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Cost-effectiveness of everolimus for the treatment of advanced neuroendocrine tumours of gastrointestinal or lung origin in Canada

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ABSTRACT

Background In 2016, everolimus was approved by Health Canada for the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional, neuroendocrine tumours (NET) of gastrointestinal (GI) or lung origin in adult patients with progressive disease. This analysis evaluated the cost-effectiveness of everolimus in this setting from a Canadian societal perspective.

Methods A partitioned survival model was developed to compare the cost per life-year (LY) gained and cost per quality-adjusted life-year (QALY) gained of everolimus plus best supportive care (BSC) versus BSC alone in patients with advanced or metastatic NET of GI or lung origin. Model health states included stable disease, disease progression, and death. Efficacy inputs were based on the RADIANT-4 trial and utilities were mapped from quality-of-life data retrieved from RADIANT-4. Resource utilization inputs were derived from a Canadian physician survey, while cost inputs were obtained from official reimbursement lists from Ontario and other published sources. Costs and efficacy outcomes were discounted 5% annually over a 10-year time horizon, and sensitivity analyses were conducted to test the robustness of the base case results.

Results Everolimus had an incremental gain of 0.616 QALYs (0.823 LYs) and CA$89,795 resulting in an incremental cost-effectiveness ratio of CA$145,670 per QALY gained (CA$109,166 per LY gained). The probability of cost-effectiveness was 52.1% at a willingness to pay (WTP) threshold of CA$150,000 per QALY.

Conclusions Results of the probabilistic sensitivity analysis indicate that everolimus has a 52.1% probability of being cost-effective at a WTP threshold of CA$150,000 per QALY gained in Canada.

Key Words Neuroendocrine tumours, gastrointestinal, lung, everolimus, cost-effectiveness, health economics, health technology assessment, Canada

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INTRODUCTION

Neuroendocrine tumours (NETs) are a relatively rare group of related but diverse malignancies originating from neuroendocrine cells in a variety of anatomical locations throughout the body (e.g., endocrine glands, endocrine islets within glandular tissue, and cells dispersed between exocrine cells)[1]. As the term indicates, gastrointestinal (GI) and/or lung NETs arise from the GI tract and the lungs. Advanced NET is a rare, progressive, and fatal malignancy. Based on the National Comprehensive Cancer Network Outcomes Database, it is estimated that 72% of GI/lung NETs are non-functional[2]. In general, non-functioning NETs are asymptomatic and often go undiagnosed until the disease has advanced[1]. Hence, as many as one third of newly diagnosed patients with NET are diagnosed at an advanced stage[3]. From year 1994 to 2009, the incidence of NETs increased from 2.48 per 100,000 to 5.86 per 100,000 in Ontario, Canada[4]. The median survival for patients with distant NET is between 4 and 70 months, while the median

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survival for patients with grade 3/4 NET is between 8 and 33 months, depending on the primary tumour site[5]. In a survey of 2,000 patients with NET from 12 countries, 71% reported that their quality of life (QoL) was negatively affected and up to 92% made lifestyle changes as a result of their NET[6].

Currently available treatment options for advanced, non-functional, progressive GI/lung NETs include surgical resection, cytotoxic chemotherapy, peptide receptor radiation therapy (PRRT), interferon, somatostatin analogues (SSAs) and molecularly-targeted therapies[6-8]. However, evidence of efficacy and safety of currently available systemic therapies is limited to small studies that lack evidence of impact on QoL outcome measures, and none is approved for advanced lung or progressive GI tract NET.

Everolimus (Afinitor®: Novartis Pharmaceuticals Corporation, East Hanover, NJ, U.S.A.) represents a significant clinical advancement in the treatment of advanced NET by controlling disease progression through inhibition of the mammalian target of rapamycin pathway, as supported by the largest clinical program (RADIANT program) in a variety of advanced NETs[9,10]. It was approved by Health Canada on 17 May 2016 for the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional NET of GI or lung origin in adults with progressive disease. Everolimus is also approved, and reimbursed in all provinces except Prince Edward Island, for the treatment of well- or moderately differentiated neuroendocrine tumours of pancreatic origin (pNET) in patients with unresectable, locally advanced, or metastatic disease that has progressed within the last 12 months.

