

## CADTH Reimbursement Recommendation

# Lutetium ( $^{177}\text{Lu}$ ) Oxodotreotide (Lutathera)

**Indication:** For the treatment of unresectable or metastatic, well-differentiated, somatostatin receptor (SSR)–positive pancreatic neuroendocrine tumours (pNETs) in adults whose disease has progressed after treatment with a somatostatin analogue (SSA), unless there is a contraindication or intolerance

**Sponsor:** Advanced Accelerator Applications

**Final recommendation:** Reimburse with conditions

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## What Is the CADTH Reimbursement Recommendation for Lutathera?

CADTH recommends that Lutathera should be reimbursed by public drug plans for the treatment of unresectable or metastatic, well-differentiated, somatostatin receptor (SSR)-positive pancreatic neuroendocrine tumours (pNETs) in adults whose disease has progressed after treatment with a somatostatin analogue (SSA), unless there is a contraindication or intolerance, if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Lutathera should only be covered to treat adult patients with unresectable or metastatic, well-differentiated, SSR-positive pNETs whose disease has progressed after treatment with a SSA, unless they could not receive an SSA.

### What Are the Conditions for Reimbursement?

Lutathera should only be reimbursed if it is prescribed by clinicians who are experts in radiopharmaceuticals, patients are treated in specialized centres with the infrastructure to safely use radiopharmaceuticals, and the cost of Lutathera is reduced.

### Why Did CADTH Make This Recommendation?

- No randomized clinical trials evaluating the efficacy or safety of Lutathera in adult patients with pNETs have been conducted.
- Evidence from a registry study and 3 observational studies showed that Lutathera controlled disease progression and prolonged survival for patients with pNETs and the benefits were considered clinically meaningful. The indirect evidence also suggested that Lutathera may control disease progression better than other drugs used to treat pNETs.
- Treatment with Lutathera may meet some important needs identified by patients, such as controlling disease progression.
- Based on CADTH's assessment of the health economic evidence, Lutathera does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Lutathera is estimated to cost the public drug plans approximately \$7.9 million over the next 3 years.

## Additional Information

### What Are pNETs?

pNETs are an uncommon type of cancer that start in hormone-producing cells of the pancreas. Less than 1 in 100,000 people develop pNETs each year.

### Unmet Needs in pNETs

pNETs are incurable, and patients with pNETs have a poor prognosis. There is a need for treatments that prolong patients' lives and improve their quality of life.

### How Much Does Lutathera Cost?

Treatment with Lutathera is expected to cost approximately \$23,333 per patient per month.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that lutetium ( $^{177}\text{Lu}$ ) oxodotreotide be reimbursed for the treatment of unresectable or metastatic, well-differentiated, somatostatin receptor (SSR)-positive pancreatic neuroendocrine tumours (pNETs) in adults whose disease has progressed after treatment with a somatostatin analogue (SSA), unless there is a contraindication or intolerance, only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

The efficacy or safety of lutetium ( $^{177}\text{Lu}$ ) oxodotreotide (henceforth shortened to " $^{177}\text{Lu}$  oxodotreotide") in patients with pNETs has not been evaluated in randomized clinical trials; the best available evidence for this review was from 1 phase IV, non-interventional, non-comparative, post-authorization retrospective registry study (NETTER-R, N = 110) and 3 observational studies (Fröss-Baron et al. [2021], Marinova et al. [2018], and Zandee et al. [2019]). pERC noted that conducting a randomized controlled trial exclusively in this patient population would not be feasible considering the lack of clinical equipoise and rarity of the condition. The NETTER-R study suggested that treatment with  $^{177}\text{Lu}$  oxodotreotide resulted in clinical benefit for patients with SSR-positive pNETs who had unresectable or metastatic, progressive disease after SSA. Median progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) criteria was 24.8 months (95% confidence interval [CI], 17.5 to 34.5) and median overall survival (OS) was 41.4 months (95% CI, 28.6 to 50.2). Although there was no comparator group and there were other methodological limitations associated with the NETTER-R study design, these results represent a clinically meaningful improvement compared with patients with pNETs treated with other available regimens in Canada according to the clinical experts. Although results of the 3 observational studies were associated with uncertainty due to the study design, results were consistent with those of the NETTER-R study. Furthermore, indirect evidence provided by the sponsor suggested that  $^{177}\text{Lu}$  oxodotreotide compared favourably to everolimus and sunitinib in PFS.

There is a need for treatments for patients with pNETs that lead to extended survival and improved health-related quality of life (HRQoL). Patients reported that currently available treatments are associated with long recovery times, have debilitating side effects and complications, and these treatments do not cure or stop the progression of their disease. Given the totality of the evidence, pERC concluded that treatment with  $^{177}\text{Lu}$  oxodotreotide may meet some important needs identified by patients, such as controlling disease progression.

