancreas or pancreatic or gastroenteropancreatic or gastro-entero-pancreatic or enteropancreatic or islet cell*) and (Neoplasm or neoplasms or tumour or tumours or tumor or tumors or cancer or cancers or cancerous or carcinoma or carcinomas or adenocarcinoma* or carcinoid or carcinoids or metastases or metastasis or metastatic or malignan*)).ti,ab.	132060
16	or/13-15	396060
17	12 and 16	257
18	17 use emez	162
19	9 or 18	291
20	exp animals/	17527328
21	exp animal experimentation/	1474294
22	exp models animal/	976307
23	exp animal experiment/	1474294
24	nonhuman/	3722192
25	exp vertebrate/	31303574
26	animal.po.	0
27	or/20-26	33144276
28	exp humans/	24810701

29	exp human experiment/	293957
30	human.po.	0
31	or/28-30	24812085
32	27 not 31	8333121
33	19 not 32	270
34	remove duplicates from 33	204

2. Literature search via PubMed

Search History

Search	Most Recent Queries	Result
#5	Search #4 AND publisher[sb]	6
#4	Search #1 AND (#2 OR #3)	122
#3	Search ((neuroendocrine[tiab] OR pancreas[tiab] OR pancreatic[tiab] OR gastroenteropancreatic[tiab] or OR gastro-entero-pancreatic[tiab] OR enteropancreatic[tiab] OR islet cell*[tiab]) AND (Neoplasm[tiab] OR neoplasms[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR cancer[tiab] OR cancers[tiab] OR cancerous[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR adenocarcinoma*[tiab] OR carcinoid[tiab] OR carcinoids[tiab] OR metastases[tiab] OR metastasis[tiab] OR metastatic[tiab] OR malignan*[tiab]))	60327
#2	Search Neuroendocrine Tumors[mh] OR Pancreatic Neoplasms[mh] OR insulinoma*[tiab] OR gastrinoma*[tiab] OR PNET[tiab] OR PNETs[tiab] OR	233728

GPNET[tiab] OR GPNETS[tiab] OR NET[tiab] OR NETS[tiab] OR panNET[tiab]

#1 Search Sunitinib[nm] OR Sutent*[tiab] OR Sunitinib*[tiab] OR SU-011248[tiab] OR SU011248[tiab] OR SU-010398[tiab] OR SU010398[tiab] OR PHA-290940AD[tiab] OR PHA290940AD[tiab] OR SU-11248[tiab] OR SU11248[tiab] OR SU-10398[tiab] OR SU10398[tiab] OR 341031-54-7[rn] OR 557795-19-4[rn] 1990

3. Cochrane Central Register of Controlled Trials (Central)

Search for trials. Issue 4 of 4, Oct 2011

Search History

ID	Search	Hits
#1	(Sutent* OR Sunitinib* OR SU-011248 OR SU011248 OR SU-010398 OR SU010398 OR PHA-290940AD OR PHA290940AD OR SU-11248 OR SU11248 OR SU-10398 OR SU10398):ti,ab,kw	92
#2	MeSH descriptor Neuroendocrine Tumors explode all trees	1119
#3	MeSH descriptor Pancreatic Neoplasms explode all trees	660
#4	(insulinoma* OR gastrinoma* OR PNET OR PNETs OR GPNET OR GPNETS OR NET OR NETs OR panNET):ti,ab,kw	2996
#5	((neuroendocrine or pancreas or pancreatic or gastroenteropancreatic or gastro-enteropancreatic or gastro-entero-pancreatic or enteropancreatic or islet cell*) AND (Neoplasm OR neoplasms OR tumour OR tumours OR tumor OR tumors OR cancer OR cancers OR cancerous OR carcinoma OR carcinomas or adenocarcinoma* OR carcinoid OR carcinoids OR metastases OR metastasis OR metastatic OR malignan*)):ti,ab,kw	1340
#6	(#2 OR #3 OR #4 OR #5)	5375
#7	(#1 AND #6)	6

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: (Sutent OR sunitinib) AND (neuroendocrine OR pancreatic)

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: Search terms: (Sutent OR sunitinib) AND (neuroendocrine OR pancreatic)

Conference abstracts:

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

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

Search terms: Search terms: (Sutent OR sunitinib) AND (neuroendocrine OR pancreatic) / last 5 years