Depending on tumour growth and other individualized factors, debulking surgery, targeted therapy, ablative therapy, SSAs, PRRT, surveillance, and chemotherapy may be considered for the treatment of unresectable or metastatic non-functional GI NET and pNET[8,11]. According to several published treatment guidelines, everolimus is recommended for the treatment of advanced pNET and should be considered for the treatment of advanced GI/lung NET[7,8,11].

To our knowledge, RADIANT-4 is the first, large, randomized, double-blind, placebo-controlled, phase III study to assess the efficacy and safety of an agent for the treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional NET of GI or lung origin in adult patients with progressive disease. In RADIANT-4, everolimus demonstrated clear superiority relative to placebo in prolonging progression-free survival (PFS). Median PFS (by central radiology review) was 11.0 months (95% confidence interval [CI]: 9.2 to 13.3) in the everolimus plus best supportive care (BSC) arm and 3.9 months (95% CI: 3.6 to 7.4) in the placebo plus BSC arm[9]. Everolimus plus BSC was associated with a statistically significant prolongation of 7.1 months and a 52% reduction in the estimated risk of disease progression or death (hazard ratio [HR]: 0.48, 95% CI: 0.35 to 0.67, $p < 0.00001$)[9]. By the second interim analysis (November 2015 data cut-off), everolimus was associated with a 27% reduction in the estimated risk of death compared with placebo (HR: 0.73, 95% CI: 0.48 to 1.11, $p = 0.071$)[12]. Although statistical significance was not achieved, it suggested a trend for survival benefit with everolimus.

Based on the results of RADIANT-4, this study assessed the cost-effectiveness of everolimus plus BSC versus BSC alone in patients with advanced (unresectable or metastatic), low or intermediate grade (well-differentiated) non-functional GI/lung NET who have progressed in the past 6 months from a Canadian societal perspective.

METHODS

Model Overview

A partitioned survival model was developed in Microsoft Excel (Microsoft Corp, Redmond, WA, U.S.A.) to assess the cost-effectiveness of everolimus plus BSC versus BSC alone in the RADIANT-4 trial patient population. The model included three mutually exclusive health states (i.e., stable disease, disease progression, and death) that characterize the typical clinical pathway for the disease until death. All patients started in the stable disease health state and transitioned to the remaining health states according to PFS and overall survival (OS) estimates. Transition from one health state to the next was unidirectional, which means patients could not move back to a previous health state.

The cost-effectiveness analysis was conducted from the Canadian societal perspective per requirements of the Institut National d'Excellence en Santé et en Services Sociaux (INESSS) for health technology assessment. Costs were reported in 2015 Canadian dollars (CA$), and health outcomes were assessed in life-years (LYs) and quality-adjusted life-years (QALYs). The cohorts were modelled from the time of initial treatment through a 10-year time horizon in monthly (30.42-day) cycles, which was assumed sufficient to capture the complexities of the disease and was consistent with the cost-effectiveness analysis of everolimus in pNET. Cost and health outcomes were discounted at 5% annually after the first year of the model, as per the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[13] and a half-cycle correction was applied.

Efficacy

In both treatment arms, everolimus plus BSC and BSC alone, Kaplan-Meier (KM) curves based on the patient-level survival data from the RADIANT-4 trial were used to determine PFS and OS in each cycle until month 26 and month 27, respectively. Kaplan-Meier curves were used rather than only parametric survival curves to provide a more accurate reflection of the trial data. However, parametric survival curves were used to extrapolate survival beyond the available trial data. For OS, applying the KM curves past month 27 would have lacked face validity, which stems from the lack of predictability at the tail end of the KM curves due to the low number of patients at risk.

For the cycles following month 26, parametric survival curves were independently fitted to the PFS KM curves in both treatment arms to estimate PFS thereafter. However, to estimate survival following month 27, a parametric curve was fitted to the OS KM curve in the everolimus plus BSC arm, and a HR was applied to the OS curve in the everolimus plus BSC arm to derive the OS curve for the BSC alone arm.

