CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Everolimus (Afinitor) for Neuroendocrine Tumours of Gastrointestinal or Lung Origin

December 1, 2016

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

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1 GUIDANCE IN BRIEF

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 for the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional neuroendocrine tumours (NETs) of gastrointestinal or lung origin (GIL) in adults with progressive disease. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding Everolimus for NETs GIL conducted by the Endocrine Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues (if applicable) are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on Everolimus for NETs GIL, a summary of submitted Provincial Advisory Group Input on Everolimus for NETs GIL, and are provided in Sections 2, 3, and 4 respectively. No input was received from registered clinicians regarding Everolimus for NETs GIL.

1.1 Introduction

Everolimus is an orally administered inhibitor of the mammalian target of rapamycin (mTOR). mTOR pathway activity is modulated by the phosphatidylinositol-3-kinase(PI3K)/AKT pathway which is known to be dysregulated in numerous human cancers, including NETs

On May 17, 2016 everolimus was issued marketing authorization without conditions by Health Canada for the treatment of unresectable, locally advanced or metastatic, well differentiated, non-functional NETs GIL origin in adults with progressive disease. The recommended dose of everolimus for NETs GIL is 10 mg once daily as long as clinical benefit is observed or until unacceptable toxicity occurs.

Everolimus has also been issued marketing authorization by Health Canada for other indications such as breast, NETs of pancreatic origin, renal cell carcinoma, subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), and renal angiomyolipoma associated with TSC. Everolimus is available in two dosage forms – tablets and tablets for oral suspensions. Tablets may be used in all approved indications above (including NETs GIL) and tablets for oral suspension are recommended only for SEGA associated with TSC.

The submitter, Novartis Pharmaceuticals Canada Inc., has requested funding for the treatment of unresectable, locally advanced or metastatic, well differentiated, non-functional NETs GIL origin in adults with progressive disease. This funding request is similar to the Health Canada approved indication.

The objective of the systematic review is to evaluate the efficacy and safety of everolimus compared to relevant comparators (e.g. best supportive care and somatostatin analogues) for the treatment of unresectable, locally advanced or metastatic, well differentiated, non-functional NETs GIL origin in adults with progressive disease.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Of the 24 potentially relevant reports identified, 16 were included in the systematic review, and reported on data from the RADIANT-4 trial. RADIANT-4 is a phase III, randomized (2:1, intervention:control), double-blind, placebo-controlled study. There were 302 patients randomized to everolimus (10mg orally per day) plus best supportive care (n=205) or placebo plus best supportive care (n=97). Randomization was stratified by previous somatostatin analogue treatment, tumour origin and WHO performance status. Key inclusion criteria included adults aged 18 years or over, with pathologically confirmed advanced (unresectable or metastatic) non-functional well-differentiated neuroendocrine tumour of lung or gastrointestinal origin. The primary outcome of the trial was progression-free survival; secondary outcomes included overall survival, objective response rate, disease control rate, health-related quality of life, WHO performance status and safety. Novartis Pharmaceuticals Corporation funded the study.

Baseline characteristics between the two treatment groups were similar, with a few differences: patients were older in the everolimus group (median age: 65 versus 60), there was a greater percentage of female patients in the everolimus group (57% versus 45%) and more patients in the placebo group were previously treated with surgery (59% versus 72%). More than half of all patients received a prior somatostatin analogue.

Median duration of treatment was 40.4 weeks in the everolimus group and 19.6 weeks in the placebo group. Crossover from placebo to open-label everolimus after progression was not allowed and patients and investigators remained masked to treatment assignment until primary analysis.

Data analysis cut-off for progression-free survival and the first interim overall survival analysis was November 28, 2014. A second pre-planned interim overall survival analysis was done November 30, 2015, after 101 deaths. A final analysis is planned at 191 deaths. Progression-free survival was determined by central radiology review, masked to treatment assignment.

The following table highlights the key efficacy outcomes of the RADIANT-4 trial:

Table 1: Highlights of Key Outcomes

	RADIANT-4	
Efficacy outcomes	**Everolimus (n=205)**	**Placebo (n=97)**
Progression-free survival, median months (95% CI)	11.0 (9.2 - 13.3)	3.9 (3.6 - 7.4)
HR (95%CI)	0.48 (0.35 - 0.67)	
p-value	<0.00001	
Progression-free survival with prior SSA, median months (95% CI)	11.1 (9.2-13.3)	4.5 (3.6-7.9)
HR (95% CI)	0.56 (0.37 - 0.85)	
p-value	not powered to detect	
Overall survival, second interim analysis		
Number of deaths	66	35
HR (95%CI)	0.73 (0.48 - 1.11)	
p-value	0.071	
HrQoL - time to definite deterioration FACT-G		
HR (95%CI)	0.81 (0.55 - 1.21)	
Harms Outcome, %	**Everolimus (n=202)**	**Placebo (n=98^)**
Grade ≥3		
Stomatitis*	9%	0
Diarrhea	7%	2%
Fatigue	3%	1%

Infections+	7%	0
Rash	1%	0
Peripheral edema	2%	1%
Nausea	1%	0
Anemia	4%	1%
Decreased appetite	1%	0
Asthenia	1%	0
Non-infection pneumonitis	1%	0
Dysgeusia	1%	0
Cough	0%	0
Pruritus	1%	0
Pyrexia	2%	0
Dyspnea	1%	1%
Hyperglycemia	3%	0
AE (any grade)		
Stomatitis*	63%	19%
Diarrhea	31%	16%
Fatigue	31%	24%
Infections+	29%	4%
Rash	27%	8%
Peripheral edema	26%	4%
Nausea	17%	10%
Anemia	16%	2%
Decreased appetite	16%	6%
Asthenia	16%	5%
Non-infection pneumonitis	16%	1%
Dysgeusia	15%	4%
Cough	13%	3%
Pruritus	13%	4%
Pyrexia	11%	5%
Dyspnea	10%	4%
Hyperglycemia	10%	2%
On treatment deaths	7 (3.5%)	3 (3.1%)
WDAE	59 (29%)	7 (7%)

AE = adverse event, **CI =** confidence interval, **HR =** hazard ratio, **HRQoL =** health-related quality of life, **NR** = not reported, **SD** = standard deviation, **TRAE** = treatment-related adverse event, **WDAE** = withdrawal due to adverse event
*HR < 1 favours everolimus

^1 protocol deviation where a patient was randomized to everolimus but received placebo
*includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration
+includes all infections
++Included in this category are pneumonitis, interstitial lung disease, lung infiltration and pulmonary fibrosis.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, the physical and emotional impact of living with NETs GIL was varied. According to CNETS Canada, respondents interviewed reported that living with their NETs cancer makes life uncertain because of the terminal nature of the disease and no cure being available. Respondents reported that the biggest challenge they face is dealing with disease symptoms such as fatigue/lack of stamina, diarrhea, bloating, and abdominal cramps. Additional challenges reported by respondents include being sick for a long time due to misdiagnosis and having to make changes in their life because of their cancer.

Respondents also stated that NETs cancer has a negative impact on patients' quality of life. All respondents interviewed indicated that their energy levels were affected negatively by their NETs cancer and as a result they have less energy and more fatigue thus affecting their ability to engage in leisure, social activities, travel and work.

CNETS Canada indicated that the most common therapies for NETs cancer patients in Canada include surgery and Somatostatin Analogues (Sandostatin, Lanreotide). Other therapies include ablative techniques, liver embolization, and chemotherapy. CNETS Canada stated that on a limited basis through clinical trials, Peptide Receptor Radionuclide Therapy (PRRT) is available.

For respondents who have not used everolimus, the expectation is that the drug would shrink tumours and that not as much tissue would have to be removed through surgery. In addition, the treatment would provide better symptom control for bloating, diarrhea, constipation and energy levels. For respondents who have experience with everolimus, the greatest benefit that respondents reported with taking everolimus was a reduction in the progression of their disease, followed by tumour shrinkage, a decrease in disease symptoms and improved wellness. Two respondents also commented that they had stability in their disease. The most common side effects respondents found with taking everolimus were fatigue, followed by mouth sores and increased diarrhea. It was noted that respondents would like their doctors to explain all the side effects of the drug, not just the most common tolerable ones. In their opinion, clear and fulsome information will allow patients to factor this information into their decision making process as to whether or not to take this treatment.

Provincial Advisory Group (PAG) Input

The Provincial Advisory Group (PAG) includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of everolimus for neuroendocrine tumours:

Clinical factors:

- No standard treatment option for patients with progressive disease
- Clarity of eligible patients

Economic factors:

- Very small patient population
- Flat pricing for most tablet strengths (2.5 mg, 5 mg, and 10mg)

Registered Clinician Input

There was no registered clinician input received for this review.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team identified one other relevant clinical trial providing supporting information for this review. Please see Section 8 comparison with other literature.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1 (regarding internal validity).

Table 2: Assessment of generalizability of evidence for Everolimus NETs GIL

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG Performance Status	The RADIANT 4 trial included patients with WHO performance score/ECOG performance status of 0 or 1	Do the trial results apply to patients with WHO performance score/ECOG performance status of 2 or more? If so, why?	No. No evidence for patients with WHO performance score of ≥2 in the RADIANT-4 trial.
	More than one line of prior chemotherapy	The RADIANT 4 trial included previously treated patients and treatment-naïve patients, but excluded patients with more than one line of prior chemotherapy.	Do the trial results apply to patients with more than one line of prior chemotherapy? If so, why?	No. The effects of treatment in this population is unknown.
	After failure of somatostatin analogues	PAG is seeking information on the use of everolimus after failure of treatment with somatostatin analogues, if available. Inclusion criteria of the RADIANT 4 trial included patients previously treated with a SSA. In a subgroup analysis of these patients (Prior-SSA), there was a 46% reduction in the relative risk of progression or death with a median PFS difference of 6.7 months in favour of everolimus.	Do the trial results apply to patients who have failed treatment with somatostatin analogues? If so, why?	Yes. RADIANT-4 trial inclusion criteria included prior-SSA use and results of subgroup analysis indicate a benefit in PFS.
	Carcinoid syndrome	The RADIANT 4 trial excluded patients with history of or active symptoms of carcinoid syndrome.	Do the trial results apply to patients with history of or active symptoms of carcinoid syndrome? If so, why?	No. This patient population was not studied in the RADIANT-4 trial. This patient population is however studied in the RADIANT-2 trial (everolimus+ octreotide long-acting repeatable versus placebo).
	Measurable disease	The RADIANT 4 trial included patients with measurable disease according to RECIST 1.0 determined by multiphasic CT or MRI. According to the trial protocol, any lesions which have been subjected to percutaneous therapies, or radiotherapy should not be considered measurable, unless the lesion has clearly progressed since the procedure.	Can the trial results apply to other definitions of measurable disease/non-measurable disease? If so, why?	Yes results can apply to patients without measurable disease and have metastatic NETs GIL, as the definition of measurable disease in RADIANT-4 is an artifact.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Intervention	Combination therapy	The RADIANT 4 trial compared everolimus monotherapy to placebo.	Can everolimus be used in combination therapy for the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional NETs of gastrointestinal or lung origin in adults with progressive disease? If so, why?	There is no data for combination us in non-functional NETs GIL patients. This is out of scope.