Using the sponsor submitted price for  $^{177}\text{Lu}$  oxodotreotide and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for  $^{177}\text{Lu}$  oxodotreotide was \$120,931 per quality-adjusted life-year (QALY) compared with everolimus and \$466,632 per QALY compared with sunitinib. At this ICER,  $^{177}\text{Lu}$  oxodotreotide is not cost-effective at a willingness-to-pay threshold of \$50,000 per QALY gained for the treatment of unresectable or metastatic, well-differentiated, SSR-positive pNETs in adults with progressive disease. A price reduction is required for  $^{177}\text{Lu}$  oxodotreotide to be considered cost-effective at a \$50,000 per QALY gained threshold.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
<p>1. Treatment with <sup>177</sup>Lu oxodotreotide should be reimbursed when initiated in patients with pNETs who meet all of the following criteria:</p> <p>1.1. adult patients with unresectable or metastatic, well-differentiated, SSR-positive pNETs</p> <p>1.2. disease has progressed after treatment with an SSA or patient has a contraindication or intolerance to SSAs.</p>	<p>Patients enrolled in the NETTER-R study had SSR-positive pNETs that were well differentiated at the time of diagnosis and had unresectable or metastatic progressive disease.</p>	—
<b>Discontinuation</b>		
<p>2. Treatment with <sup>177</sup>Lu oxodotreotide should be discontinued upon occurrence of any of the following:</p> <p>2.1. unacceptable toxicity</p> <p>2.2. disease progression assessed by clinical examination, imaging, or biomarker assessment as appropriate.</p>	<p>Clinical experts indicated that treatment with <sup>177</sup>Lu oxodotreotide would be stopped if patients experienced these criteria.</p>	<p>Serious toxicities that could lead to treatment discontinuation include, but are not limited to, permanent renal toxicities and myelotoxicity (e.g., transformation to MDS or AML).</p>
<b>Prescribing</b>		
<p>3. Prescribing of <sup>177</sup>Lu oxodotreotide should be restricted to specialized centres that have the infrastructure to handle, prepare, administer, and dispose of radiopharmaceuticals in a safe manner.</p>	<p>As per clinical expert opinion and the NETTER-R study. In the NETTER-R study, patients could have been treated with <sup>177</sup>Lu oxodotreotide under the Advanced Accelerator Applications Lutathera Compassionate Use Program.</p>	<p>The clinical experts stated that administration of <sup>177</sup>Lu oxodotreotide will require a tertiary referral centre with dedicated nuclear medicine and/or radiation oncology. Access to <sup>68</sup>Ga-PET scan or FDG PET scan is needed.</p>
<p>4. <sup>177</sup>Lu oxodotreotide should be prescribed by clinicians with expertise in the use of radiopharmaceuticals.</p>	<p>To ensure that <sup>177</sup>Lu oxodotreotide is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.</p>	—
<b>Pricing</b>		
<p>5. A reduction in price</p>	<p>The ICER for <sup>177</sup>Lu oxodotreotide is \$120,931 per QALY and \$466,632 per QALY when compared with everolimus and sunitinib, respectively.</p> <p>A price reduction of at least 41% to 63% would be required for <sup>177</sup>Lu oxodotreotide to be able to achieve an ICER of \$50,000 per QALY compared with everolimus and sunitinib, respectively.</p>	—

Reimbursement condition	Reason	Implementation guidance
<b>Feasibility of adoption</b>		
6. Organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with <sup>177</sup> Lu oxodotreotide.	Administration of <sup>177</sup> Lu oxodotreotide, a radiopharmaceutical, is resource-intensive due to its limited shelf life and complex preparation and administration. There are a limited number of specialized centres in Canada that have the infrastructure in place to prepare, administer, and dispose of <sup>177</sup> Lu oxodotreotide in a safe manner.	Jurisdictions will need to consider the significant impacts of additional resources, including nursing, pharmacy, and nuclear medicine staff when considering the feasibility of adoption.

<sup>68</sup>Ga = gallium-68; <sup>177</sup>Lu = lutetium; AML = acute myeloid leukemia; ICER = incremental cost-effectiveness ratio; FDG = fluorodeoxyglucose; MDS = myelodysplastic syndrome; QALY = quality-adjusted life-year; SSA = somatostatin analogue; SSR = somatostatin receptor.

## Discussion Points

- pERC acknowledged that pNETs are a rare and incurable type of cancer, and that there is a need for new treatment options that will prolong survival and improve HRQoL. Despite important limitations with the study designs, pERC accepted that the available evidence was supportive that <sup>177</sup>Lu oxodotreotide offers clinically meaningful improvements relative to the alternatives and that it would not be feasible to conduct a robust controlled clinical trial in this patient population.
- pERC discussed the biological plausibility of <sup>177</sup>Lu oxodotreotide conferring clinical benefit in patients with pNETs. The NETTER-1 study did not enrol patients with pNETs but patients with other types of gastroenteropancreatic neuroendocrine tumours (GEP-NETs). The clinical experts suggested that the divide between pNETs and non-pNETs may not be an important consideration. Although pNETs tend to be more aggressive and have a poorer survival outlook compared with other NETs, the clinical experts suggested that there is little basis for treatment with <sup>177</sup>Lu oxodotreotide in patients with pNETs to differ compared with other patients with non-pNETs. Given the totality of evidence, pERC concluded that <sup>177</sup>Lu oxodotreotide is well tolerated and likely to provide clinical benefit. pERC noted that there is no rationale why a peptide receptor radionuclide therapy (PRRT) such as <sup>177</sup>Lu oxodotreotide would not be effective in pNETs versus other types of NETs. pERC concluded that pNETs could be managed similarly to other NETs.
- HRQoL was considered an important outcome for patients by both clinicians and patient groups. However, the only HRQoL evidence available for this review is from 2 observational studies (Marinova et al. and Zandee et al.). The study by Marinova et al. suggests an improvement in HRQoL from baseline to 3 months follow-up after the last cycle of treatment with <sup>177</sup>Lu oxodotreotide and there was an increase in the Global Health Status score and the mean social functioning score. In the Zandee et al. study, the authors reported an increase in the mean Global Health Status score, which was consistent with results from the study by Marinova et al. However, given the non-controlled, non-comparative design of these studies, there is substantial uncertainty associated with these results. Patients indicated that the side effects of <sup>177</sup>Lu oxodotreotide were tolerable or manageable and the treatment experience was easier than the lengthy recovery from surgery or the debilitating side effects from chemotherapy or targeted therapies.

