pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Everolimus (Afinitor) for Pancreatic Neuroendocrine Tumours

August 30, 2012

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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

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1 GUIDANCE IN BRIEF

1.1 Background

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

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The systematic review included one double-blind randomized controlled trial of patients with unresectable locally advanced or metastatic well- or moderately differentiated pancreatic neuroendocrine tumour that had progressed within the last 12 months. Trial RADIANT-3 (N=410) evaluated the efficacy and safety of everolimus 10 mg daily (n=207) as compared to placebo (n=203); both groups received best supportive care.[1]

The primary endpoint of RADIANT-3 was progression-free survival. Everolimus was associated with a statistically significant increase in progression-free survival (11 months) compared to placebo (4.6 months); hazard ratio 0.35 (95% CI: 0.27, 0.45). Secondary outcomes included overall survival, response rate, duration of response and safety. Quality of life was not measured.

Overall survival did not statistically significantly differ between everolimus and placebo at the time of the first interim data analysis (February 2010); the associated hazard ratio was 1.05 (95% CI: 0.71, 1.55) and median survival was not reached in either treatment group. At the time of the second interim analysis (February 2011), median overall survival in the placebo group was 36.6 months and was not reached in the everolimus group. Estimates of overall survival are likely confounded by the crossover of placebo patients after disease progression, to open-label everolimus.

Adverse events commonly seen in the trial (occurring >15% in either group) and with a higher frequency in the everolimus group compared to placebo, included stomatitis, rash, diarrhea, fatigue, peripheral oedema and nausea. Grade 3 and 4 anemia, hyperglycemia, diarrhea and stomatitis were more frequent in the everolimus group compared to placebo. A total of 19% (39/204) of everolimus patients and 6% (12/203) of placebo patients discontinued due to adverse events.

1.2.2 Additional Evidence

pCODR received input on everolimus for pNETs from one patient advocacy group, Carcinoid-Neuroendocrine Tumour Society Canada (CNETS Canada). Provincial Advisory Group input was obtained from five of the nine provinces participating in pCODR.

1.2.3 Interpretation and Guidance

- Pancreatic neuroendocrine tumors are rare neoplasms with an estimated incidence of 1-4 cases per 100,000. Some patients are candidates for potentially curative surgery but the vast majority are managed with palliative intent due to the locally advanced or metastatic nature of their disease. Historically there have been limited systemic therapeutic options available for patients with incurable pNETs. Sunitinib recently received regulatory approval for use in patients with pNETs.
- RADIANT-3 evaluated everolimus compared to placebo and resulted in a statistically significant and clinically relevant prolongation of PFS compared to placebo. The PFS results were consistent across all predefined subgroups which increases the Clinical Guidance Panel's confidence in the observed treatment effect. Overall survival results are immature but demonstrate no statistically significant difference between the two arms at the present time.
- More grade three and four adverse events were observed on the everolimus treatment arm as compared to the placebo treatment arm (47.5% versus 31.5% and 12.3% versus 7.4% respectively). This observation is similar to those from randomized controlled trials examining the role of everolimus in other disease sites such as renal and breast carcinoma and is also consistent with the observed adverse event profile for everolimus in routine oncologic practice.

1.3 Conclusions

The pCODR Gastrointestinal Clinical Guidance Panel concluded that there is a net overall clinical benefit to everolimus in the treatment of progressing locally advanced or metastatic pNETs on the basis of one high-quality randomized placebo-controlled trial that demonstrated a clinically and statistically significant benefit in progression free survival for everolimus compared to placebo.

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

- There are more adverse events arising on everolimus compared to placebo, however, the observed adverse event profile of everolimus in RADIANT-3 appears consistent with the use of everolimus for other indications.
- An assessment of the impact of everolimus on patient quality of life was not possible as it was not formally assessed in the trial, consistent with many other randomized controlled trials in oncology.
- There is no evidence available to support an optimal sequencing of everolimus and sunitinib (also approved by Health Canada for pNETs and the subject of a previous pCODR Clinical Guidance Report). Individual treatment decisions regarding choice of everolimus or sunitinib as systemic therapy for patients with progressive, metastatic pNETs will be individualized in the context of medical comorbidities, potentially predicting preferential tolerance and toxicity avoidance of one therapy over the other.

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 everolimus (Afinitor) for pancreatic neuroendocrine tumours. 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 everolimus (Afinitor) for pancreatic NETs conducted by the pCODR Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Everolimus is approved by Health Canada for the treatment of well- or moderately differentiated neuroendocrine tumours of pancreatic origin (PNETs) in patients with unresectable, locally advanced or metastatic disease that has progressed within the last 12 months. The product monograph reported that the approval of everolimus for PNETs was based on demonstrated progression-free survival (PFS) benefit in a phase III placebo-controlled study in patients with documented progressive disease. The recommended dose is 10 mg administered orally once daily.

Health Canada also approved the use of everolimus for the treatment of subepedymal giant cell astrocytoma and metastatic renal cell carcinoma.

2.1.2 Objectives and Scope of pCODR Review

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

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 systematic review included one double-blind randomized controlled trial of patients with unresectable locally advanced or metastatic well- or moderately differentiated pancreatic neuroendocrine tumour that had progressed within the last 12 months. Trial RADIANT-3 (N=410) evaluated the efficacy and safety of everolimus 10 mg daily (n=207) as compared to placebo (n=203); both groups received best supportive care.[1] The trial does not have a termination date and is still ongoing at the time of writing this report. Treatment with everolimus is to be continued until disease progression or until the occurrence of unacceptable adverse events. Analyses of the trial outcomes were based on data collected on February 28, 2010.[2] However at this date, the number of death events did not reach 250 events; the statistical plan estimated that this number is necessary to achieve at least 80% power to demonstrate a 30% risk reduction of the overall survival (OS) estimate.[2] Therefore, interim analyses of the OS was based on data collected on February 28, 2010 and February 23, 2011. The final OS analysis will be conducted when a total of 250 death events is reached.

Included patients in RADIANT-3 had a mean age of 56.7 years and were equally distributed between males and females. The majority of patients had WHO performance score of 0 (66%), followed by score 1 (31%) and a minority of patients (3%) had score 2. Tumours were present in three or more organs in 36% of patients, and 92% of patients had hepatic metastases. Before being enrolled in the trial, 50% of included patients had received chemotherapy and 21% of them had received radiotherapy. Randomization and analysis were stratified by prior use of chemotherapy and baseline WHO performance score.

As per the data collected until February 2010, the overall survival did not statistically significantly differ between everolimus and placebo; the associated hazard ratio was 1.05 (95% CI: 0.71, 1.55). The median survival was not reached in either group at the time of the first interim analysis (February 2010), and it was reached only for the placebo group at the second interim analysis (February 2011); the median overall survival was 36.6 months among patients assigned to the placebo group. Estimates of overall survival might be confounded by the crossover of placebo patients, after disease progression, to open-label everolimus. Another confounding factor is the subsequent use of antineoplastic therapies after discontinuation of trial medication.

Everolimus was associated with a statistically significant increase in progression-free survival (11 months) compared to placebo (4.6 months); hazard ratio 0.35 (95% CI: 0.27, 0.45). Everolimus was associated with a consistent improvement of the progression-free survival across the randomization strata (WHO performance scores 0 vs. 1 or 2, and prior use of chemotherapy). RADIANT-3 did not evaluate the effect of everolimus on quality of life.

Adverse events commonly seen in the trial (occurring >15% in either group) included stomatitis, rash, diarrhea, fatigue, peripheral oedema and nausea, with a higher frequency in the everolimus group compared to placebo. Grade 3 and 4 anemia, hyperglycemia, diarrhea and stomatitis were more frequent in the everolimus group compared to placebo. A total of 19% (39/204) of everolimus patients and 6% (12/203) of placebo patients discontinued due to adverse events.[3] Adverse events leading to discontinuation of everolimus therapy included pneumonitis, pyrexia, interstitial lung disease, fatigue, and pneumonia.

Detailed information about dose interruption due to adverse events was not reported for trial RADIANT-3. There is no evidence on the effectiveness of everolimus at lower doses than the recommended 10 mg.

2.1.4 Comparison with Other Literature

One additional trial was assessed for inclusion in the review of everolimus for pancreatic NETs but was excluded on the basis of its population. RADIANT-2 included patients with low- or intermediate advanced (unresectable locally advanced or distant metastasis) neuroendocrine tumours and disease progression within the last 12 months.[4] Of the 429 randomized patients, only 26 (6%) patients had neuroendocrine tumour of pancreatic origin. Patients were randomized to receive everolimus 10 mg daily or placebo, both in conjunction with intramuscular injection of 30 mg octreotide LAR once every 28 days. For all patients, everolimus plus octreotide LAR was associated with a median progression-free survival (as reviewed by the local investigators) of 12 months compared to 8.6 months survival associated with placebo plus octreotide LAR; the hazard ratio was 0.78 (95% CI: 0.62, 0.98). It was deemed inappropriate to include RADIANT-2 in the current review because it did not stratify inclusion or analysis by the primary site of tumour, and because of the limited number of patients with pancreatic NETs.

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 drug approval was based on results obtained form an international multicentre double-blind randomized controlled trial (Study A6181111).[5] Study A6181111 compared the efficacy and safety of sunitinib 37.5 mg administered daily (n=86) to placebo (n=85). 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); a post-hoc analysis of the data indicated the test statistic did not cross the efficacy boundary.