1.2.4 Interpretation

The incidence of neuroendocrine tumours (NETs) has been steadily increasing over the past four decades, although the overall incidence of metastatic NETs appears to have remained stable. Most well-differentiated NETs arise from the gastrointestinal tract, lung or pancreas, and often have metastasized at the time of diagnosis. Functional NETs may secrete bioactive amines resulting in unique clinical syndromes (e.g., carcinoid syndrome related to high levels of circulating serotonin and other peptides).This report however, focuses on well-differentiated, non-functional NETs of gastrointestinal or lung origin. Localized or oligometastatic NETs may be surgically resected, and hepatic metastases may be treated with hepatic artery embolization or peptide receptor radiolabelled therapies. Somatostatin analogues (SSA's) are often used to treat carcinoid syndrome in functional NETs and to slow disease progression for both functional and non-functional NETs. Cytotoxic chemotherapy is rarely considered due to conflicting evidence documenting effectiveness and potential unfavourable impacts on quality of life, however, some newer agents and regimens are in early phase clinical trials. Although well-differentiated NETs often have relatively indolent biology, the 10-year overall survival is only about 50% and the prevalence of the disease in the Canadian population has continued to increase.[1]

The placebo-controlled RADIANT-4 trial examined everolimus, an oral mTOR inhibitor, for patients with metastatic, non-functional, well-differentiated NETs of GI tract or lung origin with good performance status (WHO 0-1) and radiologically confirmed progressive disease. Patients may have been on prior treatment with SSA's but combination treatment with SSA was not allowed on study. Results demonstrated that everolimus improved progression-free survival (PFS) compared to placebo with an impressive reduction in the risk of progression or death (hazard ratio [HR]: 0.48; 95% CI, 0.35-0.67). Concordant trends in overall survival (HR: 0.64 first interim analysis; HR: 0.73 second interim analysis) and quality of life (measured as time to deterioration in FACT-G scores) (HR: 0.81) favouring everolimus were observed but were not statistically significant. PFS effects appeared consistent across patient subgroups including prior SSA treatment, tumour origin (lung versus GI), and performance status. The rate of RECIST-confirmed objective response was low (2%) which is typical of mTOR inhibitor therapy for other indications in oncology, however, minor responses in target lesions were observed in 64% of everolimus treated patients compared to 26% receiving placebo.

The adverse effects of everolimus were consistent with those seen in other tumour types. A significant minority experienced adverse effects but severe adverse effects were infrequent with stomatitis the most common grade 3 event (9%). Non-infectious pneumonitis is the adverse effect of most concern and was observed in 16% of patients but was grade 3 in only 1%. Infections were more common with everolimus with grade 3 and grade 4 infection rates of 5% and 2% observed, respectively. No grade 3-4 infections occurred in placebo-treated patients. Dose reductions or interruptions occurred in 67% of patients but patients were on therapy for a median 40.4 weeks. The toxic death rate with everolimus was 1.5%.

Overall the results of the RADIANT-4 trial support the use of everolimus as an effective treatment for patients with progressive non-functional NETs. There is no evidence that combined use of everolimus with SSA is beneficial or superior to everolimus alone. The PFS benefit observed is consistent across patient strata, and clinical efficacy is further supported by the observed trends in the overall survival and quality of life data versus placebo, and is concordant with benefits of everolimus previously demonstrated in pancreatic neuroendocrine tumours.[2] Adverse events observed were generally low grade, amenable to dose modification and similar to those observed with everolimus when used for other indications. Non-infectious pneumonitis and infections are the adverse effects of greatest safety concern with everolimus.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to everolimus in the treatment of patients with progressive, incurable, non-functional non-pancreatic well-differentiated neuroendocrine tumours originating in the gastrointestinal tract or lung based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival for everolimus compared with placebo. The magnitude of PFS benefit was large and consistent with that seen in another RCT in patients with pancreatic NETs.

Overall survival and HRQoL showed concordant trends favouring everolimus although benefits is these outcomes remain unproven. The objective response rate was low. The adverse event profile was similar to that seen with everolimus in other cancer types. Pneumonitis and infection are of most concern, occur in a minority of patients, and are usually non-fatal. Minor yet troublesome adverse effects such as stomatitis, diarrhea, fatigue, rash, and edema are managed by dose interruption and modification as well as symptom control. For the optimal management of adverse effects, practitioners should be experienced in the use of everolimus in cancer therapy.

The RADIANT-4 trial confirms the efficacy of everolimus in patients with this disease. In the absence of reliably effective therapeutic alternatives, there was consensus of the CGP that everolimus should be made available for the treatment of patients with incurable, non-functional well-differentiated neuroendocrine tumours of gastrointestinal or lung origin.

PAG provided feedback on the initial recommendation and requested clarity on "documented disease progression within six months". The CGP would like to suggest the following: 'documented disease progression on first line systemic therapy within the prior six months for NETs of gastrointestinal origin' and 'documented disease progression within the prior six months for NETs of pulmonary origin'. The CGP felt that this would cover the fact that SSAs have not been studied as first line treatment for pulmonary NETs (however, noted that one trial just opened), and are accepted as first line treatment for GI NETs based on level 1 evidence from the PROMID and CLARINET studies, and is supported by the Canadian Consensus Guidelines. The CGP also indicated that specifying "radiologic progression" would be reasonable, but would not specify RECIST criteria absolutism; this is because most, if not all the trials examining new therapies for NETs that included progressive disease as an eligibility criterion for study inclusion have not specified RECIST-based criteria due, in part, to limitations in RECIST reliability when it comes to the hypervascular lesions typically associated with metastatic disease. As well, it can be difficult to radiologically assess the mesenteric disease commonly associated with NETs of small intestinal origin with RECIST criteria. Therefore, the CGP felt that leaving this specification at radiologic progression would be appropriate based on the clinical trial inclusion criteria. Lastly, the CGP reiterated that the guidance refers to non-functional disease only.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Neuroendocrine tumours (NETs) are a heterogeneous group of cancers arising from a variety of anatomic sites with approximately 50% of gastrointestinal (GI) and 25% of lung origin. Data from the Ontario Cancer Registry demonstrated an increase in the incidence of NETs in Ontario from 2.48 to 5.86 per 100,000 per year from 1994 to 2009, with metastatic disease documented in 20.8% at presentation and developing subsequent to diagnosis in an additional 38%, although the overall incidence of metastatic NETs appears to have remained stable.[1] Incidence was observed to increase significantly after the age of 50, peaking in those over 70 years of age.

The clinical spectrum of NETs may be highly variable and a significant proportion exhibit relatively indolent behavior. Important elements influencing prognosis includes extent of disease and chance of curative surgical resection, tumour differentiation and grade, primary site of origin, and presence or absence of functional syndrome (described below). Poorly differentiated NETs represent the most aggressive disease subtype and are treated with cytotoxic chemotherapy, similar to that used for small cell lung. This subtype is typically excluded from NET clinical trials and will not be further discussed here. NETs of pancreatic origin (pNET) are considered to have a unique biology and clinical course as well as being typically more responsive to cytotoxic chemotherapy and novel molecularly-targeted agents. pNETs have been studied separately from NETs of other primary origins in clinical trials and will also not be further discussed.

NETs are classified as "functional" when they present with clinical symptoms due to hypersecretion of hormones or bioactive amines, and "non-functional" when these symptoms are absent. 50% of GI NETs and 90% of lung NETs are non-functional.[3] Classic symptoms related to functional disease include episodic diarrhea and cutaneous flushing related to high levels of circulating serotonin and termed 'carcinoid syndrome'. Non-functional NETs may cause symptoms due to progressive local–regional disease and result in abdominal pain, intermittent or complete intestinal obstruction, intestinal ischemia, ascites, and constitutional symptoms secondary to bulky hepatic metastases. Treatment options for patients with advanced NETs originating in sites other than the pancreas are still very limited.

2.2 Accepted Clinical Practice

Patients with NETs should be evaluated for the possibility of curative surgical resection whenever possible and even in the context of limited metastatic disease. All patients should be assessed by a multidisciplinary team experienced in NETs management to optimize upfront and sequential diagnostic evaluations as well as surgical, local-regional and systemic therapies.

General management principles for the treatment of incurable NETs of non-pancreatic origin include the initiation of somatostatin analogue therapy for symptoms due to functional NETs (i.e. carcinoid syndrome) and consideration of locoregional therapies (e.g. surgical metastatectomy orcytoreduction, radiofrequency ablation and/or hepatic arterial embolization; bland or radioembolization). Patients with progressing or symptomatic locally advanced or metastatic disease who are not candidates for, or have progressive disease despite locoregional therapy should be considered for systemic therapy.

Long-acting formulations of the somatostatin analogues octreotide and lanreotide have been demonstrated to improve progression-free survival (PFS) in placebo-controlled randomized controlled clinical trials (RCTs) studying patients with well- and moderately-differentiated non-functional GI NETs, and are considered a standard of care. Both agents are well-tolerated and

delivered via deep intramuscular (Sandostatin LAR) or deep subcutaneous Lanreotide Autogel) injection on a q28day schedule.

Cytotoxic chemotherapy and interferon-alfa have modest antitumour activity. In a small randomized trial studying patients with NETs, improved overall survival was shown with streptozotocin plus 5-fluorouracil compared with streptozotocin plus doxorubicin.[4] However, this trial studied a mixed population of patients so has limited generalizability and power. Expert clinicians consider no one cytotoxic chemotherapy regimen superior to another for these patients, and although chemotherapy may be used selectively as a last resort it is not reliably effective.

Peptide receptor radiolabelled therapy (PRRT) utilizing Lutetium-177 has been observed to result in a statistically significant improvement in PFS for patients with somatostatin-avid tumours on somatostatin scintigraphy, with progressive disease despite optimal dosing of long-acting octreotide, compared to dose escalation of octreotide. Lutetium-177 is difficult to access in the Canadian environment

Everolimus is an orally administered inhibitor of the mammalian target of rapamycin (mTOR). mTOR pathway activity is modulated by the phosphatidylinositol-3-kinase(PI3K)/AKT pathway which is known to be dysregulated in numerous human cancers, including NETs.

Everolimus was compared to placebo in a prospective multi-center RCT involving patients with advanced non-functional lung and nonpancreatic GI NETs.[5] A statistically significant improvement in PFS was observed favoring the treatment arm with a median PFS of 11 months compared to 3.9 months for placebo (HR 0.48; 95% CI 0.35-0.67, p<.00001). A possible overall survival signal was observed at the first interim analysis that was not statistically significant and awaits further pre-planned, event-driven analyses. Results from this trial suggest that everolimus represents new therapeutic option for patients with advanced non-functional NETs of non-pancreatic origin, and the results of this trial have been endorsed for patients with progressive disease despite somatostatin analogue therapy by a consensus of Canadian experts.[6]

Patients with NETs GIL	
Line of Therapy	Treatment
1st-Line	Long acting somatostatin analogue (Octreotide LAR 30 mg IM or Somatuline Autogel 120 mg sc q 28 days)*
Maintenance	
2nd-Line	Everolimus

* Evidence based on PROMID and CLARINET trials, which do not include patients with NETs of lung origin.

