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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Liu; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

October 26, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Observational Study

Cost-effectiveness of lutetium (^{177}Lu) oxodotreotide vs everolimus in gastroenteropancreatic neuroendocrine tumors in Norway and Sweden

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Author contributions:

Leeuwenkamp OR provided analysis support in conjunction with manuscript development; Palmer J prepared the first draft of the manuscript; Leeuwenkamp OR provided critical input and review to the first draft and all subsequent drafts of the manuscript.

Institutional review board

statement: No new clinical trial or patient level data were generated as part of this analysis. All data used in the analysis have been previously published, therefore institutional review board approval was not required.

Informed consent statement: No patients were directly involved in the analysis, therefore informed consent is not applicable.

Conflict-of-interest statement:

Leeuwenkamp OR is a current employee of Advanced Accelerator Applications, which manufactures ^{177}Lu -Dotatate. Palmer J is a current employee of Ossian Health Economics and Communications, which has received consulting fees

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Abstract

BACKGROUND

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) represent a relatively rare and heterogeneous group of tumors. Currently available treatment options for patients with progressive GEP-NETs include lutetium (^{177}Lu) oxodotreotide (^{177}Lu -Dotatate) and everolimus [as well as sunitinib for patients with pancreatic NETs (P-NETs)].

AIM

To perform a health economic analysis to determine the cost-effectiveness of ^{177}Lu -Dotatate compared with everolimus in patients with unresectable or metastatic midgut-NETs or P-NETs in both Sweden and Norway.

METHODS

Simulations were performed using a three-state partitioned survival model and analyses were performed separately for patients with midgut-NETs and P-NETs. Clinical input data were sourced from an indirect comparison that utilized survival data from clinical trials of ^{177}Lu -Dotatate and everolimus. The analyses were performed from the healthcare payer perspective over a time horizon of 20 years. For Sweden, future costs and clinical outcomes were discounted at 3% *per annum*. For Norway, a discount rate of 4% *per annum* was applied.

RESULTS

For Sweden, improved survival outcomes and higher lifetime costs with ^{177}Lu -Dotatate resulted in an incremental cost-effectiveness ratio (ICER) of SEK 391194 per quality-adjusted life year (QALY) gained for midgut NETs and SEK 16764 per QALY gained for P-NETs for ^{177}Lu -Dotatate compared with everolimus. For Norway, the corresponding ICERs were NOK 244444 per QALY gained and

from Advanced Accelerator Applications.

Data sharing statement: All input data used in the analysis are available from Leeuwenkamp OR upon reasonable request.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

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Manuscript source: Unsolicited manuscript

Received: July 8, 2020

Peer-review started: July 8, 2020

First decision: August 8, 2020

Revised: August 21, 2020

Accepted: September 25, 2020

Article in press: September 25, 2020

Published online: October 26, 2020

P-Reviewer: Bergsma H, Takura T

S-Editor: Ma YJ

L-Editor: A

P-Editor: Li JH



NOK 106451 per QALY gained, respectively. One-way sensitivity analyses revealed that the results were most sensitive to changes in drug acquisition costs and health state utility values.

CONCLUSION

In both Sweden and Norway, from a healthcare provider perspective, ¹⁷⁷Lu-Dotatate is likely to be considered cost-effective relative to everolimus for the treatment of patients with unresectable or metastatic, progressive midgut-NETs or P-NETs.

Key Words: Cost; Cost-effectiveness; Neuroendocrine tumors; ¹⁷⁷Lu-Dotatate; Sweden; Norway

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Core Tip: Peptide receptor radionuclide therapy with ¹⁷⁷lutetium oxodotreotide (¹⁷⁷Lu-Dotatate; Lutathera), which targets the overexpression of somatostatin receptors, particularly the somatostatin receptor type 2 expressed on the surface of tumor cells in some neuroendocrine tumors (NETs), is an efficacious new treatment approach for patients with gastroenteropancreatic NETs. To be adopted into routine clinical practice, new treatments should also be cost-effective as well as efficacious. Long-term health economic analyses suggest that in Sweden and Norway ¹⁷⁷Lu-Dotate is likely to be cost-effective and associated with minimal budget impact relative to everolimus for the treatment of unresectable or metastatic progressive midgut or pancreatic NETs.

Citation: Palmer J, Leeuwenkamp OR. Cost-effectiveness of lutetium (¹⁷⁷Lu) oxodotreotide vs everolimus in gastroenteropancreatic neuroendocrine tumors in Norway and Sweden. *World J Clin Cases* 2020; 8(20): 4793-4806

URL: <https://www.wjgnet.com/2307-8960/full/v8/i20/4793.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i20.4793>

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors that may arise from any cell with a neuroendocrine phenotype, although around 70% of NETs emanate from cells in the gastrointestinal tract or pancreas, collectively termed gastroenteropancreatic (GEP)-NETs^[1]. Recent estimates relating to the prevalence and incidence of NETs or GEP-NETs specifically in Sweden are lacking, but in Norway in 2010 the overall incidence of all NET types was estimated at 21.3 per 100000 population and the median age at diagnosis was 65 years^[2]. Moreover, analysis of temporal trends in incidence has also shown that in Norway over the period 1993–2010 the incidence of NETs increased by 5.1% per year in women and 2.1% per year in men^[2], this increase has been attributed, in part, to increased physician and pathologist awareness of NETs, improved diagnostic techniques and improved classification^[2,3]. With regard to the incidence of GEP-NETs specifically, this has been estimated at 5.25 per 100000 population^[4]. For Sweden, this corresponds to an estimated 540 new cases per year (based on a population of 10.28 million^[5]) and for Norway the corresponding figure is approximately 280 new cases per year (based on a population of 5.30 million^[6]). Based on these estimates, GEP-NETs fulfil the European Medicines Agency (EMA) criteria for orphan disease status^[7]. Additionally, the tumor biology and malignant potential of GEP-NETs is highly variable and prognosis is influenced by the location of the primary tumor, Ki-67 (a marker of cell proliferation rate), tumor size and tumor grade, metastases, and disease stage at diagnosis^[8]. Indeed, in Norway over 40% of patients already had distant metastases at diagnosis^[2] and 5-year survival for patients with pancreatic NETs (P-NETs) with distant disease at diagnosis was just 33%^[2]. Similarly, 5-year survival rates for patients with small intestinal NETs with distant disease at diagnosis were 63% for tumors classified as low/intermediate aggressiveness^[9].