There are no randomized clinical trials directly comparing sunitinib and everolimus or evaluating combination or sequential therapy with these two drugs. However, Signorovitch et al.[6] published an indirect comparison of the overall survival between sunitinib and everolimus when used for pancreatic NETs. The comparison used data from RADIANT-3 trial of everolimus and trial A6181111 of sunitinib.[5] The analyses were adjusted for cross-trial differences; exclusion criteria, baseline demographics, performance status, time since diagnosis, disease sites, distant metastases and prior therapy.[6] The comparison reported that there was no statistically significant difference between everolimus and sunitinib in the overall survival (indirect difference, everolimus vs. sunitinib, in hazard ratio for death = 0.81, 95% CI: 0.49, 1.31) or in progression-free survival (hazard ratio for progression = 0.84, 95% CI: 0.46, 1.53).

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 everolimus from one patient advocacy group, Carcinoid-Neuroendocrine Tumour Society Canada (CNETS Canada). From a patient perspective, stabilization of 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 also expressed their ability to tolerate certain side effects if this means disease stabilization.

PAG Input

Input on the everolimus review was obtained from five of the nine provinces (Ministries of Health and/or cancer agencies) participating on pCODR. From a PAG perspective, it was noted that sunitinib also has Health Canada approval for the treatment of advanced pancreatic NETs 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

It was noted that there are no randomized controlled trials supporting either the understanding of the best sequential use of sunitinib and everolimus in pNETs or the use of everolimus as adjuvant therapy of pNETs.

2.2 Interpretation and Guidance

Burden of Illness and therapeutic options for locally advanced and metastatic pNETs

Pancreatic neuroendocrine tumors are rare neoplasms with an estimated incidence of 1-4 cases per 100,000. Some patients are candidates for potentially curative surgery but the vast majority are managed with palliative intent due to the locally advanced or metastatic nature of their disease.

A minority of cases are associated with functional clinical syndromes due to the secretion of a variety of neuroendocrine peptides (e.g. insulin, glucagon etc). Most pNETs are non-functional, resulting in symptoms due to tumor bulk and/or distant organ involvement (e.g liver) or in disease that is asymptomatic. The natural history of pNETs differs from other types of malignancies in that the majority of cases are of well differentiated histology with median survival times for those with metastatic disease extending into multiple years due to the generally indolent pace of disease progression. Unfortunately, all patients will eventually develop symptoms and die due to progressive metastatic disease.

Historically there have been limited systemic therapeutic options available for patients with incurable pNETs. Streptozocin-based chemotherapy (coupled with either 5-FU or adriamycin) is approved by Health Canada for this indication based on small, generally non-randomized trials, but is no longer readily available in this country. Other therapeutic modalities have included hepatic-directed therapies (radiofrequency ablation, surgical debulking, bland/chemo embolization) which are employed on a case by case basis with evidence limited to case series or single institutional, non-randomized trials. Peptide Receptor Radio Nucleotide Therapy (e.g. Leutetium 177/Yttrium 90/radiolabelled MIBG) has limited availablilty in Canada (Edmonton, London, Halifax) and is restricted to the minority of patients with tumors that actively take up the peptide (e.g. somatostatin or MIBG). As well, evidence from randomized trials testing optimal radioisotope-based therapies against placebo or other systemic options does not exist.

RADIANT-3: Everolimus vs Placebo in moderately or well differentiated pNETs

The RADIANT-3 trial examined everolimus, an inhibitor of the mammalian target of rapamycin (mTOR) compared to placebo, in a large phase 3 trial of 410 patients with progressive pNETs (207 in everolimus arm vs 203 in placebo arm) with a primary endpoint of progression-free survival (PFS) and secondary endpoints of objective response rate, duration of response, overall survival (OS) and safety. There was no planned interim analysis in this event-driven trial and the primary endpoint was met with a median PFS of 11 months in the everolimus arm (95% CI 8.4-13.9 months) versus 4.6 months (95% CI 3.1-5.4 months) in the placebo arm ($p<0.001$). The PFS results were consistent across all predefined subgroups which increases the Panel's confidence in the observed treatment effect.

The objective tumor response rates were low in both arms (everolimus 4.8%; 95% CI 2.3%-8.7% vs placebo 2%; 95% CI 0.5%-5%), suggesting that the predominant effect of everolimus was one of disease stabilization.

Overall survival data is not mature at this point with 146 deaths observed (approximately 250 required for data maturity) and the median overall survival on the everolimus arm not having been reached as of February 2011. Upon disease progression, patients could be unblinded and offered the option of switching to everolimus if they were on the placebo arm. A total of 148

of the 203 patients on the placebo arm (72.9%) crossed over, which will confound subsequent efforts at determining the impact of everolimus on overall survival.

More grade III and IV adverse events were observed on the everolimus treatment arm as compared to the placebo treatment arm (47.5% vs 31.5% and 12.3% vs 7.4% respectively). This observation is similar to those from randomized trials examining the role of everolimus in other disease sites such as renal and breast carcinoma and is also consistent with the observed adverse event profile for everolimus in routine oncologic practice. Twelve patients died on or within 28 days of stopping everolimus versus 4 patients dying over this interval in the placebo arm. 19% of patients on everolimus discontinued treatment due to adverse events versus 6% of placebo patients. Mean treatment duration for everolimus was 40.9 weeks versus 25.4 weeks for placebo. Similar to many oncology trials, formal assessment of quality of life was not performed due to the lack of a validated disease-specific assessment tool and in the context of other methodologic difficulties in accurately assessing quality of life on oncology clinical trials.

In this placebo-controlled randomized clinical trial for patients with locally advanced or metastatic pNETs, everolimus was observed to result in a statistically significant and clinically relevant prolongation of PFS compared to placebo. More serious adverse events and deaths on therapy were observed on the everolimus arm. OS results are immature but demonstrate no significant difference between the two arms at the present time.

2.3 Conclusions

The pCODR Gastrointestinal Clinical Guidance Panel concluded that there is a net overall clinical benefit to everolimus in the treatment of progressing locally advanced or metastatic pNETs on the basis of one high-quality randomized placebo-controlled trial that demonstrated a clinically and statistically significant benefit in progression free survival for everolimus compared to placebo.

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

- There are more adverse events arising on everolimus compared to placebo, however, the observed adverse event profile of everolimus in RADIANT-3 appears consistent with the use of everolimus for other indications.
- An assessment of the impact of everolimus on patient quality of life was not possible as it was not formally assessed in the trial, consistent with many other randomized controlled trials in oncology.
- There is no evidence available to support an optimal sequencing of everolimus and sunitinib (also approved by Health Canada for pNETs and the subject of a previous pCODR Clinical Guidance Report). Individual treatment decisions regarding choice of everolimus or sunitinib as systemic therapy for patients with progressive, metastatic pNETs will be individualized in the context of medical comorbidities, potentially predicting preferential tolerance and toxicity avoidance of one therapy over the other.

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 (GI) NETs are a group of neoplasms arising from the neuroendocrine cells of the gastrointestinal system. The annual incidence of these tumours has been estimated to be between 1 to 4 per 100,000 but appears to have been increasing over the last three to four decades.[7-10] Although relatively 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.[11]

Pancreatic NETs (pNETs) are a subset of GINETs arising from neuroendocrine cells of the pancreas and comprise 1-4% of all pancreatic neoplasms.[9,11-13] The incidence of this NET subset is estimated to be 0.2 per 100,000 but also appears to be increasing in recent decades.[11-13]

Most pNETs occur sporadically, but there are genetic syndromes linked to increased hereditary risk including; Multiple Endocrine Neoplasia type 1, von Hippel Lindau disease, neurofibromatosis 1 and tuberous sclerosis.[14]

NET cells are characterized by the presence of cytoplasmic vesicles that contain a number of functionally active peptides. These peptides can be released into the systemic circulation and pNETs are generally classified as either functional or non-functional, depending on whether the tumor secretes one or more of these peptides. The majority of pNETs (68 – 90%) are non-functional, and asymptomatic, and are often discovered incidentally as a result of imaging or other procedures performed to evaluate other symptoms or disease processes.[13,15-17] Nonfunctional tumours may cause symptoms due to tumor progression and bulk symptomatologies as well as impact on surrounding structures. Ultimately the development or progression of metastatic disease, most commonly to the liver, results in progressive illness, deterioration in quality of life and death.

Functional pNETs secrete excess quantities of functionally active peptides such as insulin, gastrin and glucagon among others. These secretory or functional tumors result in recognizable clinical syndromes (e.g. refractory peptic ulcer disease, episodic hypoglycaemia, profuse watery diarrhea) that are often misdiagnosed as being due to benign causes early in the clinical course of the disease. Not all peptide secreting tumours cause symptoms and those that are unassociated with clinical syndromes are usually conceived as clinically non-functional.