2.3 Evidence-Based Considerations for a Funding Population

Precise data describing the expected patient population potentially eligible for treatment with everolimus annually is generally unavailable. In 2009 there were approximately 600 patients diagnosed with NETs in Ontario.[1] Approximately 25% had NETs of pulmonary origin, 30% of pancreatic origin, and 30% had non-pancreatic GI NETs; 60% of patients had advanced disease at diagnosis, and one-third of diagnoses would be functional and therefore not eligible for everolimus based on the inclusion criteria of the relevant clinical trial. Although this does not account for increasing incidence and higher prevalence due to indolent clinical behavior, based on incidence rates it is estimated that about 240 patients per year in Ontario (approximately 600 patients per year in Canada) would be potential candidates for everolimus. The actual number of patients prescribed everolimus however, might be substantially lower as many patients are observed until progression, treated with locoregional therapies, or are unfit for everolimus therapy. The major indication for consideration of everolimus would be for patients with incurable local-regional or

metastatic, non-functional NETs of non-pancreatic origin with progressive disease despite optimal dose long-acting somatostatin analogue therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

Everolimus is currently in routine clinical use for specific populations of patients with metastatic renal cell carcinoma, breast cancer, and pancreatic NETs. Combination use of everolimus with somatostatin analogues either for functional or non-functional NETs represents the most obvious other population for whom the drug might be considered.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Carcinoid Neuroendocrine Tumour Society of Canada (CNETS Canada), provided input on everolimus for the treatment of unresectable, locally-advanced or metastatic, well-differentiated non-functional neuroendocrine tumours (NETs) of gastrointestinal or lung origin (GIL) in adults with progressive disease.

CNETS Canada conducted online surveys using SurveyMonkey and telephone interviews directed to patients and caregivers to collect both qualitative and quantitative information about the impact of NETs GIL on their lives and the effect of treatment. The surveys were promoted on the CNETS Canada website, Facebook page and Facebook closed support group. They were also promoted on several US based closed Facebook groups for NETs cancer. In addition, CNETS Canada invited patient and caregiver interview participation through e-mail, Support Group Leaders, NET specialists, other health care professionals and partners. There were some patients and caregivers who participated in both a survey and telephone interview, but they were counted only once. CNETS Canada reported that survey and interview responses were confidential and anonymous.

CNETs Canada received responses from 17 patients, of which seven were male and 10 female, who provided their input for on everolimus for the treatment of patients with NETs GIL. Of these 17 respondents, 10 respondents had gastrointestinal NETs five respondents had lung NETs, and two respondents had NETs cancer of the pancreas. The age ranges of respondents were between 32 and 66 with the majority in their 50s and 60s. These respondents were from New Brunswick (n=4), Quebec (n=2), Ontario (n=4), Alberta (n=1), British Columbia (n=1), Manitoba (n=1), and outside of Canada (n=4). A total of 10 respondents had experience with everolimus.

CNETS Canada also included responses collected from caregivers. There were six caregivers who participated in providing input. Four (4) of these caregivers participated in telephone interviews. Of these four caregiver respondents, two had completed the online survey. Caregiver respondents were from New Brunswick (n=2), Ontario (n=2), Manitoba (n=1), and Alberta (n=1).

From a patient's perspective, the physical and emotional impact of living with NETs GIL was varied. According to CNETS Canada, respondents interviewed reported that living with their NETs cancer makes life uncertain because of the terminal nature of the disease and no cure being available. Respondents reported that the biggest challenge they face is dealing with disease symptoms such as fatigue/lack of stamina, diarrhea, bloating, and abdominal cramps. Additional challenges reported by respondents include being sick for a long time due to misdiagnosis and having to make changes in their life because of their cancer.

Respondents also stated that NETs cancer has a negative impact on patients' quality of life. All respondents interviewed indicated that their energy levels were affected negatively by their NETs cancer and as a result they have less energy and more fatigue thus affecting their ability to engage in leisure, social activities, travel and work.

CNETS Canada indicated that the most common therapies for NETs cancer patients in Canada include surgery and Somatostatin Analogues (Sandostatin, Lanreotide). Other therapies include ablative techniques, liver embolization, and chemotherapy. CNETS Canada stated that on a limited basis through clinical trials, Peptide Receptor Radionuclide Therapy (PRRT) is available.

For respondents who have not used everolimus, the expectation is that the drug would shrink tumours and that not as much tissue would have to be removed through surgery. In addition, the treatment would provide better symptom control for bloating, diarrhea, constipation and energy levels. For respondents who have experience with everolimus, the greatest benefit that respondents reported with taking everolimus was a reduction in the progression of their disease, followed by tumour shrinkage, a decrease in disease symptoms and improved wellness. Two respondents also commented that they had stability in their disease. The most common side effects respondents found with taking everolimus were fatigue, followed by mouth sores and

increased diarrhea. It was noted that respondents would like their doctors to explain all the side effects of the drug, not just the most common tolerable ones. In their opinion, clear and fulsome information will allow patients to factor this information into their decision making process as to whether or not to take this treatment.

Please see below for a summary of specific input received from CNETS Canada. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with NETs GIL

According to CNETS Canada, NETs cancer is rare. CNETS Canada indicated that patients have to learn about it on their own and be their own advocate. CNETS Canada also state that often, doctors, in general, don't know a lot about NETs cancer.

Below were some of the key responses reported by respondents to help illustrate the impacts in regards to their experiences with NETs GIL:

- *"I have to second guess the information that doctors give me. I get different answers to the same question. I have to advocate for myself and there is a backlash."(female lung NETs patient)*

- *"The biggest issue was getting the doctor to listen. I had constipation and probably a partial bowel blockage. The primary [tumour] came out with emergency surgery after I hemorrhaged." (female gastrointestinal NETs patient)*
- *"The biggest learning is that NET cancer is like living with a chronic disease when you compare it to other cancers. It changes your thinking that you could be cancer free. This thing is a death sentence. People are dying all around us." (male gastrointestinal NETs patient)*
- *"At first there was diarrhea. There was so much diarrhea I had to get three Octreotide shots a day. I was not well enough to go out. I had to be near a bathroom." (female gastrointestinal NETs patient)*

When asked about challenges, respondents interviewed indicated that the biggest challenge they face is dealing with disease symptoms, such as, fatigue/lack of stamina, diarrhea, bloating, and abdominal cramps. Other challenges identified included being sick for a long time because of misdiagnosis, and having to make changes in how they live because of their cancer.

Below were some of the key responses reported to help illustrate the challenges faced by these respondents:

- *"I was sick for 6-7 years. I felt horrible. It was shrugged off for many years by doctors. I had diarrhea and a big tumour blocking my lung." (female lung NETs patient)*
- *"It has completely changed how I live despite my best efforts. Surviving and taking care of my health takes most of my time." (male PNETs patient)*
- *"I have five days a month that I feel bad. I have diarrhea, bouts of bloating and pain." (male gastrointestinal NETs patient)*
- *"My lack of stamina is my biggest challenge. The off switch happens fast. I can run out of steam really fast." (female gastrointestinal NETs patient)*

- *"My biggest challenge was finding out what it was. Doctors did not recognize it and shuffled me along from doctor to doctor. " (female gastrointestinal NETs patient)*

In order to gather data on the NETs patient experience, The International neuroendocrine Cancer Alliance (INCA) and Novartis Pharmaceuticals Corporation collaborated on a first global survey. The goal of the Global NETs Survey was to *"increase understanding of the experiences, needs and challenges of NET patients, and to provide insights and learnings among countries and regions to advance NET care."* Below are key findings from the international survey.

A total of 1928 NETs patients responded to the survey worldwide. The study found that most patients' quality of life was negatively affected. Specifically, the study results showed that decreased energy levels and emotional health issues were very common among respondents. Patients also had to make necessary lifestyle changes around diet, physical activity, and spend more time and money on appointments. Their work life was also negatively affected. Furthermore, 80% of those patients not working were not able to work because of their NETs. An additional 50% of those patients working had to often miss work because of their disease.

CNETS Canada submits that their patient input showed similar results to the Global NET Patient Survey. In addition, 73% of those respondents completing online surveys for CNETS Canada indicated that fatigue/weakness has the largest impact on their quality of life. A further 33% of respondents indicated that anxiety/palpitations and flushing, rash or redness has the second largest impact on their quality of life. CNETS Canada stated that both online surveys and interviews with NETs patients show that the area that most impacts quality of life are energy levels and the ability to work as they are interlinked.

CNETS Canada reported that NETs cancer has a negative impact on patients' quality of life. The summaries below are from interviews with seven respondents who reported on how NETs cancer has impacted on their day-to-day life.

Energy levels

CNETS Canada reported that all respondents interviewed indicated that their energy levels were negatively affected by their NETs cancer. They have less energy and more fatigue which affects their ability to engage in leisure and social activities, travel and work. CNETS Canada reported that one respondent indicated he plans for shorter days and doesn't start as early in the morning as he used to. A second respondent indicated his energy was down 20% compared to what it used to be. A third respondent takes a nap every day and says he is *"not at a high energy level."*

Emotional health

CNETS Canada reported that respondents' emotional health is affected in different ways with some patients being more impacted than others. CNETS Canada indicated that one respondent said his NETs cancer diagnosis was "*devastating"* and "*pretty heavy duty*." He noted that it is hard to remain positive about life and the future. A second respondent said while his emotional health hadn't been affected "*too badly,"* he is less tolerant than he used to be and "quick to rage." A third respondent gets counselling and tends to hang out with groups that deal with cancer to deal with emotional issues. A fourth respondent tries to be upbeat and positive but feels lonely and withdrawn.

Participation in leisure activities and social life

Overall, CNETS Canada reported that respondents interviewed stated that their leisure activities and social life have been greatly affected because of their NETs cancer. One respondent said while he still goes out to visit friends and sit on committees, he plans for afternoon naps and paces himself differently. Another respondent's partner broke up with her after her diagnosis and she doesn't want to go out because of this. A third respondent indicated that she stays home in

the evening now as she is too tired to go out. In addition, she can no longer play with her grandchildren the way she used to. A fourth respondent indicated that because of fatigue and energy levels, his leisure activities are "*severely curtailed*." He noted he doesn't ride his bike anymore.

Travel

According to CNETS Canada, the ability to travel has affected all respondents interviewed. For some, it means not doing personal and enjoyable travel. One respondent did not travel to attend her son's wedding because she felt it would be too much for her. Another respondent had to cancel a holiday in Europe because of fatigue. A third respondent only travels for medical reasons even though she used to enjoy personal travel. She doesn't travel because she is worried about her health and finances. A fourth respondent travels but needs to plan shorter trips and shorter days. A fifth patient finds he often gets sick after he travels.

Ability to work

CNETS Canada reported that all respondents interviewed were affected in terms of their ability to work except one person who was retired. Two respondents are off work right now because they are recovering from surgery or undergoing treatment. An additional two respondents are working reduced hours, and other three respondents stopped working soon after diagnosis. Two respondents reported that their career opportunities have been affected. One respondent is affected in terms of progressing to managerial positions and a second wonders if she will have the job she had before when she goes back to work.

Finances

CNETS Canada reported that most respondents indicated they have fewer financial resources now because they are on not working or working less than they did before their diagnosis. In some cases, expenses are higher for costs related to treatments, travel to medical appointments, certain diets, and supplements.

Relationships

CNETS Canada stated that five respondents reported strong support from their spouses, families and friends. However, in this group one respondent explained that his relationship with his spouse had changed. He stated that now the disease has become front and centre, and is a "*massive reoccupation."* Two younger respondents indicated that their NETs cancer has negatively impacted their ability to be in a relationship. For example, one respondent wanted to meet someone and start a family. CNETS Canada reported that he feels that this is no longer a possibility because of his chronic condition. Additionally, he indicated he made a decision not to have kids if he could not feel confident that he would be around when they grew up.