REFERENCES

1. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011 Feb 10;364(6):501-13.
2. Supplement to: Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:501-13. [Internet]. 2011. [cited 2011 Nov 14]. Available from: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1003825/suppl_file/nejmoa1003825_appendix.pdf
3. U.S. Food and Drug Administration. FDA briefing document. Oncologic Drugs Advisory Committee Meeting. April 12, 2011. NDA 21938/S013. Sutent® (sunitinib malate). Applicant: Pfizer, Inc. [Internet]. Rockville (MD): FDA; 2011. [cited 2011 Nov 14]. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM250379.pdf>
4. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008 Jun 20;26(18):3063-72.
5. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* [Internet]. 2008 Oct [cited 2012 Jan 23];19(10):1727-33. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2735065>
6. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011 Feb 10;364(6):514-23.
7. pan-Canadian Oncology Drug Review manufacturer submission: Sutent® (sunitinib malate); Company: Pfizer Canada. Pointe-Claire/Dorval (QC): Pfizer Canada; 2011 Nov 7.
8. Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijnen ML, Taal BG. Epidemiology and survival in patients with carcinoid disease in the Netherlands. An epidemiological study with 2391 patients. *Ann Oncol*. 2001 Sep;12(9):1295-300.
9. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003 Feb 15;97(4):934-59.
10. Lepage C, Bouvier AM, Phelip JM, Hatem C, Vernet C, Faivre J. Incidence and management of malignant digestive endocrine tumours in a well defined French population. *Gut* [Internet]. 2004 Apr [cited 2012 Jan 23];53(4):549-53. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1774002>
11. Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. *Cancer*. 2001 Oct 15;92(8):2204-10.
12. Yao JC, Eisner MP, Leary C, Dagohoy C, Phan A, Rashid A, et al. Population-based study of islet cell carcinoma. *Ann Surg Oncol* [Internet]. 2007 Dec [cited 2012 Jan 23];14(12):3492-500. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2077912>

13. Eehalt F, Saeger HD, Schmidt CM, Grutzmann R. Neuroendocrine tumors of the pancreas. *Oncologist*. 2009 May;14(5):456-67.
14. Kazanjian KK, Reber HA, Hines OJ. Resection of pancreatic neuroendocrine tumors: results of 70 cases. *Arch Surg*. 2006 Aug;141(8):765-9.
15. Pape UF, Bohmig M, Berndt U, Tiling N, Wiedenmann B, Plockinger U. Survival and clinical outcome of patients with neuroendocrine tumors of the gastroenteropancreatic tract in a German referral center. *Ann N Y Acad Sci*. 2004 Apr;1014:222-33.
16. Jensen RT, Delle FG. Promising advances in the treatment of malignant pancreatic endocrine tumors. *N Engl J Med*. 2011 Feb 10;364(6):564-5.
17. Yao JC, Hainsworth JD, Wolin EM, Pavel ME, Baudin E, Gross D, et al. Multivariate analysis including biomarkers in the phase III RADIANT-2 study of octreotide LAR plus everolimus (E+O) or placebo (P+O) among patients with advanced neuroendocrine tumors (NET) [Internet]. Abstract presented at: 2012 Gastrointestinal Cancers Symposium. 2012 Jan 19-21; San Francisco, CA. [cited 2012 Feb 8]. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=115&abstractID=88080
18. Singh S, Law C. Multidisciplinary reference centers: the care of neuroendocrine tumors. *J Oncol Pract* [Internet]. 2010 Nov [cited 2012 Jan 23];6(6):e11-e16. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988672>
19. Elias D, Lasser P, Ducreux M, Duvillard P, Ouellet JF, Dromain C, et al. Liver resection (and associated extrahepatic resections) for metastatic well-differentiated endocrine tumors: a 15-year single center prospective study. *Surgery*. 2003 Apr;133(4):375-82.
20. Que FG, Sarmiento JM, Nagorney DM. Hepatic surgery for metastatic gastrointestinal neuroendocrine tumors. *Cancer Control*. 2002 Jan;9(1):67-79.
21. Kulke MH, Siu LL, Tepper JE, Fisher G, Jaffe D, Haller DG, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. *J Clin Oncol*. 2011 Mar 1;29(7):934-43.
22. Oberg KE. Is it time to widen the use of somatostatin analogs in neuroendocrine tumors? *J Clin Oncol*. 2009 Oct 1;27(28):4635-6.
23. Kwekkeboom DJ, De Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008 May 1;26(13):2124-30.
24. Bushnell D. Treatment of metastatic carcinoid tumors with radiolabeled biologic molecules. *J Natl Compr Canc Netw*. 2009 Jul;7(7):760-4.
25. Bushnell DL Jr, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. *J Clin Oncol*. 2010 Apr 1;28(10):1652-9.