Currently available treatment options for patients with unresectable or metastatic

GEP-NETs include everolimus, sunitinib (only indicated for patients with well-differentiated P-NETs with disease progression) and ^{177}Lu -Lutetium oxodotreotide (^{177}Lu -Dotatate; Lutathera). ^{177}Lu -Dotatate was approved for use in Europe in 2017 and is a peptide receptor radionuclide therapy (PRRT) specifically targeting tumors overexpressing somatostatin receptors, particularly of type 2 (SSRT2) on the surface of tumor cells of most NETs^[10]. ^{177}Lu -Dotatate is radiolabeled with the β -emitter ^{177}Lu , which has a maximum penetration range of 2.2 mm and binds with high affinity to SSRT2, thereby delivering targeted cytotoxic radiation to tumor cells overexpressing SSRT2 with minimal damage to neighboring healthy tissue^[11]. In the phase III NETTER-1 trial, conducted in patients with advanced, progressive, somatostatin-receptor-positive midgut NETs ^{177}Lu -Dotatate plus best supportive care (BSC) with octreotide long-acting release (LAR) 30 mg was associated with a statistically significant benefit in both progression-free survival (PFS) and overall survival (OS) compared with octreotide LAR 60 mg^[12]. In the primary analysis median [95% confidence interval (CI)] PFS was not yet reached in the ^{177}Lu -Dotatate group compared with 8.4 (5.8–9.1) months in the octreotide LAR 60 mg group and the hazard ratio (95%CI) for disease progression or death for ^{177}Lu -dotatate-treated patients was 0.21 (0.13–0.33) ($P < 0.001$)^[12]. In parallel with improved survival outcomes, treatment with ^{177}Lu -Dotatate also significantly delayed deterioration in quality of life (QoL) relative to octreotide LAR 60 mg^[13]. Further, the authors of a 2015 review on QoL in patients with GEP-NETs noted that whilst QoL has been shown to improve in patients treated with PRRT (irrespective of the radionuclide used), it remains relatively unchanged from baseline in patients undergoing treatment with everolimus^[14].

In addition to clinical efficacy, novel treatments must also demonstrate cost-effectiveness relative to currently available treatments. The acquisition costs of novel treatments, particularly those used in oncology or for orphan indications are often higher than for the current standard of care. As such, healthcare policy makers and payers are increasingly stipulating that for granting reimbursement novel treatments must demonstrate not only better safety and efficacy, but also long-term cost-effectiveness relative to the current standard of care. On a European level, spending on cancer drugs has increased substantially in recent years. In 2005, spending on cancer drugs in the EU totaled EUR 7.6 billion and accounted for 12% of total healthcare spending on cancer, by 2014 these figures had increased to EUR 19.1 billion and 23%, respectively^[15]. Consequently, to maintain access and equity throughout healthcare systems the acquisition costs associated with novel cancer treatments have been subject to increasing scrutiny from payers and policy makers^[16]. In light of the importance of demonstrating the cost-effectiveness and substantiating the budget impact of new interventions the aim of the current analysis was to investigate the long-term cost-effectiveness of ^{177}Lu -Dotatate compared with everolimus in populations of patients with unresectable or metastatic, progressive P-NETs and midgut NETs in both Sweden and Norway (analyses were performed based on health economic models utilized in successful reimbursement submissions for ^{177}Lu -Dotatate in both Sweden and Norway). In addition, budget impact evaluations for Norway, Sweden and Denmark are presented to reflect the potential influence of the novel treatment options on the health care budget.

MATERIALS AND METHODS

Model structure

Long-term cost-effectiveness analysis was performed using a three-state partitioned survival model developed in Microsoft Excel, wherein the three states were PFS, post-progression survival and death, and analyses were performed separately for patients with midgut NETs and patients with P-NETs. This approach allows for independent modeling of PFS and OS based on the use of parametric survival models to extrapolate clinical data beyond the time frame of clinical studies^[17]. A series of parametric survival functions (including exponential, Weibull, Gompertz, log-logistic and log-normal models) were fitted to the survival data obtained from the NETTER-1^[12] and ERASMUS studies (AAA, data on file). The most appropriate function was determined based on a combination of visual inspection, Akaike's Information Criterion and the Bayesian Information Criterion as well as both clinical and biological plausibility. On this basis the Weibull model, was considered to be the most appropriate and best fit (for both PFS and OS) and was utilized in the base case analysis (log-normal and log-logistic functions were excluded on the basis that both have long survival tails considered to be biologically implausible). Further, the Weibull model is flexible as has

the advantage that the associated hazard rate is not constant over time in contrast to the exponential survival model.

In the analysis a cycle length of 4 wk was used and half-cycle correction was applied (note that ^{177}Lu -Dotatate is administered once every 8 wk for a total of four courses and is therefore integrated into the model every second cycle).

Clinical input data

For ^{177}Lu -Dotatate-treated patients, survival data were sourced from the NETTER-1 trial for patients with midgut-NETs and from the ERASMUS study for patients with P-NETs. The analysis for Norway was performed prior to that for Sweden, consequently for the Swedish analysis updated *post-hoc* survival data were used. For the Norwegian analysis, survival data from the primary analysis were used as *post-hoc* survival data were not yet available at the time the Norwegian analysis was performed. Baseline cohort characteristics for the simulated patient cohort were based on the NETTER-1 trial and for patients treated with everolimus survival data were sourced from the RADIANT-4^[18] trial in patients with gastrointestinal-NETs (GI-NETs) and the RADIANT-3^[19] trial in patients with P-NETs. For the survival modeling approach, a hazard ratio was applied to the baseline risk curve to compare each active treatment to a control so that ^{177}Lu -Dotatate and everolimus could be compared indirectly *via* a common comparator assuming constant proportionality.

For both treatments, missed doses or dose modifications due to toxicity were accounted for using relative dose intensity (RDI) and missed doses were also taken into account in terms of the acquisition costs for each treatment. For everolimus, an RDI of 79.4% was assumed based on data from the RADIANT-4 trial^[18]. For ^{177}Lu -Dotatate, RDI refers to the amount of the drug that is actually administered relative to the planned number of four doses, the RDI may be below 100% if patients either miss a dose or have the dose modified due to toxicity or an adverse event. A complete course of ^{177}Lu -Dotatate consists of 4 doses, but based on the findings of the ERASMUS study an RDI of 84.4% was assumed, which corresponds to a mean of 3.4 doses per patient.

Only grade 3-4 adverse events (AEs) were conservatively included in the analysis. For ^{177}Lu -Dotatate-treated patients the frequency of AEs was sourced from the NETTER-1 trial. For everolimus-treated patients the frequency of AEs was sourced from the RADIANT-4 study^[18] for midgut-NETs and the RADIANT-3 study^[19] for patients with P-NETs.

Resource utilization and costs

Drug acquisition costs and resource utilization costs associated with drug administration specific to each setting (*e.g.*, for ^{177}Lu -Dotatate specialist physician, biochemist and nurse as well as general inpatient and outpatient costs) were accounted in the analysis. For Sweden, drug acquisition costs were sourced from FASS (Pharmaceutical specialties in Sweden)^[20] and for Norway drug acquisition costs were sourced from the Norwegian Medicines Agency^[21] (Table 1). The costs of routine monitoring in each setting (*e.g.*, CT scans, blood tests *etc.*) were also captured in the analysis (resource use was country-specific owing to differences between health care systems in terms of monitoring frequency). Applying a conservative assumption, costs associated with palliative care were not captured in the analysis.

The cost of AEs was calculated as a single cost based on a weighted probability of AEs in each treatment arm. For Sweden, costs for individual AEs were not identified, therefore Norwegian AE costs were used as a proxy and converted to SEK, which included a conversion factor that corrected for the relative cost level in specialist care and the average exchange rate in the previous 12 mo. For Norway, AE costs were calculated based on DRG codes. All costs are presented in 2017 values.

Health state utilities

In the base case analysis, for Sweden, the health state utility value for the PFS state for patients with midgut-NETs was sourced from a real-world study in patients with GI-NETs conducted in the United Kingdom (AAA, data on file; Table 2). For Norway, the health state utility value for the PFS state in midgut-NET patients was sourced from NETTER-1 study. For both Sweden and Norway, utility values for all other health states were sourced from the real-world ERASMUS study conducted in the Netherlands. In both the NETTER-1 and ERASMUS studies, QoL was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire^[22] and subsequently mapped to the EQ-5D using the algorithm developed by Longworth *et al.*^[23] (2014).