- Everolimus and sunitinib were identified as relevant comparators for Canadian patients with pNETs. Indirect comparative evidence was provided by the sponsor through matching-adjusted indirect comparisons (MAICs) which compared the PFS and OS for <sup>177</sup>Lu oxodotretotide to everolimus and sunitinib. Additional published indirect evidence was also found in the literature; Khan et al. conducted similar analyses using MAICs to compare PFS and OS for <sup>177</sup>Lu oxodotretotide to everolimus and sunitinib. Both sets of MAICs favoured treatment with <sup>177</sup>Lu oxodotretotide over sunitinib and everolimus for PFS. The MAIC for OS conducted by the sponsor did not achieve statistically significant differences between <sup>177</sup>Lu oxodotretotide and everolimus or sunitinib, while MAICs published by Khan et al. did suggest greater improvement with <sup>177</sup>Lu oxodotretotide over both everolimus and sunitinib. However, all indirect comparisons were associated with limitations which introduced considerable uncertainty in the comparative evidence of <sup>177</sup>Lu oxodotretotide with everolimus and sunitinib.
- There are a limited number of centres in Canada that have the expertise and resources to administer <sup>177</sup>Lu oxodotretotide, and it is unlikely that these centres will be available in all jurisdictions. Therefore, out-of-province care may be needed for administration of <sup>177</sup>Lu oxodotretotide. pERC considered that some patients may be unable to travel outside the province or country to receive therapy. The committee suggested that jurisdictions may need to consider developing interprovincial agreements to ensure equitable access for eligible patients and their caregivers, including consideration of financial and logistic support for required travel and short-term relocation. For implementation purposes, pERC agreed that there is a need to advocate for equitable patient access so that all patients in need have timely access to therapy.

## Background

NETs are a heterogenous group of cancers that arise from the secretory cells of the diffuse neuroendocrine system. pNETs are a subset of GEP-NETs. SSRs are expressed in the majority (> 80%) of well-differentiated NETs. GEP-NETs represent the second most common type of digestive cancer in terms of prevalence. The annual incidence of pNETs is expected to be less than 1 per 100,000 persons. pNETs have a worse prognosis than NETs, and patients typically survive for less than 5 years. Due to the heterogenous nature of pNETs, different patients may not follow the same disease trajectory. Diagnosis of pNETs is typically done through biopsy. Staging of patients' disease is usually conducted using CT imaging or MRI scans, although gallium PET scans are becoming a more standard form of imaging for this group of patients.

<sup>177</sup>Lu oxodotretotide (also known as <sup>177</sup>Lu-dotatate) is considered a PRRT. <sup>177</sup>Lu oxodotretotide is a radiolabelled SSA that binds to SSRs. <sup>177</sup>Lu oxodotretotide has been approved by Health Canada for the treatment of unresectable or metastatic, well-differentiated, SSR-positive GEP-NETs in adults with progressive disease. The recommended dose is 7.4 GBq (200 mCi) as an IV infusion over 30 minutes every 8 weeks for a total of 4 doses. <sup>177</sup>Lu oxodotretotide is administered together with octreotide long-acting release (LAR) which continues monthly for up to 18 months.

## Submission History

The original CADTH review of  $^{177}\text{Lu}$  oxodotreotide conducted in 2019 included a phase III, open-label, randomized controlled trial (NETTER-1) and a phase I/II non-randomized, single-arm study (ERASMUS). The original submission received a recommendation in favour of reimbursement for patients with SSR-positive midgut NETs whose disease had progressed on a SSA and was unresectable; however, the recommendation did not support reimbursement for patients with SSR-positive foregut and hindgut NETs whose disease had progressed and was unresectable. The previous CADTH review for  $^{177}\text{Lu}$  oxodotreotide did not support use among patients with pNETs because these patients were excluded from the pivotal NETTER-1 trial. The sponsor's reimbursement request for this CADTH reassessment is for adult patients with unresectable or metastatic, well-differentiated, SSR-positive pNET tumours whose disease has progressed after treatment with an SSA, unless there is a contraindication or intolerance.

## Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a systematic review of 1 phase IV retrospective registry study in patients with SSR-positive pNETs who had unresectable or metastatic progressive disease
- patient perspectives from 1 patient group: the Canadian Neuroendocrine Tumour Society (CNETS)
- input from the public drug plans and cancer agencies that participate in the CADTH reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with pNETs
- input from 4 clinician groups, including the Canadian Association of Nuclear Medicine (CANM); a collaboration between the CHU de Québec – Université Laval Research Centre – Oncology Axis, Hôtel-Dieu de Québec – Nuclear Medicine Department, Fondation du CHU de Québec – Research Chair in Theranostics, and Association des médecins spécialistes en médecine nucléaire du Québec (AMSMNQ); the CNETS Scientific & Medical Advisory Board, and other neuroendocrine cancer treating clinicians
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

CADTH received 1 submission from CNETS for the review of  $^{177}\text{Lu}$  oxodotreotide for patients with GEP-NETs. The information used to inform the submission was based on an online questionnaire that was promoted to patients with neuroendocrine cancer on the CNETS website and across its social media platforms between February 25 to March 25, 2022. A total of 57 patients responded to the survey, including 21 (37%) patients with pNETs and

36 (63%) patients with GI-NETs; 33 (58%) patients reported having experience with <sup>177</sup>Lu oxodotreotide.

Survey respondents reported that their NET cancer negatively impacted their quality of life with symptoms of fatigue and weakness, and diarrhea having an extremely high impact on quality of life. The most commonly used therapies for the management of NET cancer reported by respondents were SSA therapies, surgery, and PRRT. Respondents indicated that benefits of currently available treatments included temporarily slowing the progression of the disease and achieving symptom control, while the challenges were long recovery times, debilitating side effects, and complications. None of the respondents reported that current treatments cured or stopped the progression of their NET cancer. Respondents described current treatments as effective for symptom control (i.e., bloating, diarrhea, constipation, and energy levels), and as slightly or not effective for stopping disease progression, shrinking or stopping tumour growth, and preventing metastasis. According to respondents, common barriers to access included lack of private payer coverage, financial difficulties, and treatment was not accessible through their physician or was not funded for their specific type of NET cancer.

All 33 respondents with experience on <sup>177</sup>Lu oxodotreotide agreed that its side effects were tolerable or manageable and the treatment experience was easier than the lengthy recovery from surgery or the debilitating side effects from chemotherapy. The most commonly reported benefits of <sup>177</sup>Lu oxodotreotide included reduction in the progression of disease (69%), tumour shrinkage (59%), and decrease in disease symptoms (45%), while the most commonly reported side effects were increased fatigue (58%), followed by nausea and vomiting (27%).