Unfortunately the majority of patients with pNETs present with metastatic (60%) or locally advanced (20%) disease[1,13] and are treated with non-curative intent with the goal of disease stabilization, prolongation of progression-free survival and improvement or stabilization of quality of life. The median overall survival for patients with metastatic pNETs is 24 to 28 months[1,11,13,18] and 60- 65% of those with advanced disease will die within five years of diagnosis.[13,14,19] Survival correlates with disease stage at presentation with those with early stage disease enjoying better survival times than those with locally advanced or metastatic disease.[13] A number of pathologic variables are utilized to define stage of disease which has

independent prognostic relevance for NETs. These include degree of differentiation (well vs poorly differentiated) as well as tumor grade which is highly dependent on the degree of proliferation within the tumor. Proliferation is commonly assessed by an assessment of mitotic count (per 10 high-powered fields) or with a Ki-67 index which is an immunohistochemical test utilizing an antibody to Mib-1 that assesses the % of cells within a sample of 2000 cells that take up the stain and therefore are actively proliferating.[11] Other prognostic markers include elevated levels of chromogranin A, a common biomarker in NETs.[20]

This review will focus primarily on well-differentiated pNETs which comprise roughly 85-90% of the pNETs patient population.

3.2 Accepted Clinical Practice

Optimal clinical management for patients with pNETs involves a multidisciplinary approach to diagnosis and treatment.[21] Surgery is the only potentially curative therapy for patients presenting with early stage disease.[11] 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 low to moderate volume liver metastases can provide effective palliation lasting months to years.[22,23] If surgical debulking is not feasible, local ablative procedures (e.g. bland embolization, chemoembolization, radiofrequency ablation), can also provide effective symptom control and reduce tumour burden.[24] Registry data suggest that these therapies may have an impact on overall survival, but there are no controlled trials evaluating the impact of debulking surgery or ablative procedures on survival. Most published data describes single institutional experiences, often comparing outcomes to historic controls, and therefore lack the rigor of clinical trial analytic frameworks and methodologies.[24]

Peptide Receptor Radio Nucleotide Therapy (PRRT) is a form of systemic therapy that capitalizes on the fact that the majority of NETs express somatostatin or other peptide receptors such as metaiodobenzylguanidine (MIBG).[25] Somatostatin analogues tagged with radionucleotides (radiation source) and administered intravenously, result in the systemic delivery of radiation preferentially to sites of disease due to binding of the therapeutic agent to the target tissue. Data supporting PRRT comes from European single institutional phase I and II studies which often accrued patients with very late stage disease.[26-28] Patients with pNETs have been included in these studies although none have examined PRRT in pNETs 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 the management of pNETs.[29] PRRT is costly, usually requires repeated hospitalization for administration (typically every 2-4 months) and is only available in 3 centers in Canada (Edmonton and London; somatostatin based PRRT or Halifax; MIBG based PRRT) and is, therefore, not easily accessible for the majority of the Canadian pNETs patient population. As well, eligibility criteria requires patients to have disease which actively takes up the peptide in question, either somatostatin or MIBG. Many patients will have non-avid disease and therefore are not candidates for PRRT.

Somatostatin analogues (Octreotide, Lanreotide) are effective in managing symptoms and improving quality of life for the majority of patients with functional neuroendocrine disease.[25,30] Data from older clinical series suggest that tumour shrinkage is observed in approximately 5-8% of NET patients treated with somatostatin analogues.[31,32] 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).[33] There is no direct evidence that somatostatin analogues have an anti-proliferative effect in pNETs. 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 pNETs. Streptozocin combined with 5-fluorouracil or adriamycin is approved for the treatment of patients with advanced pNETs based upon small trials published between 1980 and 2004 which were conducted prior to the development of current response assessment guidelines and criteria (e.g RECIST criteria).[34,35] More recent publications challenge the results of earlier trials and raise questions about the utility of these chemotherapy protocols in this patient population.[36] Streptozocin is challenging for most patients due to treatment associated toxicities and many patients with advanced pNETs 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 pharmacists), require patients to travel to treatment centers and may be associated with significant quality of life impacts while on treatment. Streptozocin is currently only available in Canada through a special access program.

Alpha-interferon alone, or in combination with somatostatin analogues, provides symptom control for a minority of patients with advanced, functional midgut (non-pancreatic) NETs and has been associated with stabilization and/or partial regression in 10-15% of patients in some series.[37,38] Interferon is associated with many side effects and is rarely used in Canada for the treatment of this disease and has never been examined specifically for pNETs.[39]

Chemotherapy and biotherapy in the treatment of neuroendocrine tumours

Most patients with high grade, poorly-differentiated NETs (not the subject of this review) benefit from cis-platinum based chemotherapy protocols with high tumor 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 the natural history and clinical behaviour of the disease.

Small non-randomized trials published since 2006 have evaluated a number of newer systemic therapies for advanced pNETs including temozolamide, either as a single agent or with capecitabine, thalidomide, and bevacizumab in combination with other agents.[40-42] A number of ongoing trials will continue to evaluate these therapeutic options as well as others but, at the time of writing, none of these are approved by Health Canada or provincially funded for this indication.

Two randomized phase III placebo-controlled trials have examined novel targeted agents for patients with progressive, metastatic, well or moderately to well differentiated pNETs. 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 and the subject of this submission.[1,19] Both agents are oral, daily dosed medications with generally favourable toxicity profiles compared to typical systemic chemotherapy. Both studies restricted eligibility to those patients with clinically or radiographically progressive disease within 12 months of study entry. This criteria ensured that all subjects had evidence of progressive disease which is an important consideration for a disease which can behave in an indolent fashion and remain stable for periods of time even without specific therapy. Both

patient populations included pre-treated as well as chemotherapy naive patients. These two trials observed similar results with a prolongation in progression –free survival (PFS) of approximately six months favouring the treatment arm. 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.

The current phase III trial under review builds on a phase II trial examining the role of everolimus in progressive, advanced pNETs. This open-label non-randomized phase II trial of daily everolimus observed a 9.6% partial response rate. a 67.8% disease stability rate and a median PFS of 9.7 months for those only on everolimsu (stratum 1) and a 4.4% response rate, an 80% disease stability rate and a median PFS of 16.7 months for those on everolimus and continuing on octreotide LAR (stratum 2).[43]

3.3 Evidence-Based Considerations for a Funding Population

Based upon the available data from a single randomized controlled trial, there now exists Level 1 evidence that patients with advanced pNETs with evidence of progressive disease and Eastern Co-operative Oncology Group performance status score of 0, or 2 could be appropriate candidates for treatment with everolimus. 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 benefit. As well, previous or concomitant treatment with somatostatin analogues would not exclude patients from therapy with everolimus. Therapeutic goals would be prolongation of progression free survival for those with progressive metastatic disease.

Given that these cancers are uncommon, the number of Canadian patients who would potentially receive this treatment is small. Because 80% of patients diagnosed with pNETs have locally advanced or metastatic disease at the time of diagnosis,[1,13] and that most patients with localized disease treated with curative intent surgery remain at risk for systemic recurrence, most patients diagnosed with pancreatic NETs would be potential candidates for treatment with everolimus at some point along their disease course.

At the present time there is no established role for adjuvant systemic treatment of pNETs for patients treated with curative intent surgery and the current study under review did not examine this question.

3.4 Other Patient Populations in Whom the Drug May Be Used

A large phase III trial assessing the potential benefit of everolimus in NETs of non-pancreatic origin has been completed and reported with results suggesting a clinical benefit in extra-pancreatic NET subtypes.[44] The primary endpoint however (PFS by central radiologic review) did not reach statistical significance and a second trial of everolimus versus placebo for non-functional, non-pancreatic NETs (RADIANT-4) is currently undergoing global activation.

Most NETs are gastroenterohepatic in origin however these diseases can also arise in lung, thymus, thyroid (medullary thyroid cancer) and skin (Merkel's cell carcinoma) as well as

presenting as pheochromocytomas and paragangliomas 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 currently enrolling patients or are in planning stages. The similarities shared by NETs arising from different anatomic sites suggest that patients with advanced well or moderately to well differentiated NETs, regardless of site of origin, could benefit from targeted therapies. Definitive data derived from clinical trials in these other NET patient populations will be challenging given the rarity of these tumours.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on everolimus (Afinitor) for pancreatic neuroendocrine tumors (pNETs) and their input is summarized below: Carcinoid-NeuroEndocrine Tumor Society Canada (CNETS Canada)

CNETS Canada conducted a qualitative study using responses obtained through telephone and email responders to gather information about the patient and caregiver experience with the medical condition and drug under review. Response was solicited via a bilingual 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 pNETs, which will lead to an extended life expectancy, is an important aspect when consideration is given to treatment. Patients are also looking for treatments that would shrink the tumor as well as preventing the further spread of the cancer to other areas of the body. Although there are side effects associated with everolimus therapy, patients indicated that they are willing to tolerate certain side effects if this means that they will benefit from the treatment. 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 pNETs.

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 neuroendocrine tumor (pNETs)

Patients with functional pNETs may experience a number of different symptoms, which are often dependent upon the hormone most strongly secreted by their particular neuroendocrine tumor. For many of these patients, the symptoms of the pNETs have a severe impact on their day-to-day living, from the anorexia and fatigue experienced by patients with glucagonoma to the continuous diarrhea experienced by patients with VIPoma. Patients with nonsecretory or nonfunctional pNETs may not experience any symptoms or may experience symptoms that do not cause a clinical syndrome.

Due to the non-specific nature of the symptoms that pNETs 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 thought that “it is all in [their] minds”. It was also noted that many hospitals do not have the appropriate diagnostic tests, which can further lead to problems with a proper diagnosis of pNETs.