Disutilities associated with treatment-related AEs were sourced from published

Table 1 Drug acquisition costs for gastrointestinal-neuroendocrine tumors and pancreatic-neuroendocrine tumor

Treatment	Dose and frequency	Cost Sweden, SEK	Cost Norway, NOK
¹⁷⁷ Lu-Dotatate 7.4 GBq (Lutathera [®])	4 administrations of 7.4 GBq, administered once every 8 wk	200000 per dose	228508 per dose
Octreotide LAR (Sandostatin [®])	60 mg or 30 mg administered once every 28 d	11957.94 (30 mg) 23915.88 (60 mg)	13673 (30 mg) 27346 (60 mg)
Everolimus (Afinitor [®])	10 mg once daily	38089.19 (1 × 30 tablet pack, 10 mg)	36525 (1 × 30 tablet pack, 10 mg)
Octreotide SC 50 µg/mL	If required	283.41 per dose	227.40 per dose
Granisetron ¹	3.1 mg/24 h depot patch administered prior to ¹⁷⁷ Lu-Dotatate	913.25 (1 × patch)	875.30
Ondansetron ¹	8 mg administered prior to ¹⁷⁷ Lu-Dotatate	1474.02 (1 × 30 tablet pack, 4 mg)	985.70 (1 × 30 tablet pack, 8 mg)
Tropisetron ¹	5 mg administered prior to ¹⁷⁷ Lu-Dotatate	1474.02 ²	749.70 (1 × 5 tablet pack, 5 mg)
Vamin ³	18%–18% infusion administered prior to/during ¹⁷⁷ Lu-Dotatate	458.08 (2 × 500 mL infusions)	202.8 (1 × 500 mL infusion)
Clinisol ³	15% infusion administered prior to/during ¹⁷⁷ Lu-Dotatate	458.08 ⁴	Not available in Norway

¹Anti-emetic required to be administered prior to administration with Lutathera.

²Cost assumed equal to ondansetron.

³Amino acid infusion required to be administered prior to and during administration of Lutathera.

⁴Cost assumed equal to Vamin. All Swedish costs are sourced from FASS (Pharmaceutical specialties in Sweden)^[20]. All Norwegian costs are sourced from the Norwegian Medicines Agency^[21]. PPP: Purchasing power parity; SC: Subcutaneous.

Table 2 Utilities used in the base case analysis

Health state	Utility (SE)	Source
Sweden		
Midgut-NET progression-free survival	0.79 (0.01)	Real world evidence ¹
Midgut-NET post-progression survival	0.74 (0.01)	ERASMUS study ²
P-NET progression-free survival	0.80 (0.01)	ERASMUS study ²
P-NET post-progression survival	0.79 (0.02)	ERASMUS study ²
Norway		
Midgut-NET progression-free survival (Lutathera)	0.75 (0.01)	NETTER-1 ^[13]
Midgut-NET post-progression survival	0.74 (0.01)	ERASMUS study ²
P-NET progression-free survival	0.80 (0.01)	ERASMUS study ²
P-NET post-progression survival	0.79 (0.02)	ERASMUS study ²

¹Real world study conducted at Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom (AAA, data on file).

²AAA data on file. Midgut-NET: Midgut neuroendocrine tumor; P-NET: Pancreatic neuroendocrine tumor; SE: Standard error.

literature^[24–27] (Table 3). QoL decrements associated with palliative/end of life care were not included in the analysis.

Time horizon, discount rate and perspective

For both Sweden and Norway, the analysis was performed from the perspective of the healthcare payer and the time horizon was 20 years reflecting a life-time analysis given the average age of NET patients at time of diagnosis. In line with national recommendations, for Sweden both future costs and clinical outcomes were discounted at a rate of 3% *per annum*, and for Norway a discount rate of 4% *per annum* was applied for both costs and outcomes.

Table 3 Disutilities for grade 3 and 4 adverse events

Event	Disutility	Ref.
Nausea	0.05	Nafees <i>et al</i> ^[24]
Vomiting	0.05	Nafees <i>et al</i> ^[24]
Diarrhea	0.05	Nafees <i>et al</i> ^[24]
Abdominal pain	0.07 ¹	Doyle <i>et al</i> ^[25]
Thrombocytopenia	0.11 ¹	Tolley <i>et al</i> ^[26]
Lymphopenia	0.11 ¹	Assumed ²
Leukopenia	0.11 ¹	Assumed ²
Stomatitis	0.11 ¹	Assumed ²
Fatigue	0.20 ¹	Swinburn <i>et al</i> ^[27]
Infections	0.11 ¹	Assumed ²
Asthenia	0.20 ¹	Assumed ³
Anemia	0.12 ¹	Swinburn <i>et al</i> ^[27]
Pyrexia	0.11 ¹	Assumed ²
Hyperglycemia	0.11 ¹	Assumed ²
Neutropenia	0.09 ¹	Nafees <i>et al</i> ^[24]
Hypertension	0.11 ¹	Assumed ²
Musculoskeletal pain	0.11 ¹	Assumed ²
Flushing	0.11 ¹	Assumed ²
Decreased appetite	0.20 ¹	Assumed ³

¹Standard error assumed to be equal to mean.²Assumed.³Assumed to be equal to fatigue.

Sensitivity analysis

A series of one-way sensitivity analyses were performed to determine key drivers of outcomes. For Sweden, the impact of changing key input values by $\pm 20\%$ was explored. For Norway key input parameters were varied by $\pm 30\%$. Sensitivity analyses were performed around drug acquisition costs, health state utility values, efficacy, resource use and the overall disutility associated with AEs.

Budget impact analysis

Budget impact analyses were performed to estimate the budget impact of introducing ¹⁷⁷Lu-Dotatate into clinical practice in Sweden and Norway. For both countries, the treatment eligible GEP-NET population was based on national population figures, incidence estimates published by Öberg *et al*^[4] (2012) and it was assumed that 40% of patients had metastasis at baseline^[28]. Market share projections for each country were based on estimates from the manufacturer of ¹⁷⁷Lu-Dotatate (AAA, data on file). In both Sweden and Norway, it was assumed that ¹⁷⁷Lu-Dotatate would replace everolimus as a treatment option. Budget impact analyses were performed over a time horizon of 5 years, in line with good practice^[29] and national guidance^[30] and costs were not discounted.

RESULTS

Cost-effectiveness of ¹⁷⁷Lu-Dotatate in Sweden

In patients with midgut NETs, treatment with ¹⁷⁷Lu-Dotatate was associated with a projected gain in quality-adjusted life expectancy of 0.48 quality-adjusted life years (QALYs) relative to everolimus (3.45 QALYs for ¹⁷⁷Lu-Dotatate *vs* 2.97 QALYs for

everolimus), which was driven by longer PFS and OS with ¹⁷⁷Lu-Dotatate (Table 4). Total lifetime costs were SEK 189818 higher with ¹⁷⁷Lu-Dotatate compared with everolimus (SEK 1,170,731 *vs* SEK 980913), which resulted in an incremental cost effectiveness ratio (ICER) of SEK 391194 (EUR 36154, September 2019 exchange rates) per QALY gained.