26. Eriksson B, Oberg K. Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: future outlook. *Ann Oncol*. 1999;10 Suppl 2:S31-S38.
27. Arnold R, Trautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, et al. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut* [Internet]. 1996 Mar [cited 2012 Jan 23];38(3):430-8. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383075>
28. di Bartolomeo M, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. *Cancer*. 1996 Jan 15;77(2):402-8.
29. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009 Oct 1;27(28):4656-63.
30. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004 Dec 1;22(23):4762-71.
31. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992 Feb 20;326(8):519-23.
32. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG, Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol*. 2005 Aug 1;23(22):4897-904.
33. Eriksson B, Oberg K, Alm G, Karlsson A, Lundqvist G, Andersson T, et al. Treatment of malignant endocrine pancreatic tumours with human leucocyte interferon. *Lancet*. 1986 Dec 6;2(8519):1307-9.
34. Frank M, Klose KJ, Wied M, Ishaque N, Schade-Brittinger C, Arnold R. Combination therapy with octreotide and alpha-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. *Am J Gastroenterol*. 1999 May;94(5):1381-7.
35. Kulke MH, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, et al. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. *Clin Cancer Res* [Internet]. 2009 Jan 1 [cited 2012 Jan 23];15(1):338-45. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100724>
36. Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung SC, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol*. 2008 Mar 10;26(8):1316-23.
37. Lowry R. Concepts & applications of inferential statistics [Internet]. Poughkeepsie (NY): Vassar College; c1998-2012. Appendix to chapter 6: z to P calculator; 2012 [cited 2012 Feb 7]. Available from: <http://faculty.vassar.edu/lowry/ch6apx.html>

38. Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, et al. Cox proportional hazard analysis of sunitinib (SU) efficacy across subgroups of patients (pts) with progressive pancreatic neuroendocrine tumors (NET) [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; 2010 Jun 4-8).
39. Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, et al. Evidence of activity and clinical benefit with sunitinib in patients with pancreatic neuroendocrine tumors (NET) [abstract]. *Ann Oncol*. 2010 Jul;21 Suppl 6:vi13. (Presented at 12th World Congress on Gastrointestinal Cancer, ESMO Conference. Barcelona, Spain; 2010 Jun 30 - Jul 3).
40. Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C. Updated overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) of sunitinib (SU) versus placebo (PBO) for patients (pts) with advanced unresectable pancreatic neuroendocrine tumors (NET) [abstract]. *J Clin Oncol*. 2011;29(15 Suppl):4008.
41. Valle J, Niccoli P, Raoul JL, Bang YJ, Borbath I, Van Cutsem E, et al. Updated overall survival data from a phase III study of sunitinib vs. placebo in patients with advanced, unresectable pancreatic neuroendocrine tumour (NET) [abstract]. *Eur J Cancer*. 2011 Sep;47 Suppl 1:S462. (Presented at 2011 European Multidisciplinary Cancer Congress. Stockholm, Sweden; 2011 Sep 23-27).
42. Valle J, Faivre S, Raoul J, Bang Y, Patyna S, Lu DR, et al. Phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of pancreatic neuroendocrine tumors (NET): impact of somatostatin analogue (SSA) treatment on progression-free survival (PFS) [abstract]. *Ann Oncol*. 2010 Oct;21 Suppl 8:viii264. (Presented at 35th ESMO Congress. Milan, Italy; 2010 Oct 8-12).
43. Vinik A, Bang YJ, Raoul JL, Valle J, Metrakos P, Hrsch D, et al. Sunitinib for treatment of pancreatic neuroendocrine tumors: patient-reported outcomes and efficacy across patient subgroups in a phase III trial [abstract]. *Pancreas*. 2011 Mar;40(2):334-5. (Presented at 3rd Annual Meeting of the North American NeuroEndocrine Tumor Society. Santa Fe, NM; 2010 Oct 29-30).
44. Vinik A, Bang Y, Raoul J, Valle JW, Metrakos P, Hrsch D, et al. Patient-reported outcomes (PROs) in patients (pts) with pancreatic neuroendocrine tumors (NET) receiving sunitinib (SU) in a phase III trial [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; 2010 Jun 4-8).
45. Hammel P, Castellano D, Van Cutsem E, Niccoli P, Faivre S, Patyna S, et al. Evaluation of progression-free survival by blinded independent central review in patients with progressive, well-differentiated pancreatic neuroendocrine tumors treated with sunitinib or placebo [abstract]. *Pancreas*. 2011 Mar;40(2):327. (Presented at 3rd Annual Meeting of the North American NeuroEndocrine Tumor Society. Santa Fe, NM; 2010 Oct 29-30).
46. Van Cutsem E, Dahan L, Patyna S, Klademenos D, Lu DR, Chao R, et al. Evaluation of progression-free survival (PFS) by blinded independent central review (BICR) in patients (pts) with progressive, well-differentiated pancreatic neuroendocrine tumours (NET) treated with sunitinib (SU) or placebo [abstract]. *Ann Oncol*. 2010 Oct;21:viii235. (Presented at 35th ESMO Congress. Milan, Italy; 2010 Oct 8-12).

47. Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, Valle JW, et al. Updated safety and efficacy results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of pancreatic neuroendocrine tumors (NET) [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; 2010 Jun 4-8).
48. European Public Assessment Report (EPAR). Assessment report for Sutent (sunitinib) [Internet]. London: European Medicines Agency; 2010 Oct 21. [cited 2011 Nov 14]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000687/WC500100433.pdf
49. Raoul JL, Niccoli P, Bang YJ, Borbath I, Lombard-Bohas C, Metrakos P, et al. Sunitinib (SU) vs placebo for treatment of progressive, well-differentiated pancreatic islet cell tumours: results of a phase III, randomised, double-blind trial [abstract]. *Eur J Cancer Suppl*. 2009 Sep;7(2-3):361. (Presented at Joint ECCO 15 - 34th ESMO Multidisciplinary Congress. Berlin, Germany; 2009 Sep 20-24).
50. Raymond E, Raoul J, Niccoli P, Bang Y, Borbath I, Lombard-Bohas C, et al. Phase III, randomized, double-blind trial of sunitinib versus placebo in patients with progressive, well-differentiated pancreatic islet cell tumours [abstract]. *Ann Oncol*. 2009;20(Suppl 7):vii11.
51. Raymond E, Harmon C, Niccoli P, Metrakos P, Borbath I, Bang Y, et al. Impact of baseline Ki-67 index and other baseline characteristics on outcome in a study of sunitinib (SU) for the treatment of advanced, progressive pancreatic neuroendocrine tumor (NET) [abstract]. *Neuroendocrinology*. 2011 Nov;94 Suppl 1:41. (Presented at 8th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease. Lisbon, Portugal; 2011 Mar 9-11).
52. Ishak J, Valle J, Van Cutsem E, Lombard-Bohas C, Ruszniewski P, Sandin R, et al. Overall survival (OS) analysis of sunitinib (SU) after adjustment for crossover (CO) in patients with pancreatic neuroendocrine tumors (NET) [abstract]. *Neuroendocrinology*. 2011 Nov;94 Suppl 1:27-8. (Presented at 8th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease. Lisbon, Portugal; 2011 Mar 9-11).
53. Strosberg J, Campos T, Kvols L. Phase II study of sunitinib following hepatic artery embolization for metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [abstract]. *Pancreas*. 2010 Mar;39(2):280-1. (Presented at 2nd Annual Meeting of the North American NeuroEndocrine Tumor Society. Charlotte, NC; 2009 Oct 2-3).
54. Barriuso J, Grande E, Quinds VM, Sereno M, Lopez C, Sepulveda J, et al. Sunitinib efficacy and tolerability in patients with neuroendocrine tumors out of a trial: a Spanish multicenter cohort [abstract]. *Ann Oncol*. 2010 Oct;21 Suppl 8:viii264. (Presented at 35th ESMO Congress. Milan, Italy; 2010 Oct 8-12).
55. Strosberg J, Campos T, Kvols L. Phase II study of sunitinib malate following hepatic artery embolization for metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [abstract]. *Neuroendocrinology*. 2009 Jul;90(1):136. (Presented at 6th Annual ENETS Conference. Granada, Spain; 2009 Mar 5-7).
56. Kulke MH, Lenz HJ, Meropol NJ, Posey J, Ryan DP, Picus J, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol* [Internet]. 2008 Jul 10 [cited 2011 Oct 26];26(20):3403-10. Available from: <http://jco.ascopubs.org/content/26/20/3403.full>

57. Britten CD, Kabbinavar F, Hecht JR, Bello CL, Li J, Baum C, et al. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. *Cancer Chemother Pharmacol*. 2008 Mar;61(3):515-24.
58. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Sutent (sunitinib malate) capsules. Company: Pfizer, Inc. Application no.: 021938 & 021968. Approval Date: 01/26/2006. Rockville (MD): The Center; 2006 [cited 2011 Nov 14]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021938s000_021968s000_Sutant.cfm.
59. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Sutent (sunitinib malate) capsules. Company: Pfizer, Inc. Application no.: 021938 & 021968. Approval date: 01/26/2006. Rockville (MD): The Center; 2006 [cited 2011 Nov 14]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021938s000_021968s000_Sutant.cfm.
60. O'Reilly EM, Niedzwiecki D, Hall M, Hollis D, Bekaii-Saab T, Pluard T, et al. A Cancer and Leukemia Group B phase II study of sunitinib malate in patients with previously treated metastatic pancreatic adenocarcinoma (CALGB 80603). *Oncologist*. 2010;15(12):1310-9.
61. Girling DJ, Stewart LA, Parmar MKB, Stenning SP. *Clinical trials in cancer: principles and practice*. Oxford (UK): Oxford University Press; 2003.
62. 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.