The majority (98%) of respondents indicated disease progression is the most important outcome of NET cancer to control, followed by fatigue (36%), diarrhea (35%) and flushing (29%). Overall, patients reported a need for equitable access to <sup>177</sup>Lu oxodotreotide for NET cancer to overcome challenges including the lack of funding for their type of NETs and travelling long distances to access treatment.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

Input was gathered from 2 clinical specialists with expertise in the diagnosis and management of pNETs. The clinical experts highlighted an unmet need for treatments that extend patients' lives and improve their quality of life because patients eventually become refractory to all currently available treatment options. The clinical experts stated that sequencing of <sup>177</sup>Lu oxodotreotide would be individualized to each patient's circumstances. In most instances, patients should have progressed on SSAs before receiving <sup>177</sup>Lu oxodotreotide. The clinical experts stated that identifying patients eligible for <sup>177</sup>Lu oxodotreotide will require gallium PET scans. They specified that there should be no strict criteria on Ki67 because there is too much variability in Ki67 among different specimens from the same patient. In addition, there is subjectivity in reading the specimens that results in variability in determining eligibility based on Ki67. Patient response to therapy was stated to be assessed through clinical assessment, radiographic information, and analysis of biomarkers (i.e., 5-hydroxyindoleacetic acid [5HIAA]). Clinical assessments were recommended to occur every few months initially, and before every cycle of PRRT. Radiographic assessments were recommended to occur every 3 to 6 months initially,

depending on the clinical needs of the patients. Discontinuation of therapy was stated to be based on serious toxicities, including permanent renal toxicities and bone marrow toxicity (e.g., myelodysplastic syndrome [MDS]), and disease progression. Administration of <sup>177</sup>Lu oxodotreotide was stated to require tertiary referral centre with dedicated nuclear medicine and/or radiation oncology.

## Clinician Group Input

Seven clinician groups provided input to CADTH for the review of <sup>177</sup>Lu oxodotreotide: 2 clinicians from the Ontario Health Cancer Care Ontario (OH-CCO) Gastrointestinal Cancer Drug Advisory Committee, 1 clinician from the Canadian Association of Nuclear Medicine (CANM), 9 clinicians from the CNETS Scientific and Medical Advisory Board (SMAB), and 1 clinician from CHU de Québec – Université Laval Research Centre – Oncology Axis, Hôtel-Dieu de Québec – Nuclear Medicine Department, Fondation du CHU de Québec – Research Chair in Theranostics, and AMSMNQ.

The clinician groups identified the following unmet needs in patients with NETs including pNETs: currently available treatments are not effective for all patients, are not well tolerated, and can lead to the development of resistance or become refractory to current treatments. Further, the clinician groups expressed the need for treatments to slow the progression of the disease, control hormonal symptoms, and improve survival (i.e., PFS).

CANM, CNETS SMAB, CHU de Québec – Université Laval Research Centre – Oncology Axis, Hôtel-Dieu de Québec – Nuclear Medicine Department, Fondation du CHU de Québec – Research Chair in Theranostics and AMSMNQ indicated <sup>177</sup>Lu oxodotreotide should be second line for patients with NETs, including pNETs, who have progressed on a somatostatin analogue. In contrast, OH-CCO indicated Lutathera should be a fourth-line treatment option following somatostatin analogues, everolimus, and sunitinib.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for <sup>177</sup>Lu oxodotreotide: considerations for initiation of therapy, considerations for discontinuation of therapy, considerations for prescribing of therapy, care provision issues, system and economic issues, and potential need for a provisional funding algorithm. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Relevant comparators</b>	
<p>NETTER-R is a phase IV, non-interventional, retrospective registry study of patients with pancreatic neuroendocrine tumours who have been treated with <sup>177</sup>Lu oxodotreotide.</p> <p>Relevant comparators for <sup>177</sup>Lu oxodotreotide may include sunitinib, everolimus, or combination temozolomide-capecitabine.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>

Implementation issues	Response
<b>Considerations for initiation of therapy</b>	
<p>Can patients treated with octreotide LAR 60 mg be eligible for treatment with <sup>177</sup>Lu oxodotretotide?</p> <p>Can patients previously treated with lanreotide be eligible for treatment with <sup>177</sup>Lu oxodotretotide?</p>	<p>pERC and the clinical experts agreed that patients who were treated with octreotide LAR 60 mg or lanreotide would be eligible for treatment with <sup>177</sup>Lu oxodotretotide.</p>
<p>PAG noted that CADTH previously did not recommend <sup>177</sup>Lu oxodotretotide re-treatment for adult patients with SSR-positive midgut neuroendocrine tumours. Should <sup>177</sup>Lu oxodotretotide re-treatment be funded for patients with unresectable or metastatic SSR-positive pancreatic neuroendocrine tumours?</p>	<p>pERC could not comment on whether re-treatment with <sup>177</sup>Lu oxodotretotide should be funded for patients with unresectable or metastatic SSR-positive pancreatic neuroendocrine tumours because there is limited data to support re-treatment.</p>
<b>Considerations for discontinuation of therapy</b>	
<p>The sponsor request is for <sup>177</sup>Lu oxodotretotide to be used after progression on a somatostatin analogue unless there is a contraindication or intolerance.</p> <p>Can pERC clarify what would constitute a contraindication or intolerance to a somatostatin analogue?</p>	<p>pERC and the clinical experts stated that contraindications to SSAs would include an anaphylactic reaction or consistent, reproducible, and severe diarrhea after an injection that takes time to resolve (i.e., greater than 1 week) or results in abdominal pain. In general, true contraindications are expected to be rare.</p>
<b>Considerations for prescribing of therapy</b>	
<p>7.4 GBq (200 mCi) of <sup>177</sup>Lu oxodotretotide is infused intravenously over 30 minutes every 8 weeks for a maximum of 4 doses.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>
<p>Administration of <sup>177</sup>Lu oxodotretotide is restricted to specialized centres that have the infrastructure to handle, prepare, administer, and dispose of lutetium in a safe manner.</p> <p>Patients may have to travel long distances to access treatment. In some jurisdictions, patients may need to be referred out of the province.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>
<b>Funding algorithm (oncology only)</b>	
<p>What is the optimal place in therapy for <sup>177</sup>Lu oxodotretotide?</p> <p>Under what clinical circumstances would <sup>177</sup>Lu oxodotretotide be preferred over everolimus, sunitinib, or temozolomide-capecitabine?</p>	<p>The NETTER-R study was retrospective and did not include a comparator group. The sponsor provided an ITC that compared <sup>177</sup>Lu oxodotretotide to everolimus and sunitinib. Although there were significant uncertainties with the results of the ITCs, the results suggested that <sup>177</sup>Lu oxodotretotide would be more efficacious over everolimus and sunitinib. The clinical experts agreed that <sup>177</sup>Lu oxodotretotide would be a preferred regimen over everolimus and sunitinib because <sup>177</sup>Lu oxodotretotide is better tolerated and, although there is no direct evidence, <sup>177</sup>Lu oxodotretotide may be more efficacious than other currently available treatment options. However, temozolomide-capecitabine may be preferred over <sup>177</sup>Lu oxodotretotide for patients with grade 3 well-differentiated pNETs. pERC agreed with the response provided by the clinical experts.</p>
<b>Care provision issues</b>	
<p><sup>177</sup>Lu oxodotretotide has a shelf life of 72 hours, which may result in wastage if the patient is not able to receive a scheduled dose for whatever reason.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>