CNETS Canada also stated that one respondent spoke about relationships in this way: *"It's been really tough on the kids and my husband. In 2011, I was 28 days in ICU. It was critical and we were far from home. We have never recovered from it and it's taken its toll. My husband had to eat off my hospital tray because we had not planned on being away for this long."*

3.1.2 Patients' Experiences with Current Therapy for NETs GIL

CNETS Canada stated that the most common therapies that respondents have experienced are surgery followed by Somatostatin Analogues (Sandostatin, Lanreotide). CNETS Canada reported that to a lesser degree, respondents have experienced chemotherapy (n=2), liver embolization (n=2), ablative techniques (n=1) and Peptide receptor radionuclide therapy (n=1).
In terms of effectiveness of therapies, CNETS Canada reported that at the very best, respondents say they slow disease progression and help control symptoms. However, on the down side, respondents indicated that they cause debilitating side effects, and complications.

CNETS Canada stated that none of the current therapies respondents are using either reverses or cures their NETs cancer.

Below were respondents' quotes from the survey and interviews. CNETS Canada indicated that respondent experience with their current therapies, other than everolimus.

- *"Having the primary removed has greatly improved the condition of my digestive tract and the current treatment seems to be keeping my condition stable, as near as can be determined by medical tests. (female gastrointestinal NETs patient)*
- *"Having lung NET very concerned that surgery was only option and removal of lung can be issue if future recurrence. Would love to have been able to have a treatment to shrink tumour prior to surgery." (female Lung NETs patient)*
- *"Removal of lung and mediastinal nets by surgery; Liver ablation led to pain, sepsis and 10 day post surgery hospital admission. Progression of disease regardless of treatments."(female Lung NETs patient)*
- *"Removal of the primary tumour, apparently, has slowed the disease progression."(male gastrointestinal NETs patient)*
- *"Sandostatin is my best friend. Helps my frequent stools and somewhat slows growth." (male gastrointestinal NETs patient)*
- *I had surgery 6 months after diagnosis. I had a small bowel re-section. In a month or two I was on Sandostatin LAR. Overall I have had slow growth since 2013. Things haven't changed dramatically with my symptoms. But it hasn't stopped or reversed it." (male gastrointestinal NETs patient)*
- *"I have bad side effects with Lanreotide and Octreotide; I am not on anything, finding relief with many health products." (female Lung NETs patient)*

When respondents were asked about access to treatment, CNETS Canada reported that 55% of respondents indicated that treatments were hard to access because of financial difficulties. CNETS Canada stated that one respondent paid $10,000 a year for needed treatment and then $5,000 a year when she was switched to another drug. According to CNETS Canada, she was not working and her husband was on a reduced income. CNETS Canada stated that other respondents had to pay for their travel and accommodation when travelling to receive treatment.
CNETS Canada indicated that having to travel within and out of province or state to access NET specialists treatment also makes it difficult to access treatments. According to CNETS Canada, respondents described how they had to travel within their province or out of province to get treatment.

3.1.3 Impact of NETs GIL and Current Therapy on Caregivers

According to CNETS Canada, caregivers are unanimous in that their experience is scary, frustrating and emotional being the caregiver of a loved one who is a NETs patient. CNET Canada reported that often caregivers are the ones who do the research on NETs cancer and carry the burden of work, home and caregiver activities.

When caregiver respondents were asked to describe their experience, the following responses were noted:

- *"It's very emotional. The patient spent a good time in denial. He wouldn't say the cancer word. I was the one who had to speak to doctors, do the research and get information."*
- *"I see what the future holds. It's very upsetting and scary for me. I took it very hard."*

- *"Even now doctors don't know about it [NET cancer]. It's stressful, scary and frustrating."*
- *"it's always being on tenterhooks wondering when the next crisis is going to happen."*

When caregivers were asked about the biggest challenges, CNETS Canada indicated that access to appropriate therapies was the biggest challenge as reported by four caregiver respondents who completed the survey. CNETS Canada stated that current treatments impact a caregiver role through frequent medical appointments. Caregiver respondents interviewed stated that their biggest challenges include the impact on their emotional health, carrying an extra load at home, helping to make decisions, being on top of information about the disease, and finances.

Below were some key responses noted from respondent interviews regarding challenges faced by caregivers:

- *As a caregiver you do the research, you are mother, father, wife, work, I do it all."*
- *" Financial is huge. I am the sole breadwinner. He [the patient] stopped working in 2015. I am working or home. I never know which bill to pay first."*
- *"Fatigue, worry, being consumed by the disease and making sure we are getting the best possible options for my husband's health. It takes a great amount of energy to stay on top of all the latest information about the disease especially around treatment options."*

According to CNETS Canada, caregivers reported that being a caregiver of a NETs patient has a negative impact in terms of quality of life. The areas impacted the most for caregivers are diminished energy levels and emotional health. CNETS Canada stated that emotional health and stress are related to not knowing if doctors are providing the correct information and treatment, the mood of the patient and the ongoing health problems that come with NETs cancer. Furthermore, leisure and social activities along with travel are also impacted. Caregiver respondents stated that there is less time for social and leisure activities and these activities are often affected by the patient's health. In addition, respondents stated that for some, there is less money.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with everolimus

Based on no experience using the drug:

CNETS Canada stated that for respondents interviewed who were not on everolimus, the biggest expectations for these respondents are that it would stop growth and shrink tumours including liver metastases for GI tract and Lung NETs patients where other treatments have not been successful. CNETS Canada also stated that in the case of Lung NETs, the expectation is that everolimus would shrink tumours and not as much lung tissue would have to be removed through surgery. Furthermore, another expectation is that it would provide better symptom control for bloating, diarrhea, constipation and energy levels. Similarly, CNETS Canada found that 93% of respondents completing online surveys indicated that the most important aspect of their disease to control was disease progression. Additionally, 47% of respondents said that the second most important aspect to control was fatigue.

CNETS Canada noted that respondents spoke about the importance of having different treatment options. One respondent indicated that it would be good to have everolimus as another treatment in the arsenal and something to fall back on if another treatment doesn't work. She noted that *"it would be good to have other options."* However, she also noted that the cost of the drug would be a factor. She said, *"The more options we have, the further we can push back that day."* Another respondent indicated that the drug should be easy to administer and affordable. She noted, *"It*

would be good to have another arrow in your quiver to treat this cancer and choices for patients; individualized care to suit patients."

When asked about the potential downsides of everolimus, respondents interviewed stated that they want clear information on the side effects of this drug so they can make their decisions on whether or not the benefits of the drug outweigh the risks. CNETS Canada reported that both patients and caregivers indicated that the potential drawback of everolimus would be the intensity of the side effects and the impact of the drug on other needed treatments for both NETs cancer and other conditions that patients have in addition to their NETs cancer.

CNETS Canada stated that one respondent said that *"if and when Afinitor is rolled out, I wish that medical staff would be forthright in terms of protocols and side effects."* Another respondent said, *"If the drug makes my arthritis worse, I could not tolerate it*." One caregiver respondent stated that "*you have to weigh the side effects with quality of life. It's worth a shot."*

Based on patients' experiences with the drug as part of a clinical trial or through a manufacturer's compassionate supply or by paying for it out of pocket or through private insurance:

CNETS Canada reported that ten (10) patient respondents indicated they had experience with everolimus and 1 caregiver's spouse was on everolimus. CNETS Canada stated that all patient respondents had GI tract or Lung NETs, except two respondents who had PNETS.

According to CNETS Canada, the greatest benefit that respondents who were surveyed indicated they experienced from taking everolimus was a reduction in the progression of their disease (56%), followed by tumour shrinkage (33%), a decrease in disease symptoms (33%) and improved wellness (33%). Two respondents also commented that they had stability in their disease.

Below were some key responses noted regarding benefit from respondents to the survey and interviews:

- *"Had tumor shrinkage or no new growth for first year and half." (male Lung NETs patient)*
- *"Worked by keeping disease in check from spreading for 3.5 years." (male gastrointestinal NETs patient)*
- *"It has stopped the progression of the disease for almost five years. Although not shrinking the tumors, it has increased my quality of life. It has also helped with most of the side effects of the cancer." (female Lung NETs patient)*
- *"It was great for me for 3 years plus."(female gastrointestinal NETs patient)*
- *"It been pretty good. It seems to have stabilized it. There was a little bit of shrinkage one time. For me, it's doing the job. How long it lasts is open to debate." (male PNETs patient)*

CNETS Canada reported that the most common side effects respondents surveyed found with taking everolimus were fatigue (80%), followed by mouth sores (60%) and increased diarrhea (20%). CNETS Canada also stated that on an individual basis, respondent's comments showed they had other side effects as well.

Below were some key responses regarding side effects from respondents to the survey and interviews:

- *"In the past, I developed mouth sores. It was really irritating when you ate. They prescribed mouthwash. Then in two days they would go down." (male PNETs patient)*
- *"I had fatigue, mouth sores and nausea and vomiting." (female lung NETs patient)*
- *"I didn't have many ill feelings from this drug." (female gastrointestinal NETs patient)*

- Caregiver respondent observations*: "There was extreme tiredness over and above the cancer. There were sores in the mouth that were managed by a prescription mouth wash. When they were really bad, he had to go on a soft diet and he had weight loss. When we were seeing shrinkage and stability, the benefits outweighed the adverse effects." (caregiver of a male lung NETs patient)*

CNETS Canada also indicated that one of the main points emphasized in respondent interviews was that respondents would like their doctors to explain all the side effects of the drug, not just the most common tolerable ones. Clear and fulsome information will allow patients to factor this information into their decision making process as to whether or not to take this treatment.

3.3 Additional Information

CNETS Canada indicated that NETs cancer is a rare disease with no cure and no remission. From an organizational perspective, CNETS Canada has identified a critical need for more treatment options for its patient community.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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 CADTH website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of everolimus for neuroendocrine tumours:

Clinical factors:

- No standard treatment option for patients with progressive disease
- Clarity of eligible patients

Economic factors:

- Very small patient population
- Flat pricing for most tablet strengths (2.5 mg, 5 mg, and 10 mg)

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that there is no current standard of care for the treatment of non-functional neuroendocrine tumours of gastrointestinal or lung origin in patients with progressive disease. Patients may be treated with somatostatin analogues or chemotherapy while other patients would receive best supportive care.

4.2 Factors Related to Patient Population

There are a small number of patients with non-functional neuroendocrine tumours of gastrointestinal or lung origin. There is an unmet need for patients whose disease has progressed or relapsed. Everolimus will provide a treatment option for these patients and it is already funded for patients with pancreatic neuroendocrine tumours.

PAG is seeking clarity on the patients suitable for treatment with everolimus as it was noted that the RADIANT 4 trial included previously treated patients and treatment-naïve patients but excluded patients with more than one line of prior chemotherapy.

PAG is seeking information on the use of everolimus after failure of treatment with somatostatin analogues, if available.

4.3 Factors Related to Dosing

The dose of everolimus is 10mg once daily, which is the same dose as for other cancers. Everolimus is available in multiple strengths for dosage adjustments. These are enablers to implementation.

Since there are three strengths of tablets, PAG has some concerns with wastage when dose adjustments are made and a different tablet strength is required prior to the patient completing the strength initially provided.

4.4 Factors Related to Implementation Costs

PAG noted there would be a small incremental budget impact due to the small number of patients but treatment cost per patient is high and duration of treatment is unknown.

Everolimus is already funded for pancreatic neuroendocrine tumours in most of the provinces. Healthcare professionals are familiar with using everolimus and managing its toxicities with dose reductions. Although some additional resources may be required to monitor and treat toxicities, additional chemotherapy chair time in the clinics is not required to administer everolimus, as it is an oral drug.