Many patients with pNETs 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. Due to the heterogeneous nature of pNETs and the variety of responses to treatments, it was noted that patients with pNETs would be ideal candidates for personalized medicine.

Even though patients with pNETs would like to be able to continue to work, the severe symptoms of the disease can preclude them from doing so. For patients who are unable to continue to work, there can be financial implications, such as not being able to afford medications or travel to receive treatments.

Input from patients indicated that surgery to remove part of the pancreas is a critical treatment to help minimize the size and impact of tumors, which have a tendency to metastasize or cause blockages. It was noted that reducing and minimizing the growth of metastases to the liver and other locations is very important to these patients.

Due to the recent advances in targeted and systemic therapies, it was noted that patients with pNETs are enjoying a better quality of life and have a greater life expectancy than before. However, patients still encounter limitations, such as the need to monitor medications carefully, pay for treatments not covered, and having to act as their own advocate.

4.1.2 Patients' Experiences with Current Therapy for pancreatic neuroendocrine tumor (pNETs)

pNETs are not currently considered curable, except for very rare cases where smaller tumors can be completely removed through surgery. Current treatments for pNETs include surgery, embolization, chemotherapy, radiofrequency ablation, biotherapy and nuclear medicine. It was noted that surgery, nuclear medicine, and somatostatin analogues can extend and improve the quality of life for patients for many years. These treatments are effective, especially in earlier stages of the disease or in cases where the tumors are less aggressive. It was noted that IV chemotherapy may be helpful in aggressive cases of pNETs.

Patient input indicated that there is a high tolerance for side effects from treatment if there is a possibility that patients will benefit from the treatment, even if only for a short-time period. However, it was also noted that tolerance for side effects is a subjective area and each patient may have a different response.

It was noted that treatment with everolimus can stabilize tumor growth and therefore, extend life expectancy. Patient input indicated that stable disease is welcomed by patients.

Some patients are not able to access all the available treatment options in their community, which may be due to a lack of knowledge that such resources exist.

4.1.3 Impact of pancreatic neuroendocrine tumor (pNETs) 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 patient. As a result, the caregiver's routine and lifestyle can be affected. Being a caregiver can be a challenging role and some report being overstressed.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Everolimus

Input from patients without direct experience with everolimus highlighted that patients with pNETs are seeking drug therapies which would help to stabilize their condition. Treatments which result in tumor shrinkage and treatments which lead to an improvement in a patient's quality of life would be considered an additional benefit. It was noted that there is currently an unmet need for these patients that everolimus would help to alleviate. Overall, patients deem that the benefits of therapy outweigh the risks for patients who are able to achieve stable disease. Patients indicated that risks such as blisters on the hands and feet, mouth sores, rashes, fatigue, and elevated creatinine clearance, would all be preferable to death from the cancer.

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 to be a benefit of treatment as well.

Patients with direct experience with everolimus indicated that it has controlled tumor growth better than existing therapies. They point out that everolimus can extend the life of a patient with pNETs and in some cases, the survival advantage can be significant. In addition, patients state that everolimus is easier to tolerate compared to other conventional chemotherapy for the treatment of pNETs and patients can remain at home while receiving this treatment.

Patient input indicated that there can be a wide range of side effects with everolimus, from one patient who experienced no side effects at all to another patient who could not tolerate the medication due to side effects. Some of the side effects experienced by patients with direct experience included mouth sores, shortness of breath, constipation, rash, brittle/thin fingernails, low blood count, and a rising creatinine level.

Many patients having direct experience with everolimus reported that their tumors were stable while on the medication and some patients even reported that there was a reduction in their tumor size.

4.3 Additional Information

CNETS Canada indicated that locating patient members in the community has been a challenge as the community of patients with pNETs is not large. CNETS Canada also highlighted that the above questions require a subjective response but are very clear.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for everolimus (Afinitor) for advanced pancreatic neuroendocrine tumor (pNETs). 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 everolimus (Afinitor) review was obtained from five of the nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, it was noted that sunitinib also has Health Canada approval for the treatment of advanced PNETs 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 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 pNETs. Everolimus 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 (SAP) at a substantial cost. Since access to streptozocin requires authorization through SAP, having an alternative option for treatment, such as everolimus, would be favourable to jurisdictions.

PAG noted that another agent, sunitinib, has Health Canada approval for the same 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.

PAG also identified that there would likely be little, if any, impact on the use of somatostatin analogues in these patients.

5.2 Factors Related to Patient Population

As advanced pNETs affects a relatively small patient population, PAG recognized that there may only be a small number of patients accessing everolimus for this indication when considering budget impact, which may be an enabler for jurisdictions if implementing a funding recommendation.

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

As sunitinib is currently approved by Health Canada for a very similar 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 jurisdictions 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 advanced pNETs.

5.3 Factors Related to Accessibility

PAG recognized that everolimus 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 everolimus is available in two different strengths, a 5mg and 10mg tablet, and the price of each tablet is the same. As a result, it was noted that any dose reductions from 10mg to 5mg would not result in a cost reduction to the jurisdictions. Furthermore, PAG also noted that the 10mg tablets are not scored and should not be broken in half to accommodate dosage reductions. Therefore, there may be drug wastage if a patient who still has a supply of 10mg tablets has their dose reduced from 10mg down to 5mg.

PAG also noted that the standard recommended dose of everolimus is 10mg once daily. This may potentially help increase patient compliance as patients would only be required to take one tablet daily.

5.5 Factors Related to Implementation Costs

PAG noted that everolimus 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 everolimus administration, it was noted that there would still be costs for physician visits, pharmacy dispensing and toxicity monitoring.

PAG also recognized that sunitinib is 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 everolimus (Afinitor) on patient outcomes (listed in **Table 1**) compared to standard therapies or placebo when used for the treatment of well- or moderately differentiated neuroendocrine tumours of pancreatic origin (PNETs) in patients with unresectable, locally advanced or metastatic disease that has progressed within the last 12 months.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs	Patients with unresectable, locally advanced or metastatic, well- or moderately differentiated pancreatic neuroendocrine tumours, whose disease has progressed within the last 12 months	Everolimus (Afinitor) 10 mg orally once daily	Placebo **Biologically targeted therapies:** Tyrosine kinase inhibitor (Sunitinib) **Cytotoxic chemotherapy** Streptozocin** **Somatostatin analogues** Peptide receptor radionuclide therapy (PRRT)†	**Overall survival** Progression-free survival Tumour response **Quality of Life** Symptoms associated with functional pancreatic neuroendocrine tumour syndromes Harms • SAE (pneumonitis, hematologic toxicity) • AE • WDAE

mTOR= mammalian target of rapamycin; **RCT=**randomized controlled trial **; SAE**=severe adverse events; **AE**= adverse events; **WDAE**=withdrawal due to adverse events

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

*** Only available through HC's special access program*

† Limited access (only available in Edmonton, Halifax and London Ont.)

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2012, Issue 5) 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 Afinitor or everolimus and pancreatic neuroendocrine tumours.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. The search is considered up to date as of June 4, 2012.

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

6.2.3 Study Selection

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

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

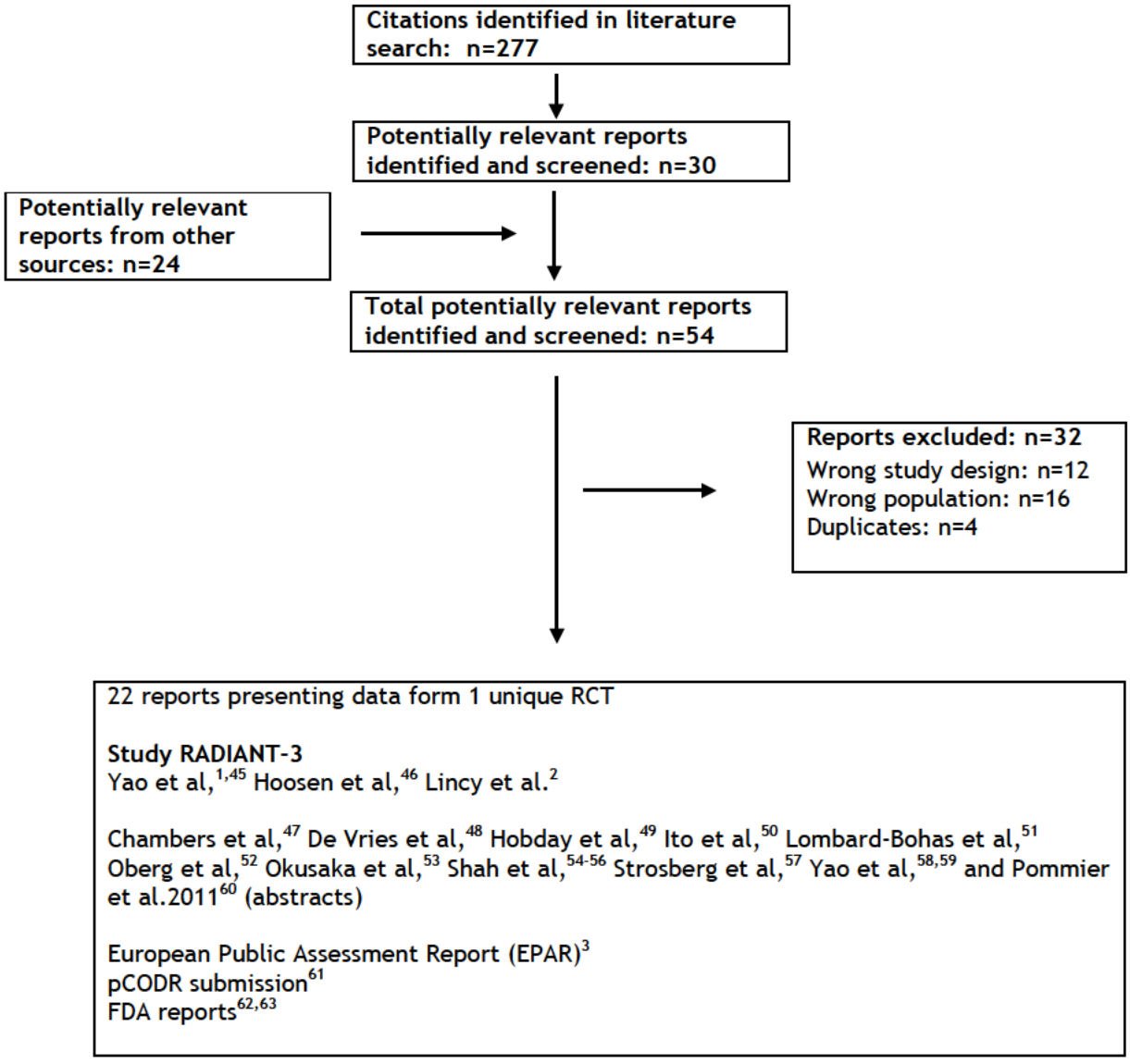
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 54 potentially relevant reports identified, 22 reports presenting data from 1 unique study were included in the pCODR systematic review[1-3,45-63] and 32 reports presenting data from 7 studies were excluded. Studies were excluded because they were wrong design[43,64-74] wrong population,[4,44,75-88] or duplicates.[89-92]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