Implementation issues	Response
<p>Administration of an amino acid solution is required before, during, and after each <sup>177</sup>Lu oxodotretotide dose. The compounded solution is either prepared within the hospital or procured externally.</p> <p>An antiemetic is also given before the amino acid solution.</p> <p>Octreotide LAR 30 mg IM also needs to be administered between 4 and 24 hours after each <sup>177</sup>Lu oxodotretotide dose and then every 4 weeks after completing <sup>177</sup>Lu oxodotretotide until disease progression or for up to 18 months following treatment initiation. Is there evidence to support alternative SSA schedules relative to <sup>177</sup>Lu oxodotretotide?</p>	<p>pERC agreed with the clinical experts, who acknowledged that there can be variability in the schedule of administration of SSAs relative to <sup>177</sup>Lu oxodotretotide depending on the institution. The clinical experts agreed that scheduling SSA therapy after PRRT can be challenging in practice, and alternative administration schedules relative to <sup>177</sup>Lu oxodotretotide may be appropriate.</p>
<p>Access to functional imaging (e.g., <sup>68</sup>Ga-PET) is needed to confirm somatostatin receptor positivity.</p> <p>Does the patient require imaging after each <sup>177</sup>Lu oxodotretotide dose and when should imaging be done?</p>	<p>pERC agreed with the clinical experts, who commented that there may be some variation in imaging for patients. A <sup>68</sup>Ga-PET scan is required before starting treatment with <sup>177</sup>Lu oxodotretotide. <sup>68</sup>Ga-PET scans are not typically conducted after each cycle of treatment with <sup>177</sup>Lu. However, SPECT scans should be conducted after each cycle to confirm treatment uptake and to assess whether the patient's disease has progressed. CT imaging is also used as another strategy for surveillance post-treatment. The clinical experts also commented that FDG PET scans may also be used to help identify when patients are progressing to higher grade disease, although this type of imaging may not be as common.</p>
<b>System and economic issues</b>	
<p>The budget impact would be influenced by the actual place in therapy for <sup>177</sup>Lu oxodotretotide (use in earlier lines vs. later lines). There may be potential indication creep if <sup>177</sup>Lu oxodotretotide is preferred over a somatostatin analogue as <sup>177</sup>Lu oxodotretotide may be better tolerated.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>
<p>Additional resources and coordination between nuclear medicine, radiation oncology, and medical oncology teams are required for imaging, blood work monitoring, and management of adverse events.</p> <p>Inpatient administration may also be required.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>
<p>In most jurisdictions, oversight and funding of radiopharmaceuticals is through other areas of the Ministry, outside of the drug programs. Inpatient funding may also be covered through a different Ministry budget.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>

<sup>68</sup>Ga = gallium-68; <sup>177</sup>Lu = Lutetium; FDG = fluorodeoxyglucose; ITC = indirect treatment comparison; LAR = long-acting release; PAG = Provincial Advisory Group; pERC = CADTH pCODR Expert Review Committee; pNET = pancreatic neuroendocrine tumour; PRRT = peptide receptor radionuclide therapy; SPECT = single-photon emission computerized tomography; SSA = somatostatin analogue; SSR = somatostatin receptor.

## Clinical Evidence

### Pivotal Studies and Protocol-Selected Studies

#### Description of Studies

The NETTER-R study was a non-interventional, non-comparative, post-authorization retrospective registry study to assess long-term efficacy and safety of treatment with <sup>177</sup>Lu oxodotreotide in patients with SSR-positive pNETs who had unresectable or metastatic, progressive disease based on radiological, biochemical, or clinical assessment. The approximate number of patients to be enrolled was based on the number of potentially eligible patients included in the Compassionate Use Program (CUP) or receiving commercial <sup>177</sup>Lu oxodotreotide at the selected study sites previously identified by investigators. Patients could have been treated with <sup>177</sup>Lu oxodotreotide under the Advanced Accelerator Applications (AAA) Lutathera CUP approved in 10 European countries since 2011–2012 or with a commercial drug. The study included 110 patients from Spain, France, and the UK who met the pre-specified criteria for inclusion. Most patients with pNETs who received treatment in this study were part of the CUP in 1 of the European Neuroendocrine Tumor Society Centers participating in this program. The retrospective data collection from medical records began on October 31, 2018, at the first study site. Follow-up visits were tentatively collected every 3 months, depending on the standard of care for local practice and source document availability at the sites. The primary objective of the NETTER-R study was to determine the efficacy of <sup>177</sup>Lu oxodotreotide in patients with pNET who met a set of pre-specified eligibility criteria. The secondary objective of the study was to determine the safety and tolerability of <sup>177</sup>Lu oxodotreotide. All inclusion criteria and none of the exclusion criteria had to be met to be eligible for the NETTER-R study. Eligibility criteria included patients with SSR-positive, unresectable or metastatic, well-differentiated pNETs with progressive disease who had been treated with <sup>177</sup>Lu oxodotreotide. Patients were not eligible if they were diagnosed with NETs of other origins.