For patients with P-NETs, the difference in projected quality-adjusted life expectancy between the two treatments was more pronounced. Treatment with ¹⁷⁷Lu-Dotatate resulted in a mean quality-adjusted life expectancy of 4.90 QALYs compared with 3.55 QALYs for patients treated with everolimus (difference 1.35 QALYs) (Table 4). Total mean lifetime costs were also SEK 22498 higher with ¹⁷⁷Lu-Dotatate (SEK 1398533 *vs* SEK 1376034), resulting in an ICER of SEK 16764 (EUR 1549) per QALY gained.

One-way sensitivity analyses showed that for patients with midgut NETs, the findings of the analysis were most sensitive to changes in drug acquisition costs for both ¹⁷⁷Lu-Dotatate and everolimus as well as assumptions around health state utility values for the PFS and PPS states (Figure 1). Similarly, for P-NET patients the ICER was most sensitive to changes in drug acquisition costs and changes in the total weighted disutility value for AEs experienced by everolimus-treated patients.

Cost-effectiveness of ¹⁷⁷Lu-Dotatate in Norway

For patients with midgut-NETs, treatment with ¹⁷⁷Lu-Dotatate led to a gain in quality-adjusted life expectancy of 1.36 QALYs relative to the use of everolimus (3.15 QALYs for ¹⁷⁷Lu-Dotatate *vs* 1.79 QALYs for everolimus). Total mean lifetime costs were NOK 331995 higher with ¹⁷⁷Lu-Dotatate compared with everolimus (NOK 985062 *vs* NOK 653066), which was primarily driven by the higher acquisition costs associated with ¹⁷⁷Lu-Dotatate (Table 4). The incremental gain in quality-adjusted life expectancy combined with higher lifetime costs resulted in an ICER of NOK 244444 (EUR 24416; September 2019 exchange rates) per QALY gained for ¹⁷⁷Lu-Dotatate *vs* everolimus.

For patients with P-NETs, the incremental gain in quality-adjusted life expectancy associated with the use of ¹⁷⁷Lu-Dotatate compared with everolimus was 2.10 QALYs (5.31 QALYs for ¹⁷⁷Lu-Dotatate *vs* 3.21 QALYs for everolimus) (Table 4), which was driven by the notably longer PFS and OS projected for patients treated with ¹⁷⁷Lu-Dotatate. Lifetime costs were NOK 223487 higher with ¹⁷⁷Lu-Dotatate than with everolimus (NOK 1280254 *vs* NOK 223487). This led to an ICER of NOK 106451 (EUR 10633) per QALY gained.

One-way sensitivity analyses revealed that for patients with midgut-NETs cost-effectiveness was most sensitive to changes in drug acquisition costs for both ¹⁷⁷Lu-Dotatate and everolimus and also to the utility value assigned to the PFS health state (Figure 2). Similarly, for P-NET patients results were most sensitive to changes in drug acquisition costs and changes in assumptions around efficacy.

Budget impact of ¹⁷⁷Lu-Dotatate

In Sweden it was assumed that the market share of ¹⁷⁷Lu-Dotatate for the treatment of patients with GEP-NETs would increase from 30% in Year 1 to 90% in Years 4 and 5 (Table 5). In Year 1, the total budget impact associated with the introduction of ¹⁷⁷Lu-Dotatate was SEK 17.3 million (EUR 1.6 million), which increased to SEK 52.2 million (EUR 4.8 million) in Years 4 and 5 (Table 5). Over a 5-year period the total budget impact associated with the introduction of ¹⁷⁷Lu-Dotatate was SEK 202 million (EUR 19 million). In Norway, the market share of ¹⁷⁷Lu-Dotatate was assumed to remain at 50% over the 5-year time horizon of the analysis and the annual budget impact associated with the introduction of ¹⁷⁷Lu-Dotatate was NOK 23.5 million (EUR 2.4 million). Over a 5-year time horizon the total budget impact was estimated at NOK 117 million (EUR 11.8 million).

An additional budget impact analysis was also performed for Denmark. In Denmark, it was assumed that ¹⁷⁷Lu-Dotatate would wholly replace lanreotide as a treatment option for GEP-NETs (and that 60 GEP-NET patients per year would be treated with ¹⁷⁷Lu-Dotatate) and the annual budget impact was estimated at DKK 27.2 million (EUR 3.6 million), which led to a total budget impact over 5 years of DKK 136 million (EUR 18.2 million).

DISCUSSION

Overall, the findings of long-term cost-effectiveness analyses suggest that in both Sweden and Norway, ¹⁷⁷Lu-Dotatate is associated with substantial gains in quality-

Table 4 Summary of base case results

	¹⁷⁷ Lu-Dotatate	Everolimus	Delta
Sweden			
Midgut-NETs			
Total costs, SEK	1170 731	980913	189818
Quality-adjusted life expectancy, QALYs	3.45	2.97	0.48
ICER, SEK per QALY gained	391194		
P-NETs			
Total costs, SEK	1398533	1376035	22498
Quality-adjusted life expectancy, QALYs	4.90	3.55	1.35
ICER, SEK per QALY gained	16764		
Norway			
Midgut-NETs			
Total costs, NOK	985062	653066	331995
Quality-adjusted life expectancy, QALYs	3.15	1.79	1.36
ICER, NOK per QALY gained	244444		
P-NETs			
Total costs, NOK	1280254	1056767	223487
Quality-adjusted life expectancy, QALYs	5.31	3.21	2.10
ICER, NOK per QALY gained	106451		

NETs: Neuroendocrine tumors; QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; P-NET: Pancreatic-neuroendocrine tumor.

adjusted life expectancy and higher lifetime costs in patients with unresectable/metastatic midgut-NETs or P-NETs. In particular, in both countries ¹⁷⁷Lu-Dotatate was most cost-effective in patients with P-NETs and was associated with an ICER below EUR 11000 per QALY gained relative to everolimus in both settings. There is no official willingness-to-pay (WTP) threshold in Sweden, in Norway an unofficial threshold of NOK 600000 (EUR 59939) per QALY gained is often cited^[31] and in high income European countries a WTP threshold of EUR 50000 per QALY gained is also frequently cited. Consequently, applying these commonly applied thresholds, ¹⁷⁷Lu-Dotatate is likely to be considered cost-effective for the treatment of patients with unresectable or metastatic midgut NETs or P-NETs in both Sweden and Norway.

Although ¹⁷⁷Lu-Dotatate was shown to be cost-effective in both midgut-NETs and P-NETs the findings in patients with P-NETs may be particularly salient to healthcare payers as historically 5-year survival rates in patients with P-NET have been low relative to patients with GI-NETs^[32]. In Sweden, total direct medical costs are also substantially higher for patients with P-NETs compared with patients with small intestine NETs. In 2013, annual per patient direct medical costs were EUR 24800 for patients with small intestine-NETs compared with EUR 37300 for patients with P-NETs^[33]. Further, overall 54% of direct costs for patients with GEP-NETs were attributable to cancer drugs and on a national level, EUR 5.1 million was spent on pharmacologic agents for the treatment of patients with GEP-NETs^[33]. In terms of budget impact, in Sweden and Denmark overall healthcare spending on cancer in 2014 was EUR 2.7 billion and EUR 1.2 billion, respectively (similar data for Norway were not available)^[15]. As such, the budget impact associated with the introduction of ¹⁷⁷Lu-Dotatate is likely to have only a minimal impact on overall spending on pharmacologic agents used in cancer treatment.