It was considered appropriate to apply a HR for the extrapolation of OS in the BSC alone arm based on visual

assessment of the cumulative log plots and the test for proportionality in OS. In addition, estimated survival probabilities are highly volatile towards the tail end of the OS KM curves, where they crossed, which likely occurred due to the low number of patients at risk. Therefore, the tail end of the OS KM curves, i.e., where the crossing of the curves occurred, lacks robustness and is inconsistent with the rest of the trial data, which exhibited a positive trend for everolimus.

Independently fitting the parametric survival curves for OS, coupled with the high risk of overfitting artefactual trends in the tails of the survival distribution that result from a single event (or the lack thereof) among small numbers of patients at risk, would have likely diminished any survival benefit derived in the everolimus plus BSC arm. As such, a HR of 0.73 (95% CI: 0.48 to 1.11; p=0.071) was used in the analysis, based on the second interim OS analysis for the RADIANT-4 trial.

Exponential, Weibull, lognormal, log-logistic, Gompertz, piecewise exponential, and gamma distributions were assessed according to best statistical fit (Akaike Information Criterion and Bayesian Information Criterion fit statistics), visual fit to the KM curve for PFS and OS (Figure 1), and the ability to be used with other curve distributions for the other health states. Progression-free survival and OS curves were generated in SAS 9.3 (SAS Institute, Cary, NC, U.S.A.) based on parametric survival functions fitted to the patient-level survival time data from the RADIANT-4 trial except when fitting the Gompertz distribution, which was generated in STATA (StataCorp LP, College Station, TX, U.S.A.).

For PFS, the Weibull distribution was chosen for the everolimus plus BSC arm (shape: 1.23, scale: 487.36) and BSC alone arm (shape: 0.98, scale: 298.43). For OS, the Weibull distribution was also chosen for the everolimus plus BSC arm (shape: 1.38, scale: 1719.71). To determine the health state membership at each cycle, the area-under-the-curve approach was used to calculate the mean time spent in a health state from the area under the selected survival curves[14]. The PFS and OS parameters were used to estimate membership in the overall stable disease health state and the number of surviving patients, respectively. As health states were mutually exclusive, membership in the disease progression health state was calculated as the complement of the sum of the membership in the stable disease and death health states.

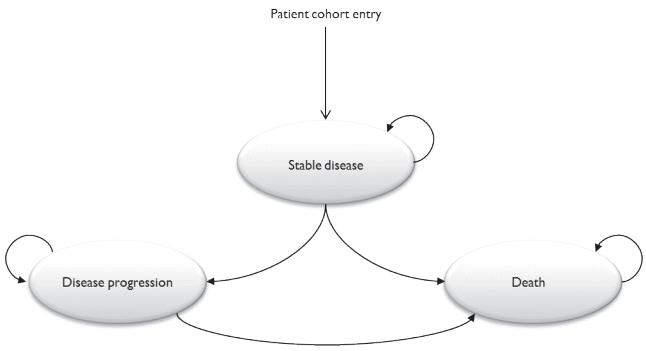

FIGURE 1 Parametric survival distributions for PFS and OS overlaid on KM data for everolimus plus BSC. PFS = progression-free survival; OS = overall survival; KM = Kaplan-Meier; BSC = best supportive care.

Adverse Events

The proportion of patients in the stable disease health state that experienced at least one grade 3/4 adverse event (AE) per cycle was calculated from the RADIANT-4 data. Any grade 3/4 treatment-related AE that occurred in at least 2% of patients in either treatment arm was included in the model. Grade 1/2 AEs were not included in the analysis as they were unlikely to have any meaningful impact on the economic analysis, and potential impact on utility scores was captured via the QoL questionnaire. Patients with grade 3/4 AEs accrued costs associated with the resources needed to manage these AEs on a per-cycle basis. Incidence rates obtained from the RADIANT-4 trial were adjusted so that these patients accrued the average cost associated with managing an adverse event per cycle. Rather than using the per-cycle AE rates from the RADIANT-4 trial data, the average AE rate weighted by the number of patients (in the stable disease health state) at risk in each cycle was calculated and implemented in the model (3.82% and 0.52% for everolimus plus BSC and BSC alone, respectively).