Patients in the NETTER-R study had a mean age of 58 years (■). Relatively equal proportions of males (53%) and females (47%) were enrolled. ■ of patients were White (■). The primary sites of metastases before patients starting treatment with <sup>177</sup>Lu oxodotreotide were the liver (96%), lymph nodes (43%), bone (29%), and lungs (4%). The liver tumour burden ranged from 10% to 25% or less (29%) and greater than 25% liver burden or more than 2 metastatic organs (36%). More than half of patients had non-functional tumours (57%), with 30% of patients with functional tumour status and the remaining without an assessment of tumour functionality (11%). Most patients had a Ki-67 index between 3% and 20% (66%) or 2% or less (24%), and a histopathological intermediate (grade 2; 65%) or low (grade 1; 27%) grade of disease. Many patients received an octreotide scan (■) or a gallium PET scan (■). For Eastern Cooperative Oncology Group Performance Status (ECOG PS), most patients who had it assessed had an ECOG PS of 0 (■) or 1 (■). Most patients received prior anticancer treatments (92%) and had received a mean 4.7 prior or concomitant therapies. Prior anticancer therapy for NET disease was received by 91% of patients; patients mostly received chemotherapy (■), radiotherapy (■), or other therapies (91%). Prior somatostatins and analogues were received by 70% of patients, mostly with lanreotide or octreotide (33% each). Prior tyrosine kinase inhibitors (TKIs) were received by 38% of patients, mostly with everolimus (33%) or sunitinib (20%). Approximately ■ of patients (■) had received prior surgical and medical procedures; patients most commonly underwent pancreatic operations (■), followed by liver operations (■) and radiotherapy (■).

## Efficacy Results

### Overall Survival

A median follow-up time of 24.5 months was reported. There were 55 patients (50%) who experienced an OS event in the NETTER-R study. The median OS was 41.4 months (95% CI, 28.6 to 50.2). Half of the patients were censored for the analysis of OS.

### Progression-Free Survival

Results for the primary end point of PFS were based on RECIST v 1.1. In the primary analysis of PFS, there were 41 PFS events (66%), of which most were disease progression (■) with ■ deaths (■). The median PFS was 24.8 months (95% CI, 17.5 to 34.5). PFS was also assessed using the RECIST v 1.1 criteria based on investigator opinion as a secondary end point. PFS based on investigator's opinion 1 were based on tumour assessments and other radiological assessments. PFS based on investigator's opinion 2 were based on other radiological, clinical, biomarker and metabolic assessments. The additional analyses of PFS were consistent with the primary analysis of PFS.

### Objective Response Rate

Objective response rate (ORR) based on the primary analysis was assessed in 62 patients. The ORR was 40.3% (95% CI, 28.1 to 53.6). None of the patients had a complete response using RECIST v 1.1 criteria. Partial response was reported in 40.3% of patients. Stable disease and progressive disease were reported for 35.5% and 21.0% of patients, respectively. Results for ORR based on investigators' opinion 1 and 2 were consistent with the primary analysis of ORR, although the response was slightly better for ORR assessed by investigator's opinion 2.

### Duration of Response

The median duration of response (DOR) was 60.7 months (95% CI, 13.1 to 62.1). At the time of the analysis, there were 8 PFS events observed. The DOR based on investigators' opinion 1 and 2 were both shorter than the primary analysis of DOR. The median DOR based on investigator's opinion 1 was 31.1 months (95% CI, 16.8 to 62.1) with ■ PFS events, while the DOR based on investigator's opinion 2 was 28.3 months (95% CI, 16.8 to 60.7) with ■ PFS events.

### Time to Progression

There was a total of ■ time to progression (TTP) events with a median TTP of 29.5 months (95% CI, 21.4 to 67.6). As with PFS, TTP was assessed via investigators' opinion 1 and 2, the results of which were both consistent with the primary analysis of TTP.

### Health-Related Quality of Life



## Harms Results

### Adverse Events

Adverse events (AEs) were reported in 79 patients (72%). The most common AEs included nausea (28%), fatigue (23%), abdominal pain (16%), vomiting (■), upper abdominal pain (■), anemia (■), diarrhea, lymphopenia, and thrombocytopenia (■). Grade 3 or 4 AEs were

reported in 30 patients (27%). The incidence of grade 3 or 4 AEs was generally infrequent, with each event occurring in less than 5% of patients. The most common grade 3 or 4 AEs were lymphopenia (1), abdominal pain, ascites, hypercalcemia, and liver abscess (1).

### **Serious Adverse Events**

Serious adverse events (SAEs) were reported in 29 patients (26%). SAEs were infrequently reported, with SAEs occurring in less than 3% of patients. The most common SAEs included liver abscess, ascites, and hypercalcemia (1).

### **Withdrawals Due to Adverse Events and Dose Modifications**

There were no treatment-emergent AEs which resulted in treatment discontinuation. Treatment-emergent AEs leading to dose modification were infrequent and occurred in 10 patients (9%). The most common treatment-emergent AEs that led to dose modifications included lymphopenia and nausea (1 each).

### **Mortality**

There was a total of 1 deaths (1) due to AEs in the NETTER-R study. The causes of death were reported to be due to abdominal abscess, hepatorenal syndrome and metabolic encephalopathy, hepatic encephalopathy, ascites, and lower respiratory tract infection and pulmonary embolism.

### **Notable Harms**

Notable harms were detailed in the CADTH Systematic Review protocol and included myelotoxicity, renal toxicity, transformation to leukemia or MDS, nausea or vomiting, and fatigue.

Hematological toxicities were reported among 1. Hematological toxicities were mostly grade 1 or 2 (1), with 5 patients with grade 3 events. Nausea and fatigue were the 2 most commonly reported AEs in the NETTER-R study, occurring in 31 patients (28%) and 25 patients (23%), respectively. Renal toxicity was infrequently reported among 6 patients (6%); of these, 3 patients had grade 1 or 2 events and 3 patients had grade 3 events. There were no reports of secondary hematological malignancies (acute leukemia or MDS) in any patient.