The findings of the cost-effectiveness analyses presented here align with previously published findings from the National Institute for Health and Care Excellence (NICE)^[34] and the Scottish Medicines Consortium^[35] in the United Kingdom as well as findings published by the Tandvårds-och läkemedelsförmånsverket (TLV; Dental and Pharmaceutical Benefits Agency) in Sweden. In particular, the NICE assessment reported that for patients with GI-NETs, when compared with everolimus or best

Table 5 Summary findings of budget impact analysis

	Year					Cumulative budget impact over 5 yr
	1	2	3	4	5	
Sweden						
Total treatment-eligible patients, <i>n</i> ¹	158	158	158	158	158	—
Projected market share for ¹⁷⁷ Lu-Dotatate, % ²	30	60	80	90	90	—
Total cost if ¹⁷⁷ Lu-Dotatate adopted, SEK	85610153	102881530	114640765	120520382	120520382	544173212
Total cost if ¹⁷⁷ Lu-Dotatate not adopted, SEK	68338777	68338777	68338777	68338777	68338777	341693885
Budget impact, SEK	17271376	34542753	46301988	52181605	52181605	202479327
Norway						
Total treatment-eligible patients, <i>n</i> ¹	100	100	100	100	100	—
Projected market share for ¹⁷⁷ Lu-Dotatate, % ²	50	50	50	50	50	—
Total cost if ¹⁷⁷ Lu-Dotatate adopted, NOK	67920975	67920975	67920975	67920975	67920975	339604875
Total cost if ¹⁷⁷ Lu-Dotatate not adopted, NOK	44438750	44438750	44438750	44438750	44438750	222193750
Budget impact, NOK	23482225	23482225	23482225	23482225	23482225	117411125

¹Number of patients annually with metastatic GEP-NETs based on an estimated incidence of 5.25 per 100000 population (Oberg *et al*^[4], 2012) (40% of patients with GEP-NETs assumed to have metastases) and population estimates from national statistics agencies.

²Assumes that all other eligible patients are treated with everolimus.

supportive care ¹⁷⁷Lu-Dotatate was considered to be cost-effective and associated with an ICER below the threshold of GBP 30000 per QALY gained. ICERs were also below GBP 30000 per QALY gained *vs* everolimus, sunitinib or best supportive care in patients with P-NETs, with the NICE appraisal also noting that for P-NETs ¹⁷⁷Lu-Dotatate met the criteria for end of life care of extending life expectancy by at least 3 mo^[34]. Additionally, the TLV conducted cost-minimization rather than cost-effectiveness analysis and reported that whilst ¹⁷⁷Lu-Dotatate was associated with higher costs than everolimus in patients with GI-NETs it was associated with lower costs than both everolimus and sunitinib in patients with P-NETs^[36].

A key limitation of the current analysis is the use of clinical input data obtained *via* an indirect comparison. Although everolimus was considered to be the most relevant comparator for ¹⁷⁷Lu-Dotatate, to date, there are no head-to-head trials that directly compare the efficacy and safety of ¹⁷⁷Lu-Dotatate with everolimus in patients with midgut NETs or P-NETs. Consequently, this necessitated the use of data sourced from indirect comparisons, which is inherently associated with a degree of uncertainty. The findings of the indirect comparison used here align with those of a recent systematic review and meta-analysis of ¹⁷⁷Lu-Dotatate *vs* everolimus in advanced P-NETs, wherein ¹⁷⁷Lu-Dotatate was associated with a significantly higher objective response rate, disease control rate and PFS relative to everolimus^[37]. Additionally, although the analysis included the incidence of grade 3–4 AEs it did not account for long-term persistent hematologic dysfunction that has recently been reported in a small proportion of GEP-NET patients undergoing treatment with ¹⁷⁷Lu-Dotatate. A recent real-world analysis reported that 4% of ¹⁷⁷Lu-Dotatate-treated GEP-NET patients experienced persistent hematologic dysfunction, occurring at a median of 41 mo post-treatment^[38], the costs and clinical implications of which should be considered in future analyses.

A further limitation in the analysis in patients with P-NETs is that only everolimus was included as a relevant comparator, based on clinical practice utilization patterns and input from local clinicians. In Europe, the tyrosine kinase inhibitor sunitinib is indicated for use in the treatment of patients with unresectable or metastatic, well differentiated P-NETs experiencing disease progression^[39]. However, as with