Resource Utilization

Per patient, per month resource utilization rates, except for AEs, were derived from a physician survey that was conducted amongst six physicians in Canada. Physicians were asked to provide details on resource use among patients with NET of GI or lung origin in the initial progression stage (which loosely corresponds to the model's stable disease health state) and in the second progression stage (which loosely corresponds to the model's disease progression health state). Based on the RADIANT-4 trial, the stable disease health state specifically represents patients with advanced, low or intermediate grade (well-differentiated), non-functional GI and/or lung NET who have progressed in the past six months. The disease progression health state represents the same group of patients who have progressed further in RADIANT-4, based on Response Evaluation Criteria in Solid Tumours criteria[15] [RECIST version 1.0].

Costs

As the recommended dose with everolimus is 10 mg daily, the unit cost in Quebec of the 10-mg tablet, at CA$186, was applied daily until disease progression. Due to the flat pricing of everolimus regardless of strength (everolimus is available in 2.5-, 5- and 10-mg tablet strengths in Canada and down dosing is recommended upon certain AEs), a dose intensity of 1.0 was assumed in the base case analysis. Per-cycle drug cost of everolimus was estimated to be CA$5,657.50 (Table I). Due to a lack of cost data in Quebec, various unit costs used in the analysis were derived from Ontario data sources under the assumption that these costs would be relatively similar in Quebec. Unit costs for drugs, including drugs used as BSC and post-progression treatments, were extracted from the IMS Health Delta PA database[16] or the Ontario Drug Benefit Formulary[17]. Dosing information for BSC and post-progression treatments were

obtained from the Cancer Care Ontario Drug Formulary[18], Medscape[19-22], and prescribing information. Costs of AEs and treatment-related procedures were obtained from the Ontario Case Costing Initiative[23]. Other direct and indirect costs, including costs of physician visits, procedures, and lab tests, were obtained from official reimbursement lists from Ontario[24,25] and other published sources[26-28]. All costs were inflated to 2015 price levels using Canada's Health Consumer Price Index[29].

Health States Utility Values

Health-related quality of life was measured using the Functional Assessment of Cancer Therapy-General (FACT-G), a validated questionnaire comprising 27 items covering four domains of health: physical, social/family, emotional, and functional well-being. Mean health state utility values for the stable disease and disease progression health states were estimated by mapping the FACT-G data from the RADIANT-4 trial to the EuroQol-5D (EQ-5D) using the Young mapping algorithm[30] (Table I). As utility rates were applied to both treatment arms equivalently, the model did not assume that everolimus had an inherent quality-of-life benefit. Any difference in health-related quality of life between treatment arms as depicted by the model results primarily occurred because patients on each treatment arm spent differing amounts of time in each health state[31].

Sensitivity Analyses

To identify key model variables, one-way sensitivity analyses (OWSA) were conducted using extreme values for all model variables. Those extreme values corresponded to the respective 95% CI bounds for continuous variables, and each category value for categorical variables or predefined values, such as cost discount and effect discount. Scenario analyses were also conducted to explore the effect on the base case results of the selected approach to modelling survival.

On the other hand, the probabilistic sensitivity analysis (PSA) was intended to quantify the range and variability of the deterministic results when the variability of all input parameters and assumptions was considered simultaneously. This was accomplished through the use of a second-order Monte Carlo simulation in which the cohort was simulated over the model time horizon including transitions from one health state to another, utilities, and costs across any selected number of iterations chosen by the user under the varying sets of assumptions.

Utility parameters were constricted on the interval zero-to-one, as the death health state has a utility of 0 and there was no reason to believe that the other health states in the model would have a negative utility value. Thus, utilities were varied along a beta distribution, which has the property of having a range from zero to one[32]. Cost parameters were varied along a gamma distribution, which is usually a good candidate to represent uncertainty in costs because costs are constrained on the interval zero-to-positive-infinity, and are often highly skewed[32]. Dose intensity was varied along a truncated normal distribution in order to prevent generation of negative numbers and to avoid a skew towards higher values. Instead, the range of possible values is symmetrical across the mean. On the other hand, the beta distribution was not considered, as mean daily dose may be greater than 100% and the gamma distribution is not recommended due to its long tail to the right, which is unlikely to reflect variance in mean daily dose. As the probability of patients in PFS and OS was derived using the survival models fitted to the patient-level data, survival curve parameters were varied along the multivariate normal distribution, which takes the correlated parameters in the survival model into consideration when randomly sampling the values from the distribution[32].