### **Critical Appraisal**

The NETTER-R study was a retrospective, non-comparative, registry-based, observational study. Without a comparison group, the safety and effectiveness of <sup>177</sup>Lu oxodotreotide relative to currently available therapies is unknown. Moreover, due to lack of an adequate control group, the estimate of long-term efficacy was compromised. In particular, no causal inference could be made whether the treatment effect (e.g., changes on PFS or OS) could be completely attributable to <sup>177</sup>Lu oxodotreotide or temporality changes in other factors, including concomitant therapies or natural course of disease. In retrospective observational cohort studies of drug effectiveness based on existing medical records, the lack of a sound study design to make an adjustment or control for potential bias has been recognized as a fatal limitation by various real-world evidence study guidance documents.

The CADTH team considered the retrospective design of the NETTER-R study could have allowed for a matched comparator group of patients who had received relevant therapies such as everolimus or sunitinib. The clinical experts consulted by CADTH for this review agreed that a retrospective study with a matched analysis incorporating a comparator group would have improved the strength of evidence for this funding request for pNETs. It was

also acknowledged that a matched analysis would be dependent on whether such data were available.

There was a large amount of censoring for all efficacy analyses. For example, in the estimate of PFS, approximately one-third of patients were censored at the date of their last evaluable tumour assessment if they had not experienced disease progression or who had not died at the time of data collection in the context of time-to-event analyses. Similarly, in the assessment of OS, half of the patients were censored on their last date of contact if they were still alive or had an unknown status. The large amount of censoring (e.g., non-informative) for most efficacy outcomes (i.e., OS, PFS, DOR, TTP) would have resulted in biased estimates of the absolute changes overtime, as illustrated by the Kaplan-Meier curves, on those efficacy outcomes and further introduced uncertainty in the true effect of  $^{177}\text{Lu}$  oxodotreotide on OS and progression of patients with pNETs.

The median follow-up time of the NETTER-R study was 24.5 months. The clinical experts consulted by CADTH for this review commented that, although no control group was part of the study, efficacy results for PFS and OS showed benefit to patients treated with  $^{177}\text{Lu}$  oxodotreotide. However, longer-term data may have benefited the study by providing evidence of the impact of treatment with  $^{177}\text{Lu}$  oxodotreotide over a longer period of time.

The NETTER-R study was conducted in Europe with patients enrolled from the UK, France, and Spain. Consultation with clinical experts engaged by CADTH for this review suggested that eligibility criteria and baseline characteristics were generally representative of Canadian patients who might be treated in clinical practice, although European countries may have more experience administering PRRT than Canada. The clinical experts commented that although 1 patient received dactolisib as a prior therapy on the NETTER-R study, this treatment is not approved by Health Canada and not used among patients living in Canada; the effect of this is expected to be low because only 1 patient received this treatment. It was also noted that the eligibility criteria of the NETTER-R study specified that patients with unresectable or metastatic pNETs be included in the study. The clinical experts confirmed that inclusion of these patients would be unlikely to affect study outcomes; pNETs are a heterogeneous group of tumours that result in aggressive disease and results of treatment with  $^{177}\text{Lu}$  oxodotreotide based on the NETTER-R study will likely apply to these patients as well.

Regarding prior therapies received by patients, it was noted that 70% of patients received prior treatment with SSAs, leaving 30% of patients who had not received prior treatment with SSAs. The funding request by the sponsor specifies that the patients' disease must have progressed after prior treatment with an SSA unless they were contraindicated or intolerant. Further, the NETTER-R study did not specify that patients must have had prior treatment with SSAs; although this is not in exact alignment with the funding request, consultation by CADTH with clinical experts for this review confirmed that the results of the NETTER-R study would still be generalizable to most patients in Canadian clinical practice.

The NETTER-R study did not include a comparator group. Consultation with clinical experts for this review suggested that a randomized trial may not have been possible because it would be unlikely for patients to have accepted assignment to a treatment group which did not include  $^{177}\text{Lu}$  oxodotreotide. In addition, treatment with PRRT has been accepted in Europe and in the US based on data from the NETTER-1 study, which was extrapolated to patients with pNETs.

## Indirect Comparisons

### Description of Studies

#### *Sponsor's ITC*

The aim of the sponsor's indirect treatment comparison (ITC) was to compare <sup>177</sup>Lu oxodotreotide to relevant comparators. Due to the lack of published clinical trial data, the sponsor conducted MAICs comparing <sup>177</sup>Lu oxodotreotide to everolimus and sunitinib. The RADIANT-3 trial, which compared everolimus to placebo, and NCT00428597, which compared sunitinib to placebo, were compared with the NETTER-R study through MAICs. Comparison of key eligibility across the trials suggested that characteristics across the trials were comparable. The median age was similar across all studies (between 56 and 58 years), with similar proportions of males and females. The majority of patients across all trials had an ECOG PS of 1 or 2, although the proportion of patients with an ECOG PS of 1 was greater in the RADIANT-3 and NCT00428597 (> 60%) than the NETTER-R study (33%). Similar proportions of patients in the NETTER-R and NCT00428597 study had a time between disease progression to randomization or receipt of study treatment between 3 and 12 months (26% and 28%, respectively). There were some differences noted across the populations of the included studies. Specifically, there were differences in the proportions of patients with organ involvement, time from disease progression to randomization or receipt of study treatment, and prior therapies. Classification of tumour functionality was not reported consistently across the trials.

#### *Khan et al.*

The aim of the ITC by Khan et al. was to use MAICs to indirectly compare PFS in patients with GI-NETs or pNETs and OS in patients with pNETs after treatment with <sup>177</sup>Lu oxodotreotide, everolimus, sunitinib, or best supportive care across different studies. Khan et al. compared <sup>177</sup>Lu oxodotreotide to everolimus and sunitinib using data from the ERASMUS, RADIANT-3, and NCT00428597 studies. The authors concluded that there were no differences in key covariates between the ERASMUS, RADIANT-3, and NCT00428597 studies. Age, ECOG PS, previous chemotherapy, and previous radiotherapy were reported to be statistically significantly associated with PFS and OS in the ERASMUS study at the 20% level and were adjusted for in the MAICs.