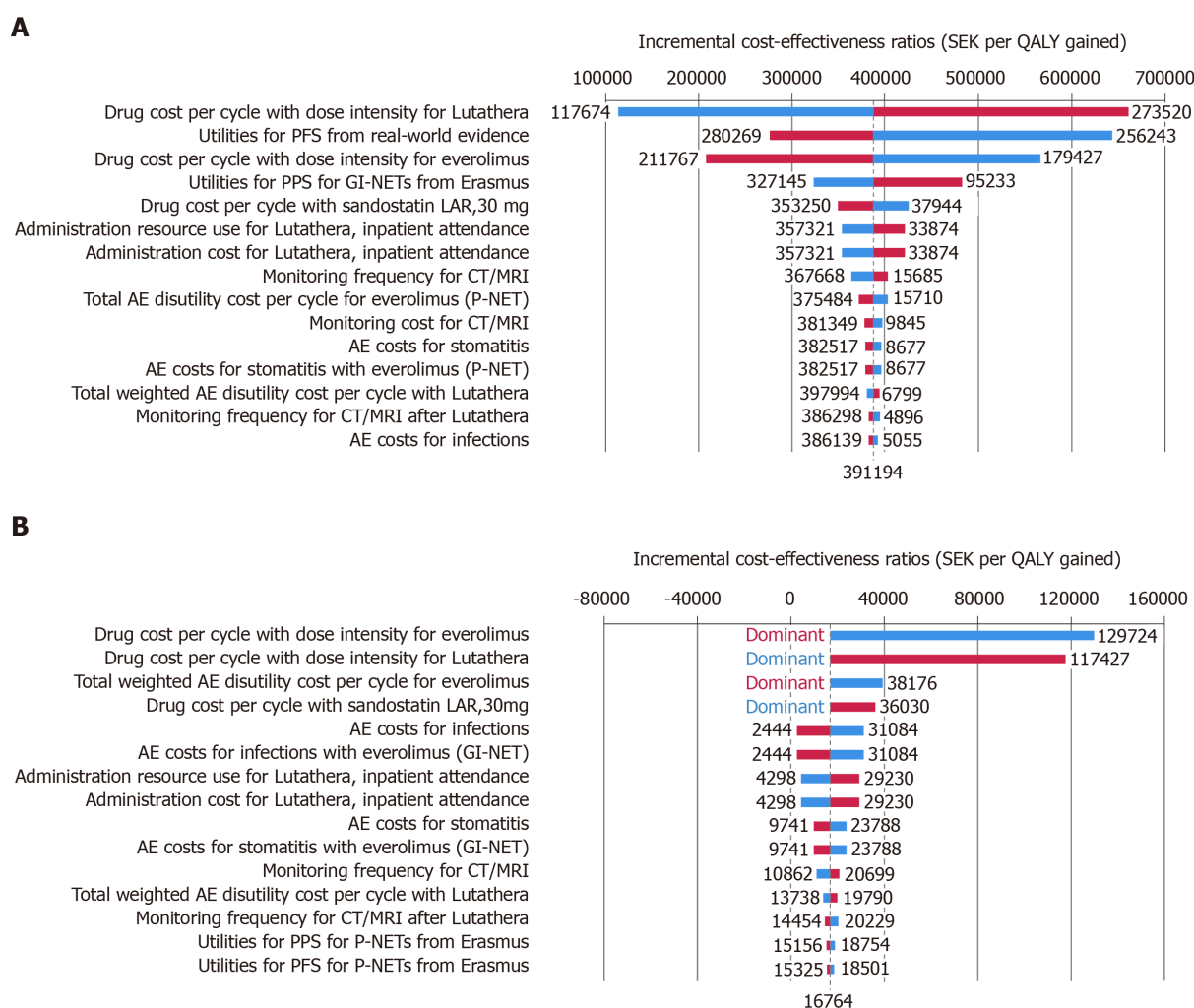


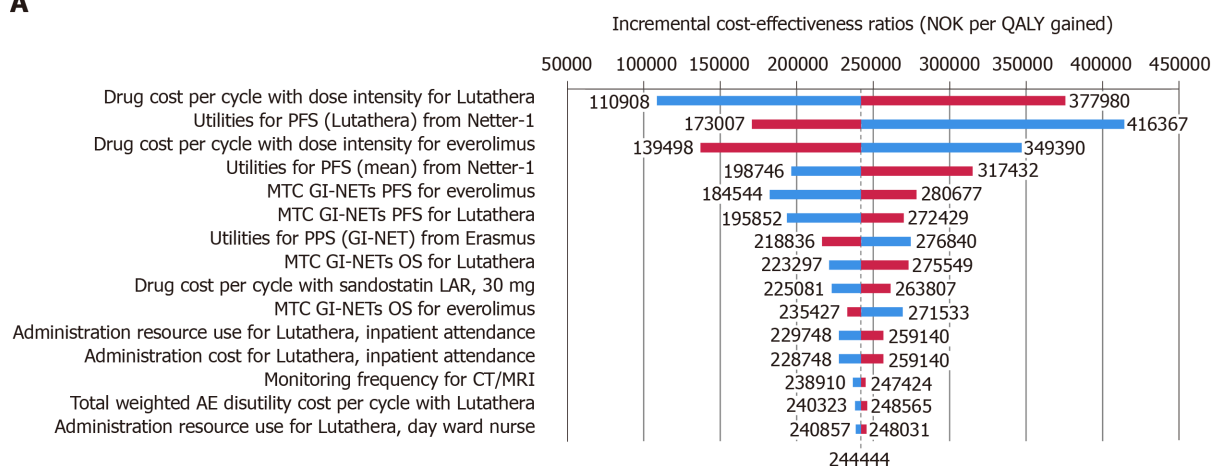
Figure 1 Summary findings of one-way sensitivity analyses for Sweden. A: One-way sensitivity analyses in midgut neuroendocrine tumors; B: One-way sensitivity analyses in pancreatic neuroendocrine tumors. QALY: Quality-adjusted life year; PPS: Post-progression survival; PFS: Progression-free survival; GI-NETs: Gastrointestinal-neuroendocrine tumors; LAR: Long-acting release; CT: Computed tomography; MRI: Magnetic resonance imaging; P-NET: Pancreatic-neuroendocrine tumor; AE: Adverse event.

everolimus, head-to-head clinical data comparing ¹⁷⁷Lu-Dotatate with sunitinib are currently lacking. Evidence from two different indirect comparisons, reported that sunitinib and everolimus were associated with similar PFS and OS in P-NET^[40,41]. Drug acquisition costs for everolimus and sunitinib were also similar in both Sweden and Norway. It is therefore feasible that given the similar efficacy profile and costs the cost-effectiveness profile of ¹⁷⁷Lu-Dotatate *vs* sunitinib would be similar to that of ¹⁷⁷Lu-Dotatate *vs* everolimus.

Additionally, although Nordic guidelines^[3] relating the treatment of patients with GEP-NETs were published prior to the approval of ¹⁷⁷Lu-Dotatate, European guidelines advocate the use of PRRT as a treatment option for patients with metastatic midgut-NETs or P-NETs^[28] and the findings of the NETTER-1 and ERAMUS trials lend further credence to the clinical evidence base for these recommendations.

For consistency, the analyses in both Sweden and Norway were performed from the healthcare payer perspective. In Sweden reimbursement decisions are based on analyses performed from a societal perspective, which takes into account indirect costs associated with lost productivity. However, the mean age of patients in the simulated cohort was 63.7 years. In Sweden, the minimum retirement age is 61 years and the mean age at retirement was 64.5 years in 2016^[42]. As such it is unlikely that the inclusion of indirect costs associated with lost productivity in this population would have a notable impact on the conclusions of the analysis. Further, both PFS and OS were projected to be longer for ¹⁷⁷Lu-Dotatate patients, suggesting that the inclusion of indirect costs would likely further reduce the ICER for ¹⁷⁷Lu-Dotatate *vs* everolimus and as such the analysis was conservative.

A



B

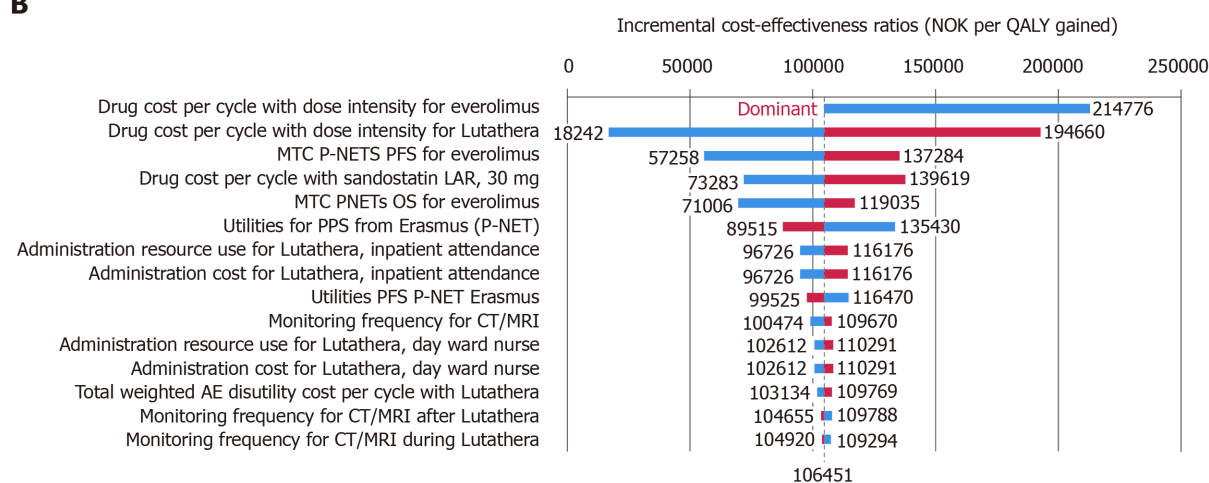


Figure 2 Summary findings of one-way sensitivity analyses for Norway. A: One-way sensitivity analyses in midgut neuroendocrine tumors; B: One-way sensitivity analyses in pancreatic neuroendocrine tumors. QALY: Quality-adjusted life year; PPS: Post-progression survival; PFS: Progression-free survival; GI-NETs: Gastrointestinal-neuroendocrine tumors; LAR: Long-acting release; CT: Computed tomography; MRI: Magnetic resonance imaging; P-NET: Pancreatic-neuroendocrine tumor; AE: Adverse event.