One randomized placebo controlled double-blind trial was included in this systematic review (**Table 2**). RADIANT-3 was a multicentre-multinational manufacturer-funded trial.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics of the included Study[1,2,45,46]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
RADIANT III[1] 82 centers in 18 countries July 2007 to May 2009* DB, PC, RCT n= 410 (Full analysis) n=407 (Safety analysis) Funded by Novartis Oncology	• Patients with biopsy-proven, advanced (unresectable or metastatic), low-grade or intermediate grade pancreatic neuroendocrine tumour • Radiological documentation of disease progression within 12 months prior to randomization • Measurable disease per RECIST criteria using triphasic CT scan or multiphasic MRI • Performance status 0-2 on the WHO† scale **Exclusion criteria:** • Poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma • Cytotoxic chemotherapy, immunotherapy or radiotherapy within 4 weeks prior to randomization • Hepatic artery embolization within the last 6 months, or cryoablation/ radiofrequency ablation of hepatic metastasis within 2 months of enrollment • Prior therapy with mTOR inhibitors • Uncontrolled diabetes mellitus	• Everolimus 10 mg (two 5 mg tablets) orally once daily vs. matching placebo • Treatment interruption or dose adjustment** were permitted in case of adverse events • Patients were permitted to remain on long-acting somatostatin analog during the study	Primary • Progression-free survival Secondary • Objective tumour response rate (CR, PR) • Overall survival • Change in chromogranin A • Safety and tolerability

CR= complete response; **DB**= double-blind; **PC**= placebo controlled; **PR**= partial response; **RECIST**= Response Evaluation Criteria in Solid Tumours; **RCT**= randomized controlled trial

* This was the patient inclusion period; the trial did not have a predetermined termination date. Study termination was based on number of events.
** The dose could be reduced to 5 mg daily or 5 mg every other day
† WHO Performance Scale, as defined in the trial, has four grades from 0 to 4 which are identical to grade 0 to 4 defined in the Eastern Cooperative Oncology Group performance status scale (ECOG).[93] However, ECOG has one additional grade, grade 5 (death).[93]

a) Trials

Trial RADIANT-3 evaluated the superiority of everolimus over placebo in prolonging progression-free survival among patients with pNETs. The trial started in July 2007 and does not have a fixed termination date; patients should continue study treatment until the documentation of disease progression or death. The final data analysis for the trial outcomes was to be conducted when approximately 282 progression-free survival events (i.e., disease progression or death from any cause) had been observed. It was estimated that a total of 282 events would allow 92.6% power to demonstrate a 33% risk reduction (hazard ratio for everolimus/placebo of about 0.67, as calculated from an anticipated 50% increase in median PFS, from 6 months in placebo arm to 9 months in the everolimus arm). A total sample size of 392 patients was to be included to achieve the desired power.

At the cut-off date of February 28th, 2010, a total of 274 progression-free survival events were observed; all trial outcomes were analysed based on data collected by this date. Results were considered final for all trial outcomes except for the overall survival; the final analysis of overall survival will take place when approximately 250 deaths have been reported.[2] The statistical plan estimated that 250 death events would be necessary to achieve at least 80% power to demonstrate a 30% risk reduction of the overall survival estimate.[2] At the cut-off date of February 2010, only 101 death events were observed; therefore, interim analyses of the overall survival were reported for data collected on February 28, 2010. Another data cut-off date (February 23th, 2011) was used to provide an updated interim analysis of the overall survival as requested by the European Medicines Agency.[2,3]

Randomization and trial medication management was supported by an interactive voice response system (IVRS). The randomization ratio was 1:1. Randomization and efficacy analysis were stratified by history of prior cytotoxic chemotherapy, and by WHO performance status (0 versus 1-2) at baseline.

Randomization codes were maintained within IVRS, and unblinding was allowed after documented disease progression during the blinded treatment phase – this was to enable patients randomized to placebo to switch to open-label everolimus. Unblinding was also allowed in the case of medical emergencies under the discretion of the treating oncologist. Beside these two cases, blinding was not to be broken until the final database lock. Nevertheless, blinding might have been difficult to maintain due to the adverse events associated with everolimus such as stomatitis, rash and diarrhea.

b) Populations

A total of 410 patients were randomized to receive everolimus (207) or placebo (203). The mean age of the randomized patients was 56.7 years. More male patients were enrolled in the trial; 55% males vs. 45% females. Slightly more patients in the everolimus arm were above 65 years: 29.5% versus 24.6% in the placebo arm. Patients were predominantly Caucasian.

More patients randomized to the everolimus arm were diagnosed with pNETs for more than 5 years (30.9% versus 22.7% for placebo). In both groups, the histologic diagnosis was predominantly well differentiated (83.2%) neuroendocrine carcinoma (71%) of pancreatic origin (98%). A total of 92% of the included patients had metastases in the liver. More patients in the placebo arm had 3 or more organs involved at the time of randomization than those in the everolimus arm (37.9% versus 33.8% respectively). All included patients had received at least one

antineoplastic surgery (including biopsy) prior to randomization, and half of them had received chemotherapy. Almost two-third of the trial patients had WHO performance status score of zero at inclusion, while only 3% of them had a score of 2.

c) Interventions

Patients received trial medication in cycles; each cycle was defined as 28 days of consecutive daily treatment with everolimus 10 mg (two 5 mg tablets) administered orally once daily or matching placebo. The mean treatment duration was 40.9 weeks for everolimus and 25.4 weeks for placebo. The median (months) follow-up for patients who discontinued treatment without PFS event and never treated with further anti-tumor therapy was similar in both arms; -0.5 months for everolimus and -0.1 months for placebo. Both groups received best supportive care (the use of somatostatin analogs; proton-pump inhibitors for gastrinoma, diazoxide, short course of steroid, feeding tube for insulinoma; pancrealipase for patients with pancreatic exocrine insufficiency; and non-specific anti-diarrheals). If patients were unable to tolerate the trial medication (grade 2 toxicity), treatment dose could be reduced to 5 mg daily or 5 mg every other day. Treatment could be interrupted if the patients experienced toxicity of grade 2, and trial medication was not permitted to be continued until recovery to grade ≤ 1 toxicity. Patients requiring a third dose reduction or experiencing grade 4 toxicity were required to discontinue trial medication.

Patients continued treatment until disease progression, until unacceptable adverse events occurred, or until death.

d) Patient Disposition

The Full Analysis Set (FAS) population included 410 patients randomised to either everolimus or placebo (**Table 3**). Patients were analyzed according to the drug and the stratum they were assigned to at randomization. The per-protocol population was part of the FAS and included 371 patients who did not have any major protocol deviation. The Safety Set included all patients who received at least one dose of the double-blind study medication with a valid post-baseline assessment.

The most common reasons for treatment discontinuation were disease progression (44.4% and 80.3% of everolimus and placebo respectively) and adverse events (17.4% and 3.4% of everolimus and placebo respectively).