As the PSA considers patient level distributions of inputs (e.g., not all patients have the same costs of BSC) and presents results according to a distribution of generated results, the results for any given simulation vary across a range of results, with a higher number of iterations yielding a more robust estimate of average cost-effectiveness and associated modeling uncertainty. Thus, the PSA was run for 1,000 iterations, and results of the PSA were used to generate a cost-effectiveness acceptability curve (Figure 2).

RESULTS

The base case analysis projected everolimus plus BSC versus BSC alone to yield mean survival times of 3.847 LYs and 3.024 LYs, respectively. The cost of treating patients with everolimus plus BSC would yield 2.857 QALYs while incurring a cost of CA$146,137. On the other hand, patients treated with BSC alone would yield 2.241 QALYs while incurring a cost of CA$56,342. At an incremental cost of CA$89,795 for 0.326 QALYs gained, the mean incremental cost-effectiveness ratio (ICER) for the base case analysis was CA$145,670 per QALY gained (CA$109,166 per LY gained) (Table II).

Results of the OWSA showed that the ICER was most sensitive to the HR for OS (everolimus plus BSC versus BSC alone), which yielded an ICER in the range of CA$113,448 and CA$227,421 when the HR was varied at 0.51 and 1.04, respectively. Time horizon, cost of everolimus, and everolimus dose intensity all have a substantial influence on the ICER as well (Table III). Scenario analyses using the parametric curves only for OS, rather than implementing the KM curves until month 27, yielded results ranging between CA$153,860 and CA$213,402 depending on the survival distribution (Table IV). The results of the PSA, which were presented using a cost-effective acceptability curve (Figure 2) yielded results consistent with the deterministic analysis. The probability of everolimus being cost-effective at a willingness to pay (WTP) threshold of CA$150,000 per QALY was 52.1%.

DISCUSSION

Results from the RADIANT-4 trial provide clinical evidence that supports the use of everolimus in the treatment of patients with advanced (unresectable or metastatic), progressive, non-functional GI/lung NET[9,12]. With the recent approval of everolimus in this patient population by Health Canada, the objective of this study was to assess the cost-effectiveness of everolimus in patients with advanced GI/lung NET from the Canadian societal perspective.

In this study, everolimus plus BSC was compared with BSC alone rather than other treatment options such as SSAs, PRRT, or sunitinib. Current treatment guidelines recommend SSAs earlier in the treatment pathway, either in patients with non-progressive disease or in treatment-naïve patients with progressive disease, whereas everolimus is

TABLE I Base case model parameters

Parameter	Everolimus	BSC
Discount rate for costs and QALYs	5%	
Time horizon	10 years	
Health state utility values [mean (SE)]		
Stable disease	0.779 (0.008)	
Disease progression	0.725 (0.010)	
Death	0.000 (0.000)	
Cost for SD without AEs[a], per cycle (initial cycle)[b] (CA$)	6,245.29	—
Cost for SD without AEs[a], per cycle (follow-up)[c] (CA$)	6,155.53	820.16
Everolimus	5,657.50	—
BSC[d]	0.34	12.95
Physician visits (initial cycle)	157.00	—
Physician visits (follow-up)	67.24	117.14
Procedures or tests	225.05	192.42
Hospitalizations and emergency room	205.40	497.65
Cost for SD with AEs, per cycle (CA$)	841.49	1,202.70
BSC[d]	0.34	12.95
AEs	319.53	358.61
Physician visits	67.24	117.14
Procedures or tests	225.05	192.42
Hospitalizations and emergency room	205.40	497.65
Indirect costs	23.93	23.93
Costs for PD, per cycle (initial cycle) (CA$)	8,248.66	9,750.50
Costs for PD, per cycle (follow-up) (CA$)	1,302.03	1,327.31
BSC[d]	2.85	3.37
Physician visits	97.44	99.85
Procedures or tests	199.25	199.07
Hospitalizations and emergency room	954.64	977.16
Indirect costs	47.86	47.86
Post-progression treatment (initial cycle)[e]	6,946.62	8,423.18
Post-progression treatment (follow-up)	—	—
Costs for Death (CA$)	6,795.61	6,795.61
End-of-life care	4,340.89	4,340.89
Indirect costs	2,454.71	2,454.71