CONCLUSION

Overall, the findings of life-long cost-effectiveness analyses for both Sweden and Norway indicate that owing to improved survival outcomes ¹⁷⁷Lu-Dotate is likely to be cost-effective and associated with minimal budget impact relative to everolimus for the treatment of patients with unresectable or metastatic progressive midgut-NETs or P-NETs.

ARTICLE HIGHLIGHTS

Research background

¹⁷⁷Lu oxodotreotide (¹⁷⁷Lu-Dotatate) is a peptide receptor radionuclide therapy that was approved for use in Europe in 2017. Findings from the phase III NETTER-1 trial, conducted in patients with advanced, progressive, somatostatin-receptor-positive midgut neuroendocrine tumors (NETs) showed that the use of ¹⁷⁷Lu-Dotatate in combination with best supportive care with octreotide long-acting release (LAR) 30 mg resulted in a significant benefit in terms of both progression-free survival (PFS) and overall survival (OS) compared with octreotide LAR 60 mg.

Research motivation

Health systems frequently have to operate within finite budgetary constraints; therefore, it is important to establish not only the efficacy but also the long-term cost-

effectiveness of new treatments as they are introduced into the healthcare system.

Research objectives

The objective of the analysis was to establish the long-term cost-effectiveness of ¹⁷⁷Lu-Dotatate compared with everolimus in patients with unresectable or metastatic midgut-NETs or pancreatic-NETs (P-NETs) in both Sweden and Norway.

Research methods

Cost-effectiveness analysis was performed using a three-state partitioned survival model, which allows for the independent modeling of PFS and OS and the extrapolation of clinical data beyond the time frame of a clinical trial. In the absence of head-to-head trials clinical input data used in the model for the P-NET analysis were sourced from an indirect treatment comparison using input data from trials of ¹⁷⁷Lu-Dotatate and everolimus.

Research results

In both Sweden and Norway, treatment with ¹⁷⁷Lu-Dotatate was associated with an incremental gain in quality-adjusted life expectancy relative to everolimus for both midgut-NETs and P-NETs, which was driven by projected improvements in PFS and OS associated with the use of ¹⁷⁷Lu-Dotatate. For Sweden, improved survival outcomes and higher lifetime costs with ¹⁷⁷Lu-Dotatate resulted in an incremental cost-effectiveness ratio (ICER) of SEK 391194 per quality-adjusted life year (QALY) gained for midgut NETs and SEK 16764 per QALY gained for P-NETs for ¹⁷⁷Lu-Dotatate compared with everolimus. For Norway the corresponding ICERs were NOK 244444 per QALY gained for midgut NETs and NOK 106,451 per QALY gained for P-NETs.

Research conclusions

In both Sweden and Norway, ¹⁷⁷Lu-Dotatate is likely to be considered cost-effective relative to everolimus for the treatment of patients with unresectable or metastatic, progressive midgut-NETs or P-NETs when considered from the perspective of the healthcare provider.

Research perspectives

Based on clinical data derived through indirect comparison ¹⁷⁷Lu-Dotatate is likely to be a cost-effective treatment option relative to everolimus for patients with midgut NETs or P-NETs based in Sweden or Norway.

REFERENCES

- 1 Klöppel G. Neuroendocrine Neoplasms: Dichotomy, Origin and Classifications. *Visc Med* 2017; **33**: 324-330 [PMID: 29177160 DOI: 10.1159/000481390]
- 2 Cetinkaya RB. Epidemiology of Neuroendocrine Neoplasms in Norway. Oslo University Hospital, Institute of Clinical Medicine, University of Oslo. 2017. [Last accessed June 18, 2019] Available from: <https://www.duo.uio.no/bitstream/handle/10852/61617/Cetinkaya-PhD-2018.pdf?sequence=1&isAllowed=y>
- 3 Janson ET, Sorbye H, Welin S, Federspiel B, Grønbæk H, Hellman P, Ladekarl M, Langer SW, Mortensen J, Schalin-Jäntti C, Sundin A, Sundlöv A, Thiis-Evensen E, Knigge U. Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *Acta Oncol* 2014; **53**: 1284-1297 [PMID: 25140861 DOI: 10.3109/0284186X.2014.941999]
- 4 Öberg K, Knigge U, Kwekkeboom D, Perren A; ESMO Guidelines Working Group. Neuroendocrine gastroentero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23** Suppl 7: vii124-vii130 [PMID: 22997445 DOI: 10.1093/annonc/mds295]
- 5 Statistics Sweden. Population statistics. [Last accessed August 28, 2019] Available from: <https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-composition/population-statistics/>
- 6 Statistics Norway. Key figures for the population. [Last accessed August 28, 2019] Available from: <https://www.ssb.no/en/befolkning/nokkeltall/population>
- 7 European Medicines Agency. Orphan designation: Overview. [Last accessed September 02, 2019] Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview>
- 8 Milione M. Prognostic factors for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs): what's better? *Endocrine* 2018; **59**: 1-3 [PMID: 28417314 DOI: 10.1007/s12020-017-1299-0]
- 9 Boyar Cetinkaya R, Aagnes B, Myklebust TÅ, Thiis-Evensen E. Survival in neuroendocrine neoplasms; A report from a large Norwegian population-based study. *Int J Cancer* 2018; **142**: 1139-1147 [PMID: 29082524 DOI: 10.1002/ijc.31137]
- 10 Childs A, Vesely C, Ensell L, Lowe H, Luong TV, Caplin ME, Toumpanakis C, Thirlwell C, Hartley JA, Meyer T. Expression of somatostatin receptors 2 and 5 in circulating tumour cells from patients with neuroendocrine tumours. *Br J Cancer* 2016; **115**: 1540-1547 [PMID: 27875519 DOI: 10.1038/bjc.2016.377]