Table 3. Patient Disposition[1]			
Screened for eligibility • Excluded	474 64		
	Everolimus n (%)	**Placebo n (%)**	**Total n (%)**
Randomized • Received allocated intervention	207 (100) 206	203 (100) 203	410 (100) 409
Discontinued treatment (%) • Disease progression • Adverse events • Consent withdrawal • Death • Protocol deviation • Lost to follow-up	141 (68.1) 92 (44.4) 36 (17.4) 4 (1.9) 4 (1.9) 4 (1.9) 1 (0.5)	177 (87.2) 163 (80.3) 7 (3.4) 4 (2.0) 3 (1.5) 0 0	318 (77.6) 255 (62.2) 43 (10.5) 8 (2.0) 7 (1.7) 4 (1.0) 1 (0.2)
Analysis • Full Analysis Set (FAS) • Safety Set • Per-protocol[3] • Open-label Set[3]	 207 (100) 204 (98.6) 182 (87.9) 1 (0.5)	 203 (100) 203 (100) 189 (93.1) 148 (72.9)	 410 (100) 407 (99.3) 371 (90.5) 149 (36.3)

e) Limitations/Sources of Bias

- A total of 39 patients were excluded from the per-protocol analysis; 25 (12.1%) everolimus patients and 14 (6.9%) placebo patients.[3] Reasons of exclusion were insufficient everolimus exposure (n=18), unknown overall response (n=17), or major protocol deviations (n=13). Furthermore, 26 patients were excluded without a major protocol deviation.[3] The unbalanced exclusion did not affect the PFS estimates [hazard ratio 0.35 (0.27, 0.45)].[61] However, the higher number of exclusions in the everolimus group might raise concerns about the clinical use of everolimus including adverse events leading to insufficient exposure or affect patients' compliance.
- To achieve the desired statistical power, it was estimated that a total of 282 events would be needed.[1] However, the final primary analysis included 274 events only. Although a difference of 8 events is not likely to significantly change PFS estimates, it is more likely to impact the statistical power of these estimates.
- PFS may be 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.

The overall-survival (OS) analysis might have been confounded by the fact that patients who had been randomized to placebo could then cross-over to open-label everolimus. Another confounder for the OS estimation could be the unbalanced subsequent use of antineoplastic therapies (37.7% of patients in the everolimus arm and 28.6% of placebo-treated patients)[61] after discontinuation of trial medications.

- Stomatitis, rash and diarrhea were more frequent in the everolimus group; therefore, blinding might have been compromised. This might have introduced a detection bias (investigator becomes aware to which

treatment the patient was assigned) which might have impacted the way tumour response was assessed, in favour of the treated group.

- Input from patient advisory group indicated that quality of life could be largely affected by pNETs. However, RADIANT-3 did not evaluate the effect of the trial medication on the quality of life.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Radiologic tumour evaluation (multiphase MRI or triphasic CT) was performed at baseline, every 12 weeks thereafter (every 3 cycles) and at the end of study treatment. A confirmation scan was performed if a partial or complete disease response was suspected.

Table 4 provides a summary of RADIANT-3 key outcomes. The analyses of all outcomes were conducted based on data collected on February 28, 2010, which included 274 progression-free survival events (progression or death). An additional analysis of the overall survival was based on data collected on February 2011 (for more details see "Trial Characteristics").

Table 4. Summary of Key Outcomes[1,3]

EFFICACY (FAS; investigator assessed)				
Outcome	**Study group**	**Median Months (95% CI)**	**HR (95% CI)**	**P value**
Progression free survival	Everolimus Placebo	11.0 (8.4 – 13.9) 4.6 (3.1- 5.4)	0.35 (0.27 – 0.45)	<0.001
Overall survival (February 2010)	Everolimus Placebo	NA	1.05 (0.71, 1.55)	0.59
Overall survival (February 2011)	Everolimus Placebo	NA 36.6 (NR)	0.89 (0.64, 1.23)	NR
Outcome	**Study group**	**n/N**	**% (95% CI)**	**P value**
Objective tumour response*	Everolimus Placebo	10/207 4/203	4.8 (2.3, 8.7) 2.0 (0.5, 5.0)	0.091
HARMS**				
Outcome	**Study group**	**n/N**	**%**	**P value**
Death	Everolimus Placebo	12/204 4/203	6 2	
SAE	Everolimus Placebo	82/204 50/203	40.2 24.6	
Any AE	Everolimus Placebo	202/204 198/203	99.0 97.5	
WDAE	Everolimus Placebo	39/204 12/203	19.1 5.9	

AE=adverse events; **FAS**=full analysis set; **HR=**hazard ratio; **NA=**not applied; **NR**=not reported; **SAE=**serious adverse events; **WDAE=**withdrawal due to adverse events

* All objective tumour responses captured in the trial were partial responses; there were no complete responses in either treatments

** Harm outcomes, including death, were summarized as on-treatment events only. On treatment events were defined as any event that occurred from the first day of treatment up to 28 days after the last administration of study drug or at the start of open-label phase

a) Efficacy Outcomes

Overall survival was defined as the time from date of randomization to date of death due to any cause. In the case of unknown patient death status, survival was censored at the date of the last contact.[46]

At the time of data-lock on February 28, 2010, there was no statistically significant difference between the two treatment groups in overall survival. The hazard ratio was 1.05 (95% CI: 0.71, 1.55; p=0.59) (**Table 5**). At that time, the median overall survival was not reached in either group.

Interpretation of these results might be complicated by the cross-over of placebo patients to open-label use of everolimus after having disease progression. A total of 148 of the 203 patients (72.9%) initially randomised to placebo were crossed-over to receive everolimus. Furthermore, the subsequent use of antineoplastic therapies (37.7% of patients in the everolimus arm and 28.6% of placebo-treated patients)[61] after discontinuation of trial medications further confounded these results.

Table 5. Overall survival[1,3,61]

	Everolimus (N=207)	Placebo (N=203)	p value
Data cut-off February 2010			
Deaths*, n (%)	51 (24.6)	50 (24.6)	
Patients with censored data, n (%)	156 (75.4)	153 (75.4)	
Overall survival • Estimated median	NA	NA	
• HR for death (95 % CI)	1.05 (0.71, 1.55)		0.59
Data cut-off February 2011			
Deaths*, n (%)	68 (32.8)	78 (38.4)	
Patients with censored data, n (%)	NR	NR	NR
Overall survival • Estimated median	NA	36.6	
• HR for death (95 % CI)	0.89 (0.64, 1.23)		NR

CI= confidence interval; **HR=**hazard ratio; NA= not applicable (median values not reached); NA= not applicable; **NR=**not reported

* Overall survival was defined as the time from date of randomization to date of death due to any cause. All reported deaths were counted as events, regardless of timing and censoring rules for assessment of progression-free survival.

b) Progression-free survival

Progression-free survival was the primary outcome in RADIANT-3 trial, and it was defined as the time from randomization to the first documentation of disease progression or death from any cause. Progression-free survival was censored for patients who did not have an event (disease progression or death) during the trial, who were lost to follow-up or withdrew their consent, who had a new cancer therapy added during the trial, and for patients who had an event documented after two or more missing tumour assessments.

Disease progression was based on the radiological evaluation and the objective tumour assessment according to RECIST criteria. The primary analysis was based on the evaluation made by the local investigator. Confirmatory analyses were based on an independent adjudicated central assessment and independent central radiology review. Irrespective of the analysis used, everolimus improved progression-free survival compared to placebo.

At the time of final data-lock for the progression-free survival analysis (February 2010), there were 109/207 (52.7%) patients in the everolimus group and 165/203 (81.3%) in the placebo group who had disease progression or death (**Table 6**). The median progression-free survival was 11 months for everolimus and 4.6 months for placebo. The associated hazard ratio was 0.35 (95% CI: 0.27, 0.45); p<0.001).

Table 6. Progression free survival (FAS, investigator assessed)[3]

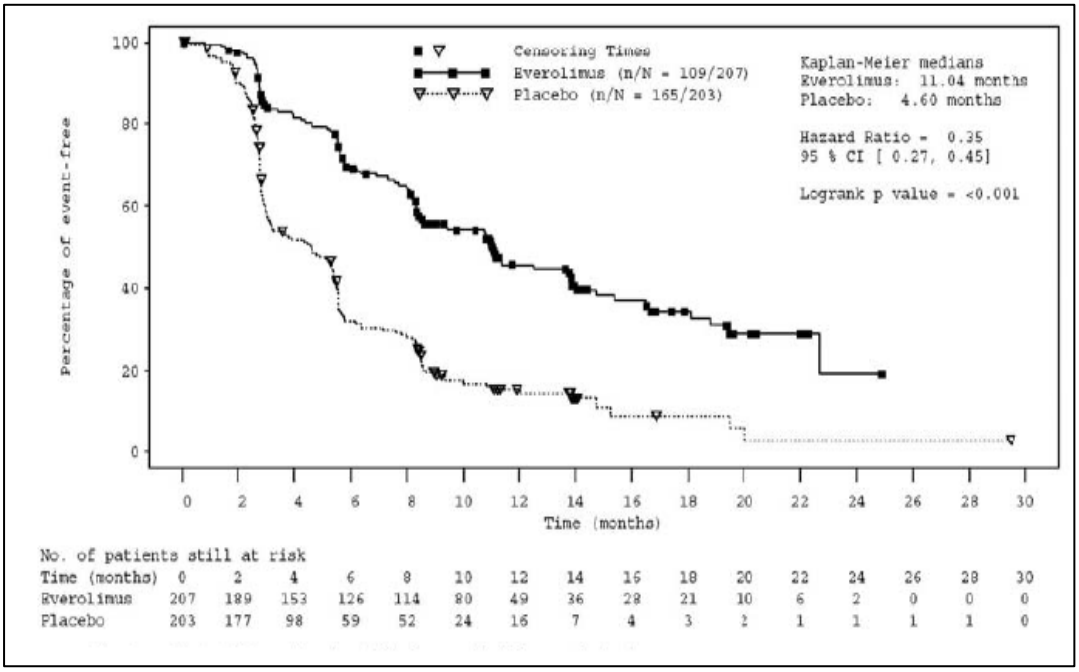
	Everolimus (N=207)	Placebo (N=203)	p value
Patients with events, n (%) • Disease progression • Death*	109 (52.7) 95 (45.9) 14 (6.8)	165 (81.3) 158 (77.8) 7 (3.4)	
Patients with censored data, n (%)	98 (47.3)	38 (18.7)	
• Ongoing without event	68 (32.9)	27 (13.3)	
• New cancer therapy	11 (5.3)	4 (2.0)	
• Inadequate assessments	7 (3.4)	3 (1.5)	
• Withdrew consent	2 (1.0)	3 (1.5)	
• Lost to follow-up	1 (0.5)	0	
Progression free survival • Estimated median, months	11.04	4.60	
• HR for PFS (95 % CI)	0.35 (0.27, 0.45)		<0.001