[a] AEs included: stomatitis, diarrhea, fatigue, infections, peripheral edema, anemia, pyrexia, and hyperglycemia.
[b] Cost for initial cycle of stable disease is calculated as the sum of costs for everolimus, BSC, initial physician visit, procedure or tests, hospitalizations, and emergency rooms.
[c] Cost for each follow-up cycle of stable disease is calculated as the sum of costs for everolimus, BSC, follow-up physician visits, procedure or tests, hospitalizations, and emergency rooms.
[d] BSC includes nutritionist visit, dexamethasone, and prednisone.
[e] Post-progression treatments include octreotide LAR, lanreotide, surgical debulking, embolization, everolimus, sunitinib, clinical trial, PRRT, ablative therapy, radiation, temozolomide + capecitabine, FOLFOX (oxaliplatin, leucovorin, fluorouracil), cisplatin + fluorouracil, cisplatin + etoposide, and observation.

Drug costs were extracted from the IMS Health Delta PA database[16] or the Ontario Drug Benefit Formulary[17]. AE costs were obtained from the Ontario Case Costing Initiative[23]. Other direct and indirect costs were obtained from official reimbursement lists from Ontario[24,25] and other published sources[26-28]. BSC = best supportive care; QALYs = quality-adjusted life years; SE = standard error; SD = stable disease; AEs = adverse events; CA$ = Canadian dollars; PD = progressive disease; LAR = long-acting release; PRRT = peptide receptor radionuclide therapy.

recommended in patients with progressive disease on SSA therapy[8]. On the other hand, PRRT data are lacking (i.e., median PFS and OS have not been reached) in this patient population, and PRRT is not readily available in treatment centres across the country. Moreover, everolimus and sunitinib can only be compared in pNET, an indication in which both share similar marketing authorization and a similar patient population in their respective clinical trials. Lastly, there is a paucity of outcome data for chemotherapy in GI/lung NET, and feedback from clinical experts indicated BSC is an appropriate comparator.

At an incremental cost of CA$89,795, everolimus plus BSC extends QALYs compared with BSC alone by 0.616 QALYs, for an ICER of CA$145,670 per QALY gained. Although Canada has no official WTP threshold, many currently funded therapies in oncology indications have ICERs, as estimated by the Economic Guidance Panel, in the range of CA$100,000 per QALY to CA$200,000 per QALY[33]. In this context, PSA results indicate that everolimus has a 52.1% probability of being a cost-effective therapy for patients with advanced GI/lung in Canada when using a WTP threshold of CA$150,000 per QALY.

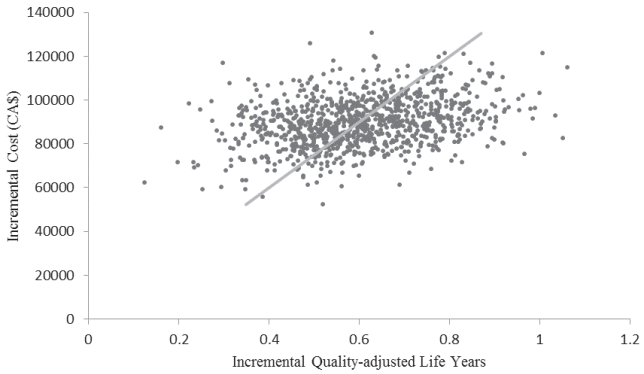

FIGURE 2 Cost-effectiveness acceptability curve.