- 11 Lutathera, INN-lutetium (¹⁷⁷Lu) oxodotreotide. European Summary of Product Characteristics. [Last accessed June 18, 2019] Available from: https://www.ema.europa.eu/en/documents/product-information/Lutathera-epar-product-information_en.pdf
- 12 **Strosberg J**, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, Mittra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O'Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Lebtahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srirajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregni E, Öberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruzsniwski P, Kwekkeboom D, Krenning E; NETTER-1 Trial Investigators. Phase 3 Trial of ¹⁷⁷Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017; **376**: 125-135 [PMID: 28076709 DOI: 10.1056/NEJMoa1607427]
- 13 **Strosberg J**, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, Baum RP, Kunz P, Hobday T, Hendifar A, Oberg K, Sierra ML, Thevenet T, Margalet I, Ruzsniwski P, Krenning E; NETTER-1 Study Group. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With ¹⁷⁷Lu-Dotatate in the Phase III NETTER-1 Trial. *J Clin Oncol* 2018; **36**: 2578-2584 [PMID: 29878866 DOI: 10.1200/JCO.2018.78.5865]
- 14 **Jiménez-Fonseca P**, Carmona-Bayonas A, Martín-Pérez E, Crespo G, Serrano R, Llanos M, Villabona C, García-Carbonero R, Aller J, Capdevila J, Grande E; Spanish Neuroendocrine Tumor Group (GETNE). Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. *Cancer Metastasis Rev* 2015; **34**: 381-400 [PMID: 26245646 DOI: 10.1007/s10555-015-9573-1]
- 15 **Jönsson B**, Hofmarcher T, Lindgren P, Wilking N. The cost and burden of cancer in the European Union 1995-2014. *Eur J Cancer* 2016; **66**: 162-170 [PMID: 27589247 DOI: 10.1016/j.ejca.2016.06.022]
- 16 **Aggarwal A**, Ginsburg O, Fojo T. Cancer economics, policy and politics: What informs the debate? *J Cancer Policy* 2014; **2**: 1-11 [DOI: 10.1016/j.jcpo.2014.02.002]
- 17 **National Institute for Health and Care Excellence Decision Support Unit**. Partitioned survival analysis technical support document. [Last accessed September 02, 2019] Available from: <http://nicedsu.org.uk/technical-support-documents/partitioned-survival-analysis/tsd/>
- 18 **Yao JC**, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyre N, Sachs C, Valle JW, Fave GD, Van Cutsem E, Tessler M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours; Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016; **387**: 968-977 [PMID: 26703889 DOI: 10.1016/S0140-6736(15)00817-X]
- 19 **Yao JC**, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebowitz D, Öberg K; RAD001 in Advanced Neuroendocrine Tumors; Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 514-523 [PMID: 21306238 DOI: 10.1056/NEJMoa1009290]
- 20 FASS (Pharmaceutical specialities in Sweden) website. [Last accessed August 28, 2019] Available from: <https://www.fass.se/LIF/startpage?userType=2>
- 21 Norwegian Medicines Agency legemiddelsøk. [Last accessed September 02, 2019] Available from: <https://www.legemiddelsok.no/>
- 22 **Aaronson NK**, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365-376 [PMID: 8433390 DOI: 10.1093/jnci/85.5.365]
- 23 **Longworth L**, Yang Y, Young T, Mulhern B, Hernández Alava M, Mukuria C, Rowen D, Tosh J, Tsuchiya A, Evans P, Devianee Keetharuth A, Brazier J. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess* 2014; **18**: 1-224 [PMID: 24524660 DOI: 10.3310/hta18090]
- 24 **Nafees B**, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008; **6**: 84 [PMID: 18939982 DOI: 10.1186/1477-7525-6-84]
- 25 **Doyle S**, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. *Lung Cancer* 2008; **62**: 374-380 [PMID: 18467000 DOI: 10.1016/j.lungcan.2008.03.019]
- 26 **Tolley K**, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ* 2013; **14**: 749-759 [PMID: 22941034 DOI: 10.1007/s10198-012-0419-2]
- 27 **Swinburn P**, Wang J, Chandiwana D, Mansoor W, Lloyd A. Elicitation of health state utilities in neuroendocrine tumours. *J Med Econ* 2012; **15**: 681-687 [PMID: 22364284 DOI: 10.3111/13696998.2012.670175]
- 28 **Pavel M**, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape UF, Öberg K; Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016; **103**: 172-185 [PMID: 26731013 DOI: 10.1159/000443167]
- 29 **Sullivan SD**, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, Orlewska E, Penna P, Rodriguez Barrios JM, Shau WY. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health* 2014; **17**: 5-14 [PMID: 24438712 DOI: 10.1016/j.jval.2013.08.2291]
- 30 **International Society for Pharmacoeconomics and Outcomes Research**. Pharmacoeconomic guidelines around the world. [Last accessed September 25, 2019] Available from: <https://tools.ispor.org/PEguidelines/>
- 31 **Korman M**, Wisløff T. Modelling the cost-effectiveness of PCSK9 inhibitors vs. ezetimibe through LDL-C reductions in a Norwegian setting. *Eur Heart J Cardiovasc Pharmacother* 2018; **4**: 15-22 [PMID: 28444187 DOI: 10.1093/ehjcvp/pvx010]
- 32 **Lawrence B**, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of

- gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 1-18, vii [PMID: 21349409 DOI: 10.1016/j.ecl.2010.12.005]
- 33 **Lesén E**, Granfeldt D, Houchard A, Berthon A, Dinot J, Gabriel S, Björstad Å, Björholt I, Elf AK, Johanson V. Cost-of-illness of metastatic gastroenteropancreatic neuroendocrine tumours in Sweden-A population-based register-linkage study. *Eur J Cancer Care (Engl)* 2019; **28**: e12983 [PMID: 30652364 DOI: 10.1111/ecc.12983]
- 34 **National Institute for Health and Care Excellence**. TA539 August 2018. Lutetium (¹⁷⁷Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumors. [Last accessed September 03, 2019] Available from: <https://www.nice.org.uk/guidance/ta539>
- 35 **Scottish Medicines Consortium**. Lutetium (¹⁷⁷Lu) oxodotreotide 370MBq/mL solution for infusion. June 2018. [Last accessed September 04, 2019] Available from: <https://www.scottishmedicines.org.uk/media/3557/Lutetium-177-Lu-oxodotreotide-lutathera-final-june-2018-for-website.pdf>
- 36 Tandvårds-och läkemedelsförmånsverket. Underlag för beslut i landstingen Lutathera (lutetium (¹⁷⁷Lu)oxodotreotid). [Last accessed September 04, 2019] Available from: https://www.tlv.se/download/18.500ea4181641067957a50823/1529492321767/bes180614_lutathera_underlag.pdf
- 37 **Satapathy S**, Mittal BR. ¹⁷⁷Lu-DOTATATE peptide receptor radionuclide therapy versus Everolimus in advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis. *Nucl Med Commun* 2019; **40**: 1195-1203 [PMID: 31658219 DOI: 10.1097/MNM.0000000000001103]
- 38 **Bergsma H**, van Lom K, Raaijmakers MHGP, Konijnenberg M, Kam BLBLR, Teunissen JJM, de Herder WW, Krenning EP, Kwekkeboom DJ. Persistent Hematologic Dysfunction after Peptide Receptor Radionuclide Therapy with ¹⁷⁷Lu-DOTATATE: Incidence, Course, and Predicting Factors in Patients with Gastroenteropancreatic Neuroendocrine Tumors. *J Nucl Med* 2018; **59**: 452-458 [PMID: 28775205 DOI: 10.2967/jnumed.117.189712]
- 39 Sunitinib European Summary of Product Characteristics. [Last accessed August 29, 2019] Available from: https://www.ema.europa.eu/en/documents/product-information/sutent-epar-product-information_en.pdf
- 40 **Signorovitch J**, Swallow E, Kantor E, Wang X, Klimovsky J, Haas T, Devine B, Metrakos P. Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: a matching-adjusted indirect comparison. *Exp Hematol Oncol* 2013; **2**: 32 [PMID: 24314093 DOI: 10.1186/2162-3619-2-32]
- 41 **Ishak KJ**, Rael M, Hicks M, Mittal S, Eatock M, Valle JW. Relative effectiveness of sunitinib versus everolimus in advanced pancreatic neuroendocrine tumors: an updated matching-adjusted indirect comparison. *J Comp Eff Res* 2018; **7**: 947-958 [PMID: 30168349 DOI: 10.2217/ce-2018-0020]
- 42 **European Commission 2018**. The Swedish pension system and pension projections until 2070. [Last accessed September 02, 2019] Available from: https://ec.europa.eu/info/sites/info/files/economy-finance/final_country_fiche_se.pdf



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