CI= confidence interval; **HR=**hazard ratio; **NR=**not reported; **PFS=**progression free survival

* Death counted in the progression-free survival included all death events that occurred between the time of randomisation and February 2010. Events were censored at the last adequate tumour assessment if on of the following occurred: (a) absence of an event before cut-off; (b) the event occurred after a new anticancer therapy (including open-label everolimus) was given; or (c) the event occurred after two or more missing tumor assessments

The Kaplan-Meier progression-free survival curves showed a treatment effect from the time of the first tumour assessment (at approximately 3 months) and this effect persisted until the time of data-lock (**Figure 1**).

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



Pre-specified Subgroup analyses for progression-free survival

The consistency of the treatment effect across predefined patient subsets was explored (**Table 7**). Prespecified Subgroup results based on age group, gender, race, WHO performance status, geographic region, tumour grade, prior treatment with long-acting stomatostatin analog, and prior chemotherapy were all consistent with the primary PFS analysis.

Table 7. Subgroup analysis for progression-free Survival[1]				
Subgroups	**N**	**Hazard ratio**	**95% CI**	**p-value**
All subjects- local investigator review	410	0.35	(0.27, 0.45)	<0.001
Age				
• ≤65 years	299	0.39	(0.29, 0.53)	<0.001
• >65 years	111	0.36	(0.22, 0.58)	<0.001
Sex				
• Male	227	0.41	(0.30, 0.58)	<0.001
• Female	183	0.33	(0.23, 0.48)	<0.001
Race				
• White	322	0.41	(0.31, 0.53)	<0.001
• Asian	74	0.29	(0.15, 0.56)	<0.001
Region				
• America	185	0.36	(0.25, 0.52)	<0.001
• Europe	156	0.47	(0.32, 0.69)	<0.001
• Asia	69	0.29	(0.14, 0.56)	<0.001
Tumour Grade				
• Well differentiated	341	0.41	(0.31, 0.53)	<0.001
• Moderately differentiated	65	0.21	(0.11, 0.42)	<0.001
WHO performance				
• 0	279	0.39	(0.28, 0.53)	<0.001
• 1 or 2	131	0.30	(0.20, 0.47)	<0.001
Previous chemotherapy				
• Yes	189	0.34	(0.24, 0.49)	<0.001
• No	221	0.41	(0.29, 0.58)	<0.001
Previous long acting SSA				
• Yes	203	0.40	(0.28, 0.57)	<0.001
• No	207	0.36	(0.25, 0.51)	<0.001
CI= confidence interval; **SSA=** stomatostatin analogs				

Stratified analyses for progression-free survival

Randomization was stratified by prior cytotoxic chemotherapy usage (yes vs. no) and WHO performance status score (0 vs. 1or 2). The hazards ratios estimated within each of these strata supported the primary PFS results.(**Table 8**)

Table 8. Stratum Analysis of Progression-Free Survival[61]*								
	Prior cytotoxic chemotherapy				No prior cytotoxic therapy			
	WHO PSS= 0 N=119		WHO PSS=1 or 2 N=70		WHO PSS=0 N=160		WHO PSS=1 or 2 N=61	
	Ever. n=60	Plc. n=59	Ever. n=36	Plc. n=34	Ever. n=80	Plc. n=80	Ever. n=31	Plc. n=30
PFS events, n% • Progression • Death	26 (43) 24 (40) 2 (3)	51 (86) 51 (86) 0	25 (69) 20 (56) 5 (14)	31 (91) 27 (79) 4 (12)	42 (53) 39 (49) 3 (4)	58 (73) 56 (70) 2 (3)	16 (52) 12 (39) 4 (13)	25 (83) 24 (80) 1 (3)
Hazard ratio 95% CI	0.31 (0.19, 0.50)		0.31 (0.17, 0.54)		0.47 (0.31, 0.70)		0.24 (0.12, 0.48)	
CI= confidence interval; **Ever=** everolimus; **PFS=**progression-free survival; **Plc=**placebo; **PSS=**performance scale score * Data reported in this table were provided in Health Canada Module 2.7.3, part of the submission material								

c) Tumour response

Tumour response was a secondary outcome. Objective response rate was defined as the proportion of patients with complete response or partial response according to RESICT.

A total of 10/207 (5%) everolimus patients and 4/203 (2%) placebo patients had objective tumour responses (all partial responses) (**Table 9**).

Table 9. Tumour response (FAS, investigator assessed)[1,3]			
	Everolimus (N=207)	Placebo (N=203)	p value
Patients with stable disease, n (%)	151 (72.9)	103 (50.7)	
Patients with progressive disease, n (%)	29 (14.0)	85 (41.9)	
Objective response rate, n (%) • Complete response • Partial response	10 (4.8) 0 10 (4.8)	4 (2.0) 0 4 (2.0)	0.091 0.091
FAS= full analysis set; **HR=**hazard ratio; **NR=**not reported			

d) Quality of life

Quality of life was not evaluated in RADIANT-3 trial.

e) Symptoms associated with functional pancreatic neuroendocrine tumour syndromes

RADIANT-3 did not evaluate the effect of everolimus on specific symptoms association with pancreatic NETs.

Harms Outcomes

Safety summaries, including death, summarized only on-treatment events. On treatment events were defined as any event that occurred from the first day of treatment to 28 days after the last administration of study drug or at the start of open-label phase.

a) Deaths and other serious adverse events

Serious adverse events that occurred in ≥2% of patients are listed in **Table 10**. Serious adverse events were defined as those that resulted in death or were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, or resulted in a congenital anomaly or birth defect.

Twelve (6%) and four (2%) everolimus and placebo patients respectively died on-treatment during the trial. Adverse events were the primary cause of death for 7 (3.4%) everolimus patients and one (0.5%) placebo patient. During the open-label phase, 3/149 (2%) patients died while using everolimus due to adverse events.

Table 10: Deaths and Serious adverse events in ≥1% of patients, safety Population [3]		
	Everolimus N=204	**Placebo N=203**
Death* (on treatment), n (%)	12 (5.9)	4 (2.0)
• Death due to disease progression	5 (2.5)	3 (1.5)
• Adverse events as primary cause of death	7 (3.4)	1 (0.5)
o Infections and infestations	2 (1.0)	0
o Cardiac disorders	1 (0.5)	0
o General disorders	1 (0.5)	0
o Hepatobiliary disorders	1 (0.5)	0
o Renal and urinary disorders	1 (0.5)	0
o Respiratory, thoracic, and mediastinal disorders	1 (0.5)	1 (0.5)
Serious adverse events, n (%)	82 (40.2)	50 (24.6)
• Gastrointestinal disorders	27 (13.2)	20 (9.9)
o Abdominal pain	6 (2.9)	5 (2.5)
o Diarrhea	5 (2.5)	2 (1.0)
o Nausea	3 (1.5)	4 (2.0)
o Vomiting	2 (1.0)	4 (2.0)
• Respiratory, thoracic and mediastinal disorders	23 (11.3)	4 (2.0)
o Pneumonia	7 (3.4)	0
o Dyspnea	6 (2.9)	2 (1.0)
o Pulmonary embolism	5 (2.5)	1 (0.5)
• Infections and infestations	21 (10.3)	8 (3.9)
o Pneumonia	3 (1.5)	2 (1.0)
• General disorders and administration site conditions	17 (8.3)	8 (3.9)
o Pyrexia	8 (3.9)	3 (1.5)
o Asthesia	5 (2.5)	2 (1.0)
• Metabolism and nutrition disorders	15 (7.4)	9 (4.4)
o Dehydration	4 (2.0)	2 (1.0)
o Hypercalcemia	2 (1.0)	3 (1.5)
• Renal and urinary disorders	11 (5.4)	5 (2.5)
o Renal failure	3 (1.5)	1 (0.5)
o Renal failure acute	2 (1.0)	3 (1.5)
• Cardiac disorders	10 (4.9)	2 (1.0)
• Blood and lymphatic system disorders	9 (4.4)	3 (1.5)
o Anemia	7 (3.4)	3 (1.5)
• Hepatobiliary disorders	9 (4.4)	2 (1.0)
• Psychiatric disorders	5 (2.5)	3 (1.5)
o Confusional state	3 (1.5)	3 (1.5)
• Investigations	5 (2.5)	2 (1.0)
• Nervous system disorders	4 (2.0)	5 (2.5)
• Injury, poisoning and procedural complications	3 (1.5)	2 (1.0)
• Neoplasms	2 (1.0)	2 (1.0)
• Musculoskeletal and connective tissue disorders	1 (0.5)	5 (2.5)