Deterministic sensitivity analyses indicate that the ICER is most sensitive to the approach used to extrapolate survival, especially the HR used to derive the extrapolation of OS in the BSC arm, which ranged from a -22.1% to 56.1% change in the ICER. In addition, the time horizon, unit cost of everolimus, and dose intensity all have substantial effects on the ICER. When the time horizon is reduced to five years, the ICER increases to CA$217,135 (Δ49%). On the other hand, when the dose intensity of 79.4% from the RADIANT-4 trial is used, the ICER decreases to CA$116,855 (Δ-20%). With the exception of these few variables that have an outsized impact on the ICER results, the OWSA illustrates that most variables, when varied, produce less than ±10% change in the ICER, demonstrating the relative robustness of the results.

As evident by incorporating the KM data from the RADIANT-4 trial to estimate PFS and OS in the model until month 26 and 27, respectively, survival at two years aligns with survival reported in the RADIANT-4 trial (76.7% in the everolimus plus BSC arm and 61.5% in the BSC alone arm compared with 77% in the everolimus plus BSC arm and 62% in the BSC alone arm as reported in the updated OS analysis)[12]. Long-term projections of OS for everolimus plus BSC and BSC alone over 10 years were 6.2% and 2%, respectively, whereas published estimates ranged from 17.5% to 18.7% in metastatic patients with neuroendocrine tumours in Ontario[4]. Although the Weibull distribution underestimates 10-year survival compared with the exponential, lognormal, and log-logistic distributions,

TABLE II Base case results

	Everolimus	BSC	Incremental
Life years	3.847	3.024	0.823
Stable disease	1.270	0.897	0.373
Disease progression	2.577	2.127	0.450
Quality-adjusted life years	2.857	2.241	0.616
Stable disease	0.990	0.699	0.290
Disease progression	1.868	1.542	0.326
Total costs (CA$)	146,136.80	56,341.75	89,795.05
Everolimus	86,225.47	0.00	86,225.47
BSC	93.14	225.61	-132.47
Physician visits	4,194.81	3,809.75	385.06
Procedures or tests	9,590.97	7,152.97	2,438.00
Hospitalization	32,648.71	30,299.15	2,349.57
AE treatment	154.57	17.19	137.38
Post-progression treatment	6,184.47	7,620.78	-1,436.31
End-of-life care	3,547.34	3,828.63	-281.30
Indirect costs	3,497.32	3,387.67	109.65
Cost (CA$) per LY gained	—	—	109,166.17
Cost (CA$) per QALY gained	—	—	145,669.68

BSC = best supportive care; LYs = life years; QALYs = quality-adjusted life years; CA$ = Canadian dollars; AEs = adverse events.

TABLE III One-way sensitivity analyses

Variable	Value		ICER (CA$ per QALY)
	Base case	Sensitivity analysis	
Base case			145,670
Time horizon	10 years	5 years	217,135
		30 years	137,200
Discount rate	5%	1.5% (costs)	150,484
		1.5% (efficacy)	129,415
Stable disease state utility	0.7791	0.7928	144,473
		0.7651	146,910
Progressive disease state utility	0.7248	0.7407	143,003
		0.7087	147,401
Unit costs of everolimus	CA$186.00	CA$168.35	123,484
		CA$234.09	169,445
Dose intensity of everolimus	1.00	0.79	116,855
		1.00	145,670
Post-progression treatment costs (everolimus plus BSC)	CA$6,946.62	CA$13,893.24[a]	155,702
		CA$3,473.31[b]	140,653
Post-progression treatment costs (BSC alone)	CA$8,423.18	CA$16,846.36[a]	133,307
		CA$4,211.59[b]	151,851
PFS parametric function (everolimus plus BSC)	Weibull	Exponential	153,070
		Lognormal	165,156
		Log-logistic	168,018
		Piecewise exponential	155,196
		Gamma	162,599
PFS parametric function (BSC alone)	Weibull	Exponential	145,519
		Lognormal	150,826
		Log-logistic	148,427
		Piecewise exponential	148,847
		Gamma	156,187
OS parametric function (extrapolation following month 27)	Weibull	Exponential	127,500
		Lognormal	123,810
		Log-logistic	129,007
		Piecewise exponential	170,453
OS HR	0.73	0.5133	113,448
		1.0378	227,421

[a] 50% of the base case cost
[b] 200% of the base case cost
ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; BSC = best supportive care; PFS = progression-free survival; OS = overall survival; KM = Kaplan-Meier; HR = hazard ratio.

the ICERs ranged from CA$123,810 to CA$129,007 when selecting these distributions, which suggests that the predicted benefits of everolimus are not overestimated.