4.5 Factors Related to Health System

PAG noted that everolimus is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.6 Factors Related to Manufacturer

PAG identified that the flat pricing structure (for 2.5 mg, 5 mg, and 10mg tablets) is a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

No registered clinical input was received.

6 SYSTEMATIC REVIEW

6.1 Objective

The primary objective of this systematic review is to evaluate the efficacy and safety of everolimus compared to best supportive care for the treatment of unresectable, locally advanced or metastatic, well differentiated, non-functional neuroendocrine tumours (NETs) of gastrointestinal or lung (GIL) origin in adults with progressive disease.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished double-blind randomized controlled trial Published or unpublished non-blinded randomized controlled trial	Adults with unresectable, locally advanced or metastatic, well differentiated, non-functional neuroendocrine tumours (NETs) of gastrointestinal or lung origin with progressive disease	Everolimus (Afinitor®), 10 mg tablet orally, once daily	Placebo (best supportive care) Octreotide Lanreotide Pasireotide	Efficacy PFS OS ORR DCR HRQoL Safety Withdrawals due to AEs Serious AEs AEs Dose reductions Duration of treatment
PFS: progression-free survival; OS: overall survival; ORR: objective response rate; DCR: disease control rate; HRQoL: health-related quality of life; AE: adverse event				

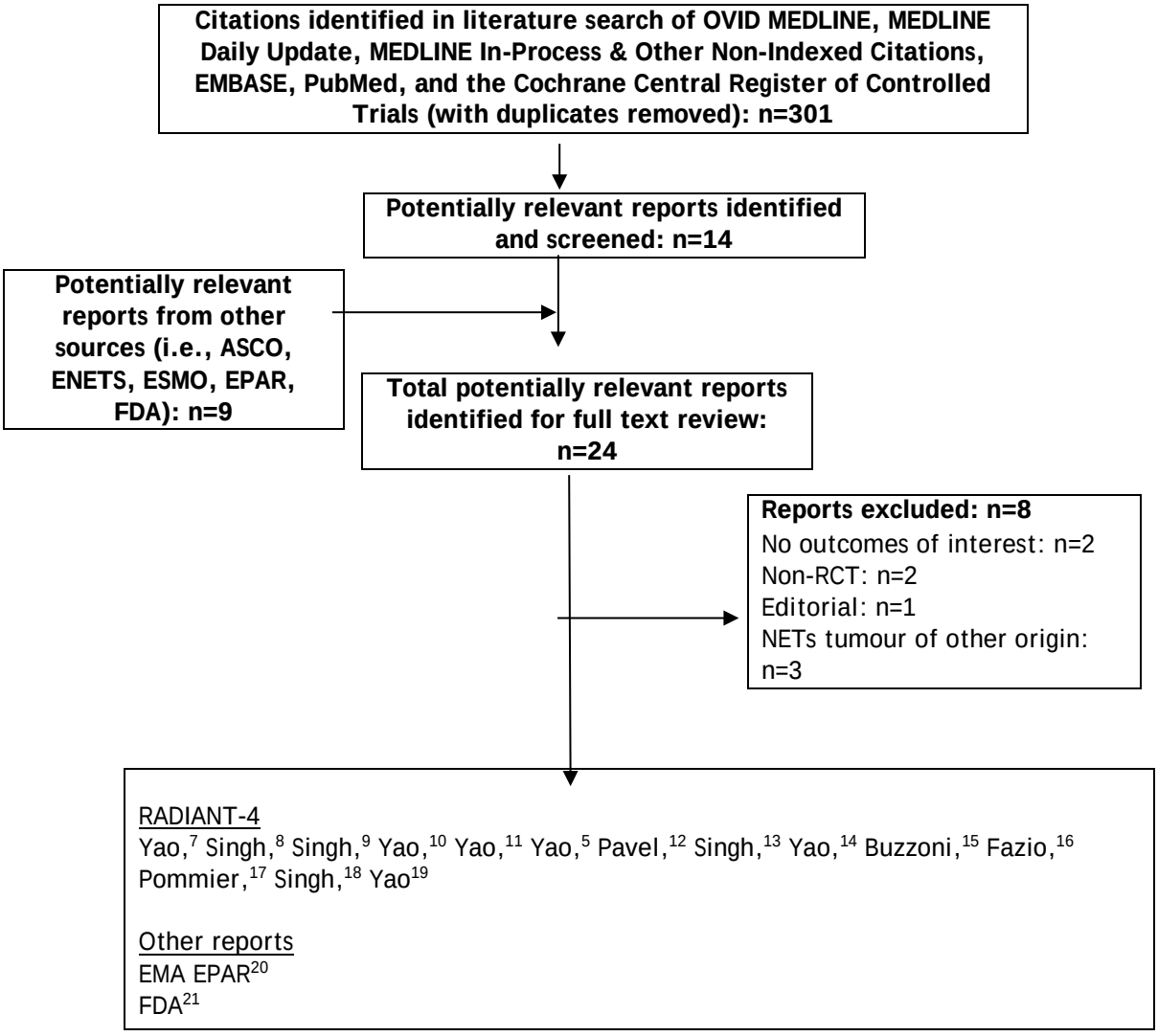
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 22 potentially relevant reports identified, 16 reports were included in the pCODR systematic review[5,7-21] and 8 studies were excluded. Studies were excluded because they did not contain outcomes or interest (n=2), were not randomized controlled trials (n=2), were of editorial nature (n=1) or were of NETs tumour of other origin (n=3).

Figure 1. **QUOROM flow diagram for inclusion and exclusion of studies**



Note: Additional data related to RADIANT-4 study were also obtained through requests to the Submitter by pCODR[22,23]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: RADIANT-4 (NCT01524783)[5,24] **Characteristics:** Phase III, randomized (2:1 ratio intervention:control), double-blind, placebo-controlled study N= 302 randomized; n= 205 allocated to everolimus* 97 centres in 25 countries (Austria, Belgium, Canada, China, Colombia, Czech Republic, Germany, Greece, Hungary, Italy, Japan, Lebanon, Netherlands, Poland, Russia, Saudi Arabia, Slovak Republic, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom, USA) **Patient Enrolment Dates:** April 3, 2012 - August 23, 2013 **Primary analysis data cut-off:** November 28, 2014 (final PFS + first interim OS) **Secondary OS interim analysis:** November 30 2015 **Funding:** Novartis Pharmaceuticals Corporation	<u>Key Inclusion Criteria (all of):</u> • Adult (aged ≥18 years) • Pathologically confirmed, advanced (unresectable or metastatic), non-functional, well-differentiated (grade 1 or 2 according to the 2010 WHO classification) neuroendocrine tumours of lung or gastrointestinal origin • Documented radiological disease progression within 6 months • Measurable disease according to modified RECIST version 1.0 • WHO performance score/ECOG of 0 or 1 • Adequate bone marrow, liver and kidney function • Patients previously treated with a somatostatin analogue, interferon, one line of chemotherapy, peptide receptor radionuclide therapies, or a combination of these were eligible if disease progression was documented during or after last treatment • Antineoplastic therapy discontinued for at least 4 weeks (or 6 months in case of peptide receptor radionuclide therapies) <u>Key Exclusion Criteria (any of):</u> • History of or presented with carcinoid syndrome, poorly differentiated histology or pancreatic neuroendocrine tumours • More than one line of chemotherapy, treatment with mTOR inhibitors • Hepatic intra-arterial embolization within 6 months • Cryoablation or radiofrequency ablation of hepatic metastases within 2 months • Chronic treatment with corticosteroids or other immunosuppressive agents	<u>Intervention</u> Everolimus: 10 mg orally per day + best supportive care <u>Comparator</u> Placebo + best supportive care	<u>Primary:</u> PFS <u>Secondary:</u> OS ORR DCR HRQoL WHO performance status/ECOG Pharmokinetics Changes in chromogranin A Neuron-specific enolase levels Safety
*n=203 treated, 2 did not receive intervention			

PFS: progression-free survival, defined as the time from randomization to death or progression as per modified RECIST version 1.0 criteria; OS: overall survival; ORR: objective response rate; DCR: disease control rate; HRQoL: health related quality of life;

a) Trials

One trial met the inclusion criteria for review. The RADIANT-4 trial was a phase III, double-blind, placebo-controlled trial where patients were randomly assigned in a 2:1 ratio to receive oral everolimus at a dose of 10 mg per day or identical placebo. Both groups were provided with best supportive care. Best supportive care included treatment deemed necessary by the physician except anti-tumour agents like somatostatin analogues, interferons, tumour ablative procedures, radiation, and concurrent chemotherapy.

Randomization was stratified by previous somatostatin analogue treatment (defined as continuous somatostatin analogue treatment for ≥12 weeks), tumour origin (based on prognostic level, grouped into two strata: stratum A—better prognosis: appendix, caecum, jejunum, ileum, duodenum, or neuroendocrine tumour of unknown primary origin versus stratum B—worse prognosis: lung, stomach, colon (other than caecum) or rectum), and WHO performance status/ECOG (0 versus 1). Patients, investigators and study sponsor were masked to treatment assignment. Sponsor conducted the analysis.

All randomly assigned patients were included in the full analysis set. Analyses were done on an intention-to-treat basis for the primary end-point. Safety population included all patients who received at least one dose of the study drug with at least one post-baseline safety assessment. There were two data cut-offs for RADIANT-4: primary analysis (final PFS + first interim OS) on November 28, 2014; and second interim OS analysis on November 30, 2015.

b) Populations

A total of 302 eligible patients were enrolled and randomly assigned to everolimus 10 mg per day (205 patients) or placebo (97 patients). 18 Canadian patients were enrolled across 7 sites.

Of the 205 patients allocated to everolimus, one patient withdrew his/her consent prior to receiving the intervention and one patient received the wrong allocated intervention (placebo). A total of 203 patients received everolimus as the allocated intervention. Among the 203 who received everolimus as the allocated intervention, one protocol deviation occurred where a patient received everolimus for 28 days despite having no pathologically confirmed, well differentiated, advanced NETs or GI or lung origin violating inclusion criteria. A total of 97 patients were allocated to the placebo group, and 97 patients received placebo as the intervention. One protocol deviation occurred where the patient was randomized despite being HCV-positive at screening and meeting exclusion criteria; they were treated with placebo for 29 days before discontinuation. Therefore, the safety population comprised 202 patients in the everolimus group and 97 patients in the placebo group. See the following table as a summary of the major protocol deviations.

Table 5: Major protocol deviations, full analysis set[20]

Protocol deviation	Everolimus+BSC N=205 n (%)	Placebo+BSC N=97 n (%)	All patients N=302 n (%)
Any protocol deviation	71 (34.6)	29 (29.9)	100 (33.1)
Any major protocol deviation	4 (2.0)	1 (1.0)	5 (1.7)
No pathologically confirmed, well differentiated, advanced, NET of GI of lung origin	2 (1.0)	0	2 (0.7)
Patient has not discontinued treatment prior to the day of randomization as follows: prior SSA and/or IFN and/or chemotherapy for at least 4 weeks and/ or prior PRRT for at least 6 months	1 (0.5)	1 (1.0)	2 (0.7)
New anti-neoplastic therapy administered prior to first tumor assessment	0	1 (1.0)	1 (0.3)
Patient received treatment other than randomized treatment	1 (0.5)	0	1 (0.3)
Any minor protocol deviation	69 (33.7)	28 (28.9)	97 (32.1)

- A patient may have multiple protocol deviations
- Major protocol deviations are those leading to exclusion from the per protocol set.

The following table summarizes the population in the RADIANT-4 trial. Baseline characteristics appear similar.