* Deaths counted in adverse events were summarized as on-treatment events only. On treatment events were defined as any event that occurred from the first day of treatment to 28 days after the last administration of study drug or at the start of open-label phase

b) Any adverse event

An adverse event was defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing of the informed consent form, and included events reported within the 28 days following the discontinuation of treatment.[3]

Adverse events, due to any cause, were frequent in both treatment groups (**Table 11**); everolimus 202/204 (99%) vs. placebo 198/203 (97.5).[3] Most of these adverse events were considered by the investigator to be of grade 1 (mild) or 2 (moderate) intensity. Grade 3 (severe) and 4 (life-threatening or disabling) adverse events were reported less frequently in both treatment groups. The most common adverse events of grade 3 and grade 4 intensities were anaemia (8.4% grade 3 and 4; 22% all grades), hyperglycemia (7.9% grade 3 and 4; 19% all grades), diarrhea (5.4% grade 3 and 4; 47% all grades), and stomatitis (4.9% grade 3 only; 54% all grades).

Table 11: All-causality Adverse Events*, safety Population[3,61]

Events	**Everolimus N=204**			**Placebo N=203**		
	All n(%)	Gr 3 (%)	Gr 4 (%)	All n(%)	Gr3 (%)	Gr4 (%)
Any Adverse event	202 (99.0)	47.5	12.3	198 (97.5)	31.5	7.4
Stomatitis	110 (53.9)	4.9	0	25 (12.3)	0	0
Rash	107 (52.5)	NR	NR	32 (15.8)	NR	NR
Diarrhoea	95 (46.6)	4.9	0.5	48 (23.6)	2.5	0
Fatigue	89 (43.6)	2.5	0.5	54 (26.6)	2.0	0.5
Oedema peripheral	73 (35.8)	1.0	0	24 (11.8)	1.0	0
Nausea	65 (31.9)	2.5	0	66 (32.5)	2.0	0
Headache	61 (29.9)	NR	NR	30 (14.8)	NR	NR
Pyrexia	60 (29.4)	NR	NR	25 (12.3)	NR	NR
Decreased appetite	59 (28.9)	1.5	0	36 (17.7)	1.5	0
Vomiting	58 (28.4)	1.0	0	42 (20.7)	2.5	0
Weight decreased	57 (27.9)	NR	NR	23 (11.3)	NR	NR
Anaemia	45 (22.1)	6.9	1.5	18 (8.9)	2.0	0
Cough	44 (21.6)	NR	NR	22 (10.8)	NR	NR
Epistaxis	43 (21.1)	NR	NR	3 (1.5)	NR	NR
Pruritus	39 (19.1)	NR	NR	26 (12.8)	NR	NR
Hyperglycemia	39 (19.1)	7.4	0.5	20 (9.9)	3.0	0.5
Dysgeusia	38 (18.6)	NR	NR	10 (4.9)	NR	NR
Asthenia	36 (17.6)	2.9	0	40 (19.7)	3.4	0
Dyspnea	34 (16.7)	2.0	0.5	15 (7.4)	0.5	0
Abdominal pain upper	32 (15.7)	NR	NR	15 (7.4)	NR	NR
Nasopharyngitis	31 (15.2)	NR	NR	14 (6.9)	NR	NR

Gr=grade; **Grade 3**= severe adverse events; **Grade 4**= life-threatening or disabling events; **NR=**not reported

* based on MedDRA preferred term of adverse events – events listed are those that occurred in >15% of patients in either group

Adverse events requiring dose reduction or interruption occurred more frequently in the everolimus group compared to placebo group.[61] A total of 125/204 (61%) everolimus patients and 55/203 (27%) placebo patients had adverse events that led to dose interruption or dose reduction. Dose adjustments as a result of adverse events were more common in the everolimus group for the following system organ classes: gastrointestinal disorders (+17.1%), respiratory, thoracic and mediastinal disorders (+14.2%), blood and lymphatic system disorders (+12.7%) and general disorders and administration site conditions (+6.4%).

Detailed information about impact of dose interruption on efficacy was not reported for trial RADIANT-3. There is no evidence on the effectiveness of everolimus at lower doses than the recommended 10 mg.

c) Withdrawal due to adverse events

A total of 19% (39/204) of everolimus patients and 6% (12/203) of placebo patients discontinued due to adverse events.[3] The most common adverse events leading to treatment discontinuation were pneumonitis (2.9%), pyrexia (1.5%), interstitial lung disease (1.0%), fatigue (1.0%), pneumonia (1.0%), and increased aspartate aminotransferase (1.0%).

6.4 Ongoing Trials

One phase II trial is ongoing and could potentially be included in the current review.[94] CALGB is an open-label randomised trial evaluating the effects of everolimus and octreotide together with or without bevacizumab in treating patients with locally advanced or metastatic pancreatic neuroendocrine tumors that cannot be removed by surgery The trial started in October 2010 and is estimated to terminate in June 2012. Progression-free survival is the primary trial outcome; secondary outcomes include response rate, toxicity and overall survival.

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 everolimus for pancreatic neuroendocrine tumours. 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 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 to 2012 Week 06 (emez); **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present (pmez)

#	Searches	Results
1	(everolimus* or Afinitor* or Affinitor* or "RAD 001" or RAD001 or rad001a or rad 001a or SDZ-RAD or SDZRAD or certican* or Zortress* or 159351-69-6).ti,ab,ot,sh,hw,rn,nm.	10031
2	exp Neuroendocrine Tumors/ or exp Pancreatic Neoplasms/ or (insulinoma* or gastrinoma* or PNET or PNET or GPNETS or GPNETS or NET or NETs).ti,ab.	428753
3	((neuroendocrine or pancreas or pancreatic or gastroenteropancreatic 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.	141731
4	1 and (2 or 3)	802
5	4 use pmez	117
6	*Everolimus/ or (everolimus* or Afinitor* or Affinitor* or "RAD 001" or RAD001 or rad001a or rad 001a or SDZ-RAD or SDZRAD or 159351-69-6 or certican* or Zortress*).ti,ab.	5415
7	exp *Neuroendocrine Tumor/ or exp *pancreas tumor/ or (insulinoma* or gastrinoma* or PNET or PNETS or GPNET or GPNETs or NET or NETs).ti,ab.	326070
8	((neuroendocrine or pancreas or pancreatic or gastroenteropancreatic 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.	141731
9	6 and (7 or 8)	348
10	9 use emez	249
11	5 or 10	366
12	exp animals/	17847961

13	exp animal experimentation/	1519075
14	exp models animal/	1013486
15	exp animal experiment/	1519075
16	nonhuman/	3849536
17	exp vertebrate/	32518163
18	animal.po.	0
19	or/12-18	34415712
20	exp humans/	25838791
21	exp human experiment/	301028
22	human.po.	0
23	or/20-22	25840183
24	19 not 23	8576467
25	11 not 24	355
26	remove duplicates from 25	277

2. Literature search via PubMed

Search History

Search	Query	Items found
#5	Search **#4 AND publisher[sb]**	15
#4	Search **#1 AND (#2 OR #3)**	127
#3	Search **((neuroendocrine[tiab] or pancreas[tiab] or pancreatic[tiab] or gastroenteropancreatic[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**	63346

Search	Query	Items found
	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]))	
#2	Search **Neuroendocrine Tumors[mh] OR Pancreatic Neoplasms[mh] OR insulinoma*[tiab] OR gastrinoma*[tiab] OR PNET[tiab] OR PNETS[tiab] OR GPNETStiab] OR GPNETS[tiab] OR NET[tiab] OR NETs[tiab]**	241198
#1	Search **everolimus* OR Afinitor* OR Affinitor* OR RAD 001 OR RAD001 OR rad001a OR rad 001a OR SDZ-RAD OR SDZRAD OR certican* OR Zortress* OR 159351-69-6[rn] OR everolimus [Supplementary Concept]**	1987

3. Cochrane Library

ID	Search	Hits
#1	(everolimus* OR Afinitor* OR Affinitor* OR RAD 001 OR RAD001 OR rad001a OR rad 001a OR SDZ-RAD OR SDZRAD OR certican* OR Zortress* OR 159351-69-6):ti,ab,kw	351
#2	insulinoma* OR gastrinoma* OR PNET OR Ss OR GPNET OR GPNETS OR NET OR NETs OR ((neuroendocrine or neuro endocrine or pancreas or pancreatic or gastroenteropancreatic 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*))	10701
#3	(#1 AND #2)	

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: (Afinitor OR everolimus) AND
(neuroendocrine OR neuro endocrine)

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: Afinitor or everolimus

Conference abstracts:

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

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

Search terms: Afinitor or everolimus / last 5 years

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