Health state utility values were estimated by mapping the FACT-G data from the RADIANT-4 trial to the EQ-5D. As these data represent the only QoL data collected in advanced, progressive, well-differentiated, non-functional GI/lung NETs, the model accurately reflects the quality-of-life experience in the relevant patient population.

Nevertheless, the model has various limitations. The model simplified the underlying disease/treatment process into three health states. However, given the indolent nature of disease and multiple lines of therapy, there are likely multiple periods of stable disease interspersed with disease progression events. Nevertheless, the structure does align with that of other economic evaluations in oncology, including those conducted in NETs.

The lack of longer-term data from the RADIANT-4 trial, in addition to the low number of patients at risk towards the end of the trial, limits the ability to provide accurate long-term projections of OS with high confidence. As an alternative to extrapolating survival using the

TABLE IV Scenario analyses

Description	ICER (CA$ per QALY)
Base case	145,670
PFS, parametric curves only	
Weibull	140,095
Exponential	150,830
Lognormal	164,520
Log-logistic	164,923
Piecewise exponential	156,694
Gamma	171,701
OS, parametric curves only	
Weibull	180,366
Exponential	155,964
Lognormal	153,860
Log-logistic	159,624
Piecewise exponential	213,402
OS, parametric curves only, applying HR=0.5133	
Weibull	103,028
Exponential	87,392
Lognormal	85,341
Log-logistic	90,038
Piecewise exponential	123,975
OS, parametric curves only, applying HR=1.0378	Dominated

ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; PFS = progression-free survival; OS = overall survival; HR = hazard ratio.

within-trial data, as was executed in the model, long-term extrapolation using real-world data may have been more informative. However, real-world evidence of advanced GI/lung NETs in Canada was not a feasible option. In addition, the model did not explore the limited use of SSAs post discontinuation with everolimus based on prior treatments. It also did not explore the increased use of PRRT in the progressive state.

Although the quality-of-life data used in the model were derived from the RADIANT-4 trial, the Young algorithm used to map FACT-G data from the RADIANT-4 trial to EQ-5D is most relevant to the UK setting. A mapping algorithm relevant to Canada would have been preferred. However, such a mapping algorithm did not currently exist for Canada.

Resource-use data for patients with advanced GI/lung NET were also noticeably missing from the analysis. Instead, resource-use values in the model relied on physician responses. As physicians responded in a qualitative manner (i.e., not using collected data to inform their responses), the resource-use estimates are highly subjective and vulnerable to various biases. In addition, as costs for some resources were not readily available in Canadian reimbursement lists, a few were derived from United Kingdom reimbursement lists and converted to Canadian dollars.

To the best of our knowledge, this is the first study to assess the cost-effectiveness of everolimus among patients with advanced, non-functional, progressive GI/lung NET in Canada. While further studies may be warranted when additional clinical or real-world data are available, this study provides initial results on the cost-effectiveness of everolimus in Canada based on the currently available data.

CONCLUSIONS

As a treatment option in patients with advanced (unresectable or metastatic), progressive, non-functional GI/lung NET, everolimus is predicted to offer clinical benefits compared with BSC alone, with an estimated ICER of CA$145,670 per QALY (CA$109,116 per LY) from a Canadian societal perspective. The results of the PSA indicate that everolimus has a 52.1% of being cost-effective in this patient population at a WTP threshold of CA$150,000 per QALY.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: AC is an employee of Analytica Laser, and AP was an employee of Analytica Laser at the time of the analysis. JFR is an employee of Wellmera. Both Analytica Laser and Wellmera have received compensation for the overall economic study design, analysis, and preparation of the manuscript. MPN and MT are employees of Novartis Pharmaceuticals Corporation.

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