Table 6: Baseline patient characteristics in the RADIANT-4 trial[5]

	Everolimus (n=205)	Placebo (n=97)
Age, median (range)	65 (22 – 86)	60 (24 – 83)
Sex, female (%)	116 (57%)	44 (45%)
WHO performance status/ECOG*		
0	149 (73%)	73 (75%)
1	55 (27%)	24 (25%)
Primary tumour site		
Lung	63 (31%)	27 (28%)
Ileum	47 (23%)	24 (25%)
Rectum	25 (12%)	15 (16%)
NET tumour unknown origin	23 (11%)	13 (13%)
Jejunum	16 (8%)	6 (6%)
Stomach	7 (3%)	4 (4%)
Duodenum	8 (4%)	2 (2%)
Colon	5 (2%)	3 (3%)
Caecum	4 (2%)	1 (1%)
Appendix	1 (1%)	0
Other	6 (3%)	2 (2%)
Tumour grade+		
Grade 1	129 (63%)	65 (67%)
Grade 2	75 (37%)	32 (33%)

	Everolimus (n=205)	Placebo (n=97)
Time from initial diagnosis to randomization		
≤6 months	26 (13%)	12 (12%)
>6 months to ≤18 months	51 (25%)	25 (26%)
>18 months to ≤36 months	41 (20%)	22 (23%)
≥36 months	87 (42%)	38 (39%)
Previous treatments		
Surgery	121 (59%)	70 (72%)
Chemotherapy	54 (26%)	23 (24%)
Radiotherapy	44 (22%)	19 (20%)
Locoregional and ablative therapies	23 (11%)	10 (10%)
Somatostatin analogues	109 (53%)	54 (56%)
Disease sites		
Liver	163 (80%)	76 (78%)
Lymph node or lymphatic system	85 (42%)	45 (46%)
Lung	45 (22%)	20 (21%)
Bone	42 (21%)	15 (16%)
Peritoneum	25 (12%)	8 (8%)
Liver tumour burden		
None	34 (17%)	14 (14%)
≤10%	119 (58%)	61 (63%)
>10% to 25%	29 (14%)	8 (8%)
>25%	21 (10%)	14 (14%)
Unknown	2 (1%)	0
*one patient in the everolimus group had a WHO performance status of 2 +tumour grade not available for one patient in everolimus group		

More than half of the patients received prior somatostatin analogues, mainly octreotide. The following table outlines prior somatostatin analogues in the full analysis set.

Table 7: Prior somatostatin analogues (SSA) in the full analysis set[20]

	Everolimus (n=205)	Placebo (n=97)	All patients (n=302)
Prior somatostatin analogues	109 (53.2)	54 (55.7)	163 (54.0)
Type of prior SSA*, n(%)			
Octreotide LAR	84 (77.1)	42 (77.8)	126 (77.3)
Octreotide s.c.	12 (11.0)	11 (20.4)	23 (14.1)
Pasireotide LAR	2 (1.8)	1 (1.9)	3 (1.8)
Lanreotide	18 (16.5)	5 (9.3)	23 (14.1)
Other LAR	4 (3.7)	1 (1.9)	5 (3.1)
Other s.c.	3 (2.8)	0	3 (1.8)
Duration of exposure to prior SSA (months)			
n	109 (53.2)	54 (55.7)	163 (54.0)

	Everolimus (n=205)	Placebo (n=97)	All patients (n=302)
Mean (SD)	24.18 (25.3)	21.09 (20.3)	23.2 (23.7)
Median	15.90	14.87	14.95
Min-Max	0.0 – 103.5	0.0-77.3	0.0 – 103.5
Duration of exposure to prior SSA categories (n(%)			
< 6 months	25 (22.9)	15 (27.8)	40 (24.5)
6 months to < 2 years	46 (42.2)	21 (38.9)	67 (41.1)
2 years to < 5 years	27 (24.8)	13 (24.1)	40 (24.5)
>5 years	11 (10.1)	5 (9.3)	16 (9.8)
Time since last prior exposure to SSA, n(%)			
Ongoing	0	0	0
<4 weeks	0	0	0
4 weeks to < 8 weeks	43 (39.4)	25 (46.3)	69 (41.7)
8 weeks to < 24 weeks	43 (39.4)	19 (35.2)	62 (38.0)
24 weeks to < 2 years	16 (14.7)	6 (11.1)	22 (13.5)
2 years to < 5 years	6 (5.5)	3 (5.6)	9 (5.5)
>5 years	1 (0.9)	1 (1.9)	2 (1.2)

*patients could have been exposed to more than one type of SSA

c) Interventions

Patients in the intervention group received 10 mg everolimus orally, daily. Median duration of treatment was 40.4 weeks in the everolimus group (range 0.7 – 120.4) versus 19.6 weeks in the placebo group (range 4.0 – 130.3). Crossover from placebo to open-label everolimus after progression was not allowed and patients and investigators remained masked to treatment assignment until primary analysis.

d) Patient Disposition

All patients randomized were assessed for efficacy with a multiphasic CT or MRI every 8 weeks during the first 12 months, and every 12 weeks thereafter.

Dose reductions and treatment interruptions for a maximum of 28 days were allowed. Two dose reductions were allowed: from 10 mg to 5 mg per day and then to 5 mg every other day. Crossover from placebo to open-label everolimus after progression was not allowed and patients and investigators remained masked to treatment assignment until primary analysis.

Median relative dose intensity, defined as the ratio of administered doses to planned doses) was 0.9 in the everolimus group and 1.0 in the placebo group. Dose reductions or temporary treatment interruptions occurred in 135 of 202 (67%) patients in the everolimus group and 29 of 98 (30%) of patients in the placebo group.

e) Analysis

Sample size was estimated based on the ability to detect a clinically meaningful improvement in progression-free survival, defined as a 41% reduction in the risk of disease progression or death. Given the assumption that median PFS would be approximately 5 months in the placebo group, this corresponded to a prolongation in median PFS from 5 to 8.5 months with everolimus. With 2:1 randomization and a one-sided type 1 error rate of 2.5%, a total of 176 PFS survival events were needed to provide 91.3% power. Adjusting for an estimated dropout rate of 15%, a sample size of 285 patients was calculated.

Data analysis cut off for progression-free survival and the first interim overall survival analysis was November 28, 2014. A second pre-planned interim overall survival analysis was done November 30, 2015. A final overall survival analysis will be done at 191 deaths.

Progression-free survival was determined by central radiology review, masked to treatment assignment and local assessment, was done in real time. Progression-free survival according to investigator assessment was a pre-specified supportive analysis.

f) Limitations/Sources of Bias

RADIANT-4 was sponsored by Novartis Pharmaceuticals Corporation, the maker of everolimus.

As with all studies, there are potential sources of bias:

- Although data was collected via data management systems and the funder's (Novartis Pharmaceuticals Corporation) statistical team was blinded, data was analyzed by the funder's statistical team. This may lead to detection bias; though risk of bias appeared minimal.
- Though real time blinded independent central radiological assessment occurred with an end-point of progression (and not overall survival), inadvertent unblinding may occur due to the appearance of adverse events due to the drug. This may lead to detection bias.
- As with many RCTs, only the healthiest patients within a disease are eligible to be enrolled in a trial. Due to the inclusion of only the best of the best (in this case, WHO performance score/ECOG of 0 or 1), generalizability of the results of the trial to all those with the disease condition may not be possible. This may lead to sampling bias.
- The use of subsequent treatments following the treatments under study may impact the overall survival of patients under treatment. This can happen due to the type of subsequent treatment used in second line or due to sequencing of treatments.

Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Progression-free survival events- November 2014 data cut-off, intention-to-treat analysis

Median progression-free survival, as assessed by central review, was 11.0 months (95% CI: 9.2 – 13.3) in the everolimus group and 3.9 months (95% CI 3.6 – 7.4) in the placebo group. Everolimus was associated with a 52% reduction in the estimated risk of disease progression or death (HR 0.48, 95% CI: 0.35 – 0.67, p<0.00001).

Estimated progression-free survival at 12 months, as assessed by central review, was 44% in the everolimus group and 28% in the placebo group.

Investigator assessed findings were consistent with central review. Median progression-free survival was 14.0 months (95% CI: 11.2 - 12.7) in the everolimus group and 5.5 months (95% CI: 3.7 - 7.4) in the placebo group. According to investigator assessment, everolimus was associated with a 61% reduction in the estimated risk of disease progression or death (HR 0.39, 95% CI: 0.28 - 0.54, p<0.00001).

Treatment effect appeared to be consistent across sub-groups.

Table 8: Progression-free survival, full analysis set, RADIANT-4 trial, data cut-off of November 28, 2014

	Everolimus (n=205)	Placebo (n=97)	HR for disease progression or death with everolimus (95% CI)	p-value
Central Radiology Review				
Progression-free survival events+	113 (55%)	65 (67%)		
Progression	104 (51%)	60 (62%)		
Death	9 (4%)	5 (5%)	0.48 (0.35 - 0.67)	<0.00001
Number censored	92 (45%)	32 (33%)		
Median progression-free survival, months	11.0 (9.2 - 13.3)	3.9 (3.6 - 7.4)		
Local Radiology Review				
Progression-free survival events+	98 (48%)	70 (72%)		
Progression	88 (43%)	63 (65%)		
Death	10 (5%)	7 (7%)	0.39 (0.28 - 0.54)	<0.00001
Number censored	107 (52%)	27 (28%)		
Median progression-free survival, months	14.0 (11.2-17.7)	5.5 (3.7 - 7.4)		
+includes disease progression and death				

Table 9: Progression-free survival by sub-groups, data cut-off of November 28, 2014 (NOTE: due to small sample size, study was not powered to detect differences in subgroups and no p-values are presented)

	Everolimus	Placebo	HR for disease progression or death with everolimus (95% CI)
Patients with GI NETs[9]	n=118	n=57	
Median PFS by central review, months	13.1	5.4	0.56
95% CI	9.2 - 17.3	3.6 - 9.3	(0.37 - 0.84)
Patients with NETs unknown primary[9]	n=23	n=13	
Median PFS by central review, months	13.6	7.5	0.60
95% CI	4.1 - NE	1.9-18.5	0.24 - 1.51
Patients with LUNG[16]	n=63	n= 27	
Median PFS by central review, months	9.2	3.6	0.50
95% CI	6.8-10.9	1.9 - 5.1	0.28 - 0.88
Patients with prior SSA[15]	n=109	n=54	
Median PFS by central review, months	11.1	4.5	0.56
95% CI	9.2-13.3	(3.6-7.9)	(0.37 - 0.85)
Patients with prior chemotherapy[17]	n=54	n=23	
Median PFS by central review, months	9.2	2.1	0.35
95% CI	(5.6 - 11.7)	(1.9 - 3.7)	(0.19 - 0.64)
+includes disease progression and death NE: not evaluable			

Overall survival

November 28, 2014 – interim analysis

As the progression-free survival results were significant, a planned interim analysis for overall survival was done after a total of 70 deaths (37% of the total targeted 191 deaths for the final OS analysis) at the November 28, 2014 data cut-off; a 36% reduction in the estimated risk of death relative to placebo was found, though statistical significance was not attained (HR 0.64, 95% CI: 0.40 – 1.05). Estimates of overall survival at the 25th percentile (25% of patients having survival events) were 23.7 months (95% CI 17.6 – 27.3) in the everolimus group and 16.5 months (95% CI 9.0 – 21.0) in the placebo group. Data not mature enough to provide estimation on median overall survival.

November 30, 2015 – secondary interim analysis

A pre-planned secondary interim OS analysis was done based on 101 deaths (53% of the targeted 191 deaths): 66 (32%) in the everolimus group and 35 (36%) in the placebo group. Median duration of study follow-up was 33.4 months. Everolimus was associated with a 27% reduction in the estimated risk of death compared to placebo, though statistical significance was not attained (HR = 0.73, 95% CI: 0.48-1.11, p=0.071).[14]

Cross-over

In RADIANT-4, crossover was not permitted until after the primary analysis if improvement in PFS was statistically significant.

Final analysis

Final overall survival analysis will be performed after a total of 191 deaths.

Objective response

Objective response rate (ORR) was defined as the proportion of patients with best overall response of complete response or partial response. ORR was calculated based on the full analysis set (all patients who underwent randomization). Confirmed objective responses (by central radiology review; all partial response) were recorded in four (2%) patients receiving everolimus and in one (1%) receiving placebo.

Disease stabilization (stable disease), best overall response was seen in 165 patients (81%) in the everolimus group compared with 62 patients (64%) in the placebo group.

Everolimus was associated with a higher disease control rate[5](calculated by adding the number of patients with stable disease to those with partial response or complete response) compared with placebo: 169 patients (82%) in the everolimus group versus 63 patients (65%) in the placebo group.[10]

Of patients that were assessed, 117 (64%) in the everolimus group and 22 (26%) in the placebo group had some degree of tumour shrinkage. A total of 33 patients, 21 in the everolimus group and 12 in the placebo group, were not included in the best percentage change analysis per central radiology review.

Exposure

Median duration of treatment was almost twice as long in the everolimus group (40.4 weeks (range 0.7 – 120.4) as in the placebo group (19.6 weeks, (range 4.0 – 130.3) after median follow-up of 21 months. Mean duration of exposure (mean treatment duration) at the November 2014 data cut-off was 46.7 weeks (standard deviation (SD): 32.5) in the everolimus group and 35.0 weeks (SD: 32.7) in the placebo group.

After discontinuation of therapy, 3 (1.5%) of patients in the everolimus arm and 2 (2.1%) in the placebo arm, received everolimus as the first subsequent line of therapy. Cross-over was not permitted during the double-blind period.

Median relative dose intensity, defined as the ratio of administered doses to planned doses, was 0.9 in the everolimus group and 1.0 in the placebo group.

Dose reductions or temporary treatment interruptions occurred in 135 (67%) of 202 patients in the everolimus group and 29 (30%) of 98 patients in the placebo group. See Table below for further details.

Table 10: Number of patients requiring dose interruptions and/or reductions of study drug, as copied from pCODR submission, from the November 2014 data cut-off

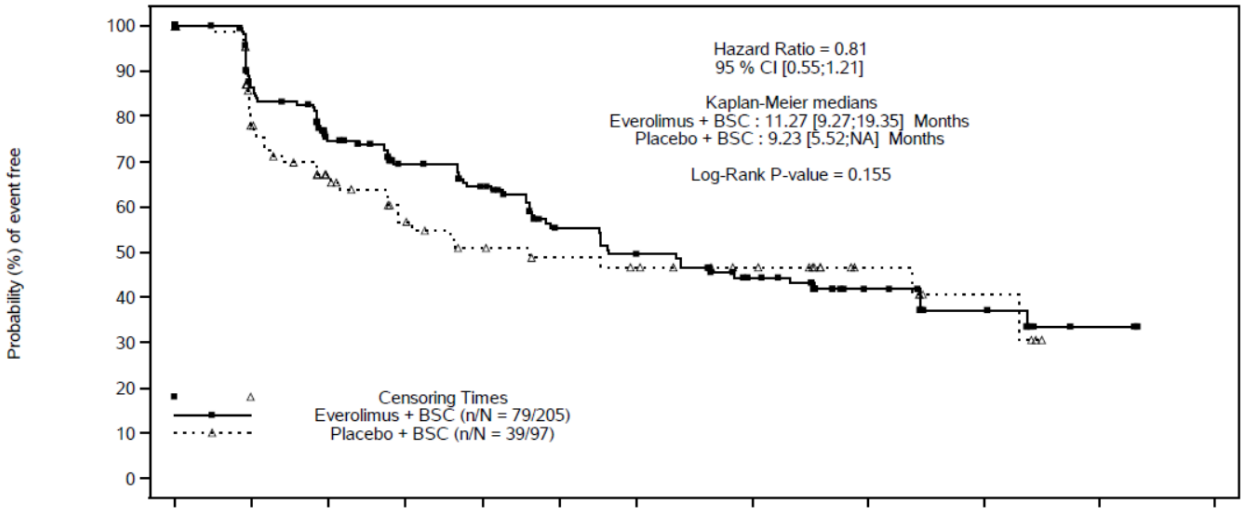
	Everolimus n=202	Placebo n=98
Interruptions and/or reductions		
Total number of patients requiring dose interruption and/or reduction	135 (67%)	29 (30%)
1 dose interruption and/or reduction	30 (15%)	14 (14%)
≥2 dose interruptions and/or reductions	105 (52%)	15 (15%)
Number requiring dose interruption	128 (63.4)	28 (28.6)
Number requiring dose reduction	91 (45.0)	7 (7.1)
Reasons for dose interruptions and/or reduction		
Adverse event	132 (65%)	16 (16%)
Concomitant medication affecting drug exposure	5 (3%)	1 (1%)
Dispensing error	2 (1%)	0
Dosing error	21 (10%)	14 (14%)
Re-escalation	71 (35%)	4 (4%)
Scheduling conflict	7 (4%)	3 (3%)

Quality of Life[12,13]

Health-related quality of life (HRQoL) was measured with FACT-G, a validated questionnaire with 4 domains: physical, social/family, emotional and functional well-being. FACT-G was completed at baseline, every 8 weeks until 12 months after randomization, and every 12 weeks thereafter. Time to definite deterioration (TTD) of ≥7 points (minimal important difference, MID) in FACT-G total score (range 0 – 108) was a pre-specified secondary trial endpoint with Kaplan-Meier method and Cox model to derive the hazard ratio. A post-hoc analysis included TTD for FACT-G subscale scores using ≥3 point MID, and determined association between disease progression and HRQoL outcomes by fitting linear mixed models. Two mapping algorithms were selected to translate the FACT-G into EQ-5D utility scores: one is a UK-based value set, and the other is a US-based value set.

In the pre-specified analysis (≥7 points MID), no statistical differences were observed between the treatment arms in TTD of FACT-G total score (HR: 0.81, 95% CI: 0.55-1.21).

Figure 2. Kaplan-Meier plot of time to deterioration in FACT-G total score by at least 7 points, full analysis set[20]



No.of patients still at risk

Time (Months)	0	2	4	6	8	10	12	15	18	21	24	27
Everolimus + BSC	205	137	106	85	75	57	50	38	20	11	3	0
Placebo + BSC	97	59	42	31	25	22	20	16	8	4	0	0

In the post-hoc analysis (≥3 point MID), TTD for the physical (HR: 1.01, 95% CI: 0.69-1.53), social (HR: 0.72, 95%CI: 0.45-1.28), emotional (HR: 0.57, 95% CI: 0.36-0.93) and functional (HR: 0.94, 95% CI: 0.60-1.46) well-being subscale scores were maintained for everolimus versus placebo. In the linear mixed model, FACT-G total score at week 8 was 79.5 (95% CI: 77.7-81.3) for everolimus and 80.0 (95% CI: 77.6-82.5) for placebo, declining to 75.7 (95% CI: 73.2-78.2) for everolimus and 77.8 (95% CI: 73.5-82.1) for placebo at week 48.

In a pooled analysis, 284 patients were included in the analysis from baseline to study end. Difference in FACT-G total score pre- vs post-progression was significant: 79.7 versus 74.8 (difference 4.91, 95% CI: 3.71 – 6.11). Differences in subscale scores from pre- to post-progression were: physical 22.4 vs 20.9 (1.5, 95% CI: 1.05-1.95); emotional 17.6 vs 16.4 (1.14, 95% CI: 0.78-1.49), social/family 21.6 vs 20.9 (0.69, 95% CI 0.24-1.14) and functional 18.2 vs 16.9 (1.34, 95% CI: 0.86-1.82).[13]

Using the US-based value set, the utility was found to be 0.826 (95% CI: 0.815 – 0.836) pre-progression and 0.795 (95% CI: 0.783-0.807) post-progression. Using the UK-based value set, the utility was found to be 0.779 (95% CI: 0.763-0.796) pre-progression and 0.725 (95% CI: 0.705-0.744) post-progression.

Harms Outcomes

Safety analysis was performed at the time of the first data cut-off, November 2014. On-treatment deaths, defined as those occurring during receipt of study medication or within 30 days of discontinuing therapy, were similar between the treatment groups: seven deaths (3.5%) occurred in the everolimus group and three (3.1%) occurred in the placebo group. Four of the seven deaths in the everolimus group were considered to be related to the primary disease and/or disease progression. Of the remaining three deaths, one death was due to respiratory failure, one death was due to septic shock and one death was due to cardiac failure. One of the three deaths in the placebo group were considered to be related to the

primary disease and/or disease progression. Of the remaining two deaths, one death was due to lung infection ad one death was due to dyspnoea.

The below table lists the treatment-related adverse events that occurred in at least 10% of patients. The most common adverse events were stomatitis, diarrhoea, fatigue, infections, rash and peripheral oedema. The most common grade 3 or 4 drug-related adverse events included stomatitis, diarrhoea, infections, anaemia and fatigue.

Table 11: Treatment-related adverse events reported in at least 10% of patients (safety population)

	Everolimus (n=202)					Placebo (n=98)				
	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis*	127 (63%)	72 (36%)	37 (18%)	18 (9%)	0	19 (19%)	17 (17%)	2 (2%)	0	0
Diarrhoea	63 (31%)	30 (15%)	18 (9%)	13 (6%)	2 (1%)	16 (16%)	10 (10%)	4 (4%)	2 (2%)	0
Fatigue	62 (31%)	35 (17%)	20 (10%)	5 (2%)	2 (1%)	24 (24%)	17 (17%)	6 (6%)	1 (1%)	0
Infections+	59 (29%)	12 (6%)	33 (16%)	10 (5%)	4 (2%)	4 (4%)	1 (1%)	3 (3%)	0	0
Rash	55 (27%)	42 (21%)	12 (6%)	1 (<1%)	0	8 (8%)	6 (6%)	2 (2%)	0	0
Peripheral oedema	52 (26%)	30 (15%)	18 (9%)	4 (2%)	0	4 (4%)	2 (2%)	1 (1%)	1 (1%)	0
Nausea	35 (17%)	26 (13%)	6 (3%)	2 (1%)	1 (<1%)	10 (10%)	7 (7%)	3 (3%)	0	0
Asthenia	33 (16%)	8 (4%)	22 (11%)	2 (1%)	1 (<1%)	5 (5%)	4 (4%)	1 (1%)	0	0
Anemia	33 (16%)	5 (2%)	20 (10%)	8 (4%)	0	2 (2%)	0	1 (1%)	1 (1%)	0
Decreased appetite	32 (16%)	22 (11%)	9 (4%)	1 (<1%)	0	6 (6%)	2 (2%)	4 (4%)	0	0
Non-infectious pneumotitis++	32 (16%)	5 (2%)	24 (12%)	3 (1%)	0	1 (1%)	0	1 (1%)	0	0
Dysgeusia	30 (15%)	26 (13%)	3 (1%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Pruritus	26 (13%)	19 (9%)	6 (3%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Cough	26 (13%)	18 (9%)	8 (4%)	0	0	3 (3%)	3 (3%)	0	0	0
Pyrexia	22 (11%)	14 (7%)	4 (2%)	2 (1%)	2 (1%)	5 (5%)	4 (4%)	1 (1)	0	0
Hyperglycemia	21 (10%)	5 (2%)	9 (4%)	7 (3%)	0	2 (2%)	2 (2%)	0	0	0
Dyspnoea	21 (10%)	4 (2%)	15 (7%)	2 (1%)	0	4 (4%)	2 (2%)	1 (1)	0	1 (1)

*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.
+All types of infections are included.
++Included in this category are pneumonitis, interstitial lung disease, lung infiltration and pulmonary fibrosis.

The below tables list select adverse events occurring in greater than 20% of patients, by NETs origin sub-group.[18]

Table 12: Treatment-related adverse events reported in at least 20% of patients (safety population) by gastrointestinal subgroup[18]

	Everolimus (n=117)		Placebo (n=58)	
	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis*	71.8	7.7	22.4	0
Infections+	59.0	12.8	22.4	3.4
Diarrhea	44.4	11.1	43.1	3.4
Peripheral edema	40.2	2.6	6.9	1.7
Fatigue	36.8	5.1	41.4	1.7
Rash	29.1	0.9	10.3	0
Nausea	28.2	3.4	17.2	1.7
Cough	26.5	0	22.4	0
Anemia	23.9	6.8	12.1	1.7
Pyrexia	22.2	1.7	8.6	0
Dysgeusia	22.2	0.9	5.2	0
Decreased appetite	21.4	1.7	22.4	1.7
Asthenia	21.4	2.6	10.3	0

*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.
+All types of infections are included.

Table 13: Treatment-related adverse events reported in at least 20% of patients (safety population) by unknown primary subgroup

	Everolimus (n=22)		Placebo (n=13)	
	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis*	63.6	13.6	15.4	0
Infections+	45.5	0	38.5	0
Fatigue	40.9	4.5	23.1	0
Diarrhea	36.4	4.5	23.1	0
Abdominal pain	31.8	13.6	15.4	0
Nausea	27.3	0	23.1	0
Peripheral edema	27.3	4.5	15.4	0
Weight decreased	27.3	4.5	7.7	0
Cough	27.3	0	7.7	0
Asthenia	22.7	4.5	15.4	0
Decreased appetite	22.7	0	7.7	0
Dyspnea	22.7	0	7.7	0

*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.
+All types of infections are included.

In the everolimus group and placebo group, 59 (29%) and 7 (7%), respectively, discontinued study treatment due to adverse events. Treatment discontinuation attributed to grade 3 or 4 adverse events were reported in 36 (18%) and 5 (5%) in the everolimus and placebo group, respectively. The most frequent adverse events leading to treatment discontinuation in everolimus versus placebo were stomatitis (3% versus 0%), gamma-glutamyl transferase increased (1.5% versus 0%) and diarrhea (1.5% versus 0%).[20]

Following discontinuation of study drug, antineoplastic therapy was used by 41.5% of patients in the everolimus arm and 55.7% of patients in the placebo arm. The most common therapy used was SSA, following by alkylating agents, radiotherapies, pyrimidine analogues, surgical procedures, and protein-kinase inhibitors. Use of subsequent therapy were used with similar frequencies in the two treatment arms with the exception of radiotherapies and protein-kinase inhibitors, which were used with a slightly higher frequency in the placebo arm.

Non-infectious pneumonitis occurred in 32 patients (16%) in association with everolimus treatment. Grade 3 pneumonitis occurred in three patients (1%) and no grade 4 cases were reported.

6.4 Ongoing Trials

One ongoing phase II trial was identified: the LUNA trial (NCT01563354).[25] This is a 3-arm trial to evaluate pasireotide LAR/everolimus alone/in combination in adult patients with advanced (unresectable or metastatic) neuroendocrine carcinoma (typical and atypical) of the lung and thymus. The RADIANT-4 trial included patients with NETs of lung origin.

Table 14: Ongoing trials of everolimus in NETs GIL

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: LUNA trial **Characteristics:** phase II, prospective, multicenter, randomized, open-label, 3-arm **N=** 120 expected to be randomized; 40 per treatment arm; 124 currently enrolled **Study start date:** August 2013 **Estimated completion:** October 2016 **Funding:** Novartis	<u>Key Inclusion Criteria:</u> Histological confirmed advanced well differentiated typical and atypical carcinoid tumours of the lung or thymus Patients of all treatment lines including naïve patients At least one measurable lesion of disease on CT scan or MRI Radiological documentation of disease progression within 12 months prior to randomization Adequate liver, renal, and bone marrow function WHO performance status of 0-2 <u>Key Exclusion Criteria:</u> Poorly differentiated neuroendocrine carcinoma Non-neuroendocrine thymoma Patients with severe functional disease requiring symptomatic treatment with somatostatin analogs Prior therapy with mTOR inhibitors History of liver disease Baseline QTcF >470msec Uncontrolled diabetes mellitus despite adequate therapy	1) pasireotide LAR 2) everolimus 3) pasireotide LAR + everolimus	<u>Primary:</u> Proportion of patients progression-free at 9 months according to RECIST v1.1 <u>Secondary:</u> Progression-free survival Disease control rate Time to response Duration of response Biochemical response rate Rate and severity of adverse events

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team provide additional information on one other relevant clinical trial providing supporting information for this review.

The CGP, in addition to best supportive care, identified an additional relevant comparator: somatostatin analogues. There was one ongoing trial identified (details described in Section 6.4) that evaluates pasireotide LAR, everolimus alone, and pasireotide LAR + everolimus combination in adult patients with advanced (unresectable or metastatic) neuroendocrine carcinoma (typical and atypical) of the lung and thymus; however, as the trial is ongoing results are not yet available. The CGP also identified one completed randomized controlled trial comparing octreotide (an SSA) to placebo: the PROMID trial.[26]

The PROMID trial was a placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours. Treatment-naïve patients were randomly assigned to either placebo or octreotide LAR 30 mg intramuscularly in monthly intervals until progression or death.

The main inclusion criteria of the PROMID trial were locally inoperable or metastatic NETs; midgut primary tumour or tumour of unknown origin believed to be of midgut origin if a primary within the pancreas, chest or elsewhere was excluded by CT scan or MRI.

An indirect comparison between RADIANT-4 and PROMID was not deemed feasible due to the inclusion criteria of the type of NETs tumours:

- PROMID: midgut, functional and non-functional
- RADIANT-4: gastrointestinal and lung, only non-functional.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Endocrine 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 NETs GIL. 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 CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

The Endocrine Clinical Guidance Panel is comprised of 3 clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). 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 AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** May 2016**, Embase** 1974 to 2016 June 06**, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

Line #	Searches	Results
1	Everolimus/ or (Afinitor* or everolimus* or Zortress* or Disperz* or Advacan* or Certican* or Votubia* or Xience* or Evertor* or RAD001 or "RAD 001" or RAD001a or RAD 001a or SDZRAD or SDZ RAD or 9HW64Q8G6G or UNII9HW64Q8G6G or 159351-69-6 or "0159351696" or 1245613-55-1).ti,ab,ot,kf,kw,hw,rn,nm.	26094
2	exp Neuroendocrine tumors/ or ((neuroendocrine adj3 (tumo?r* or carcinoma* or neoplasm* or cancer*)) or carcinoid* or paraganglioma* or argentaffinoma* or somatostatinoma* or NET).ti,ab,kf,kw.	428187
3	exp Gastrointestinal Tract/ or exp Lung/ or (gastrointestin* or GI or digestive or intestine* or intestinal* or ileum or jejunum or duodenum* or esophag* or oesophag* or stomach or mouth or tongue or saliva* or pharyn* or lung or lungs or pulmonary or bronchi* or bronchus or bronchoalveolar or alveoli or alveolar or pleura).ti,ab,kf,kw.	4631624
4	1 and 2 and 3	506
5	limit 4 to english language	474
6	5 use cctr	18
7	5 use ppez	81
8	6 or 7	99

9	*everolimus/ or (afinitor* or everolimus* or Zortress* or Disperz* or Advacan* or Certican* or Votubia* or Xience* or Evertor* or RAD001 or "RAD 001" or RAD001a or RAD 001a or SDZRAD or SDZ RAD or 9HW64Q8G6G or UNII9HW64Q8G6G).ti,ab,kw.	16832
10	exp Neuroendocrine tumor/ or ((neuroendocrine adj3 (tumo?r* or carcinoma* or neoplasm* or cancer*)) or carcinoid* or paraganglioma* or argentaffinoma* or somatostatinoma* or NET).ti,ab,kw.	427862
11	exp Gastrointestinal Tract/ or exp Lung/ or (gastrointestin* or GI or digestive or intestine* or intestinal* or ileum or jejunum or duodenum* or esophag* or oesophag* or stomach or mouth or tongue or saliva* or pharyn* or lung or lungs or pulmonary or bronchi* or bronchus or bronchoalveolar or alveoli* or alveolar or pleura).ti,ab,kw.	4604531
12	9 and 10 and 11	385
13	12 use oemezd	279
14	limit 13 to english language	264
15	14 and conference abstract.pt.	161
16	limit 15 to yr="2011 -Current"	143
17	14 not 15	103
18	8 or 17	202
19	remove duplicates from 18	136
20	19 or 16	279

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#3	Search **#40 AND #42 AND publisher[sb]** Filters: **English**	18

Search	Query	Items found
#2	Search **Neuroendocrine tumors[mh] OR (neuroendocrine[tiab] AND (tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab] OR cancer[tiab] OR cancers)) OR carcinoid*[tiab] OR paraganglioma*[tiab] OR argentaffinoma*[tiab] OR somatostatinoma*[tiab] OR NET[tiab]** Filters: **English**	211645
#1	Search **Everolimus[mh] OR Afinitor*[tiab] OR everolimus*[tiab] OR Zortress*[tiab] OR Disperz*[tiab] OR Advacan*[tiab] OR Certican*[tiab] OR Votubia*[tiab] OR Xience*[tiab] OR Evertor*[tiab] OR RAD001[tiab] OR RAD 001[tiab] OR RAD001a[tiab] OR RAD 001a[tiab] OR SDZRAD[tiab] OR SDZ RAD[tiab] OR 9HW64Q8G6G[tiab] OR UNII9HW64Q8G6G[tiab] OR 159351-69-6[rn] OR 0159351696[rn] OR 1245613-55-1[rn]** Filters: **English**	4676

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

   Clinical trial registries:

   U.S. NIH ClinicalTrials.gov
   http://www.clinicaltrials.gov/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
   http://www.canadiancancertrials.ca/

   Search: Afinitor/everolimus, neuroendocrine tumours

   Select international agencies including:

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

   European Medicines Agency (EMA):
   http://www.ema.europa.eu/

   Search: Afinitor/everolimus, neuroendocrine tumours

   Conference abstracts:

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

   American Society of Hematology
   http://www.hematology.org/

   Search: Afinitor/everolimus, neuroendocrine tumours - last 5 years

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-Present) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974 to 2016 June 06) via Ovid; The Cochrane Central Register of Controlled Trials May 2016) via Ovid; 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, everolimus and neuroendocrine tumours of gastrointestinal or lung origin.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of September 1, 2016.

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 Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. 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.

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. 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.

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.

Data Analysis

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

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 clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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