### Efficacy Results

#### *Sponsor's ITC*

**PFS:** The median PFS of <sup>177</sup>Lu oxodotreotide before adjustment was [REDACTED]. After adjustment, the median PFS of <sup>177</sup>Lu oxodotreotide was [REDACTED], which was longer than the median PFS of everolimus at [REDACTED]. The hazard ratio (HR) for PFS between <sup>177</sup>Lu oxodotreotide and everolimus [REDACTED].

The median PFS of <sup>177</sup>Lu oxodotreotide before adjustment was [REDACTED]. After adjustment, the median PFS of <sup>177</sup>Lu oxodotreotide remained the same at [REDACTED], which was longer than the median PFS of sunitinib at [REDACTED]. The HR for PFS also favoured <sup>177</sup>Lu oxodotreotide over sunitinib [REDACTED].

**OS:** The median OS of <sup>177</sup>Lu oxodotreotide before adjustment was [REDACTED]. After adjustment, the median PFS of <sup>177</sup>Lu oxodotreotide was [REDACTED]. The median OS of everolimus was [REDACTED]. The 95% CI of HR for OS between <sup>177</sup>Lu oxodotreotide and everolimus [REDACTED], even though the point estimate was in favour of <sup>177</sup>Lu oxodotreotide over everolimus [REDACTED].

The median OS of <sup>177</sup>Lu oxodotreotide before adjustment was [REDACTED]. After adjustment, the median OS of <sup>177</sup>Lu oxodotreotide remained the same at [REDACTED], which was longer than the median OS of sunitinib at [REDACTED]. The HR for OS failed to show a statistically significant difference in favour of <sup>177</sup>Lu oxodotreotide over sunitinib [REDACTED].

### *Khan et al.*

**PFS:** The MAIC suggested that PFS was longer in patients treated with <sup>177</sup>Lu oxodotreotide compared with sunitinib (HR = 0.36; 95% CI, 0.18 to 0.70) and everolimus (HR = 0.46; 95% CI, 0.30 to 0.71). Results of the sensitivity analyses also supported improvement with <sup>177</sup>Lu oxodotreotide over sunitinib and everolimus.

**OS:** The MAIC suggested that OS was longer in patients treated with <sup>177</sup>Lu oxodotreotide compared with sunitinib (HR = 0.42; 95% CI, 0.25 to 0.72) and everolimus (HR = 0.53; 95% CI, 0.33 to 0.87). Results of the sensitivity analyses also supported improvement with <sup>177</sup>Lu oxodotreotide over sunitinib and everolimus.

## Harms Results

There were no analyses for harms conducted in either ITC.

## Critical Appraisal

### *Sponsor's ITC*

Patient demographic and disease characteristics across the 3 studies were mostly similar. However, there were some differences regarding organ involvement, time from initial diagnosis, time between disease progression and randomization, tumour functionality, and prior treatments. Residual confounding bias may exist as the matching adjustment was limited to a number of pre-identified covariates. As mentioned, the MAICs chosen for comparisons between <sup>177</sup>Lu oxodotreotide and everolimus or sunitinib were designed based on the combination of covariates that resulted in the highest effective sample size (ESS). The ESS for the MAICs between <sup>177</sup>Lu oxodotreotide versus everolimus and <sup>177</sup>Lu oxodotreotide versus sunitinib were [REDACTED] and [REDACTED], respectively. The reductions in ESS for these MAICs may indicate that there was not much overlap between the individual patient-level data of the NETTER-R study and the RADIANT-3 and NCT00428597 studies, with less overlap between the NETTER-R and RADIANT-3 study than NETTER-R and NCT00428597. Because there was not high overlap between patients across the studies, this may be an indicator of heterogeneity across patient characteristics. This may suggest the presence of additional unknown prognostic and predictive factors and introduce bias into the comparisons of efficacy between <sup>177</sup>Lu oxodotreotide and everolimus or sunitinib.

The results of the MAICs suggested that <sup>177</sup>Lu oxodotreotide was favoured over everolimus and sunitinib for PFS, but not for OS. It should be noted that the median OS was not reached in either the RADIANT-3 and NCT00428597 studies. Therefore, the efficacy analyses of the sponsor's MAICs, particularly for OS, is of limited interpretability.

In general, the MAICs rely on statistical assumptions and a limited list of known predictive and prognostic covariates which are difficult to confirm. The MAIC has resulted in a significant reduction of sample size by excluding more than half of NETTER-R patients, which would have compromised the generalizability and reliability of the results.

### *Khan et al.*

Some differences in baseline characteristics were observed across the included studies. There were some noted differences in patients' sex, tumour functionality, and previous treatments. These characteristics were not included in the matching between the ERASMUS and the NCT00428597 and RADIANT-3 studies. After matching, these characteristics were not well balanced. It is possible that these differences in patient characteristics may affect the validity of the comparisons between <sup>177</sup>Lu oxodotretotide and everolimus and sunitinib.

The authors conducted matching with key covariates between the ERASMUS study and the comparator studies (NCT00428597 and RADIANT-3). The ESS after matching with the sunitinib comparator group in the NCT00428597 study was 77% of the initial sample. However, the ESS was much lower after matching with the everolimus group in the RADIANT-3 study, which was 35%. Characteristics of patients which were unadjusted for were not well balanced as illustrated through the differences in patients' sex, previous surgery, and tumour functionality. Therefore, any unknown covariates are likely not balanced across studies. It is likely that there is little patient overlap between the ERASMUS and comparator studies, although more so with the RADIANT-3 study.

As mentioned previously, OS was not reached in either the RADIANT-3 and NCT00428597 studies. Therefore, the efficacy analyses for OS based on immature data may suffer from high uncertainty.

## Other Relevant Evidence

Three separate non-comparative observational studies by Fröss-Baron et al., Marinova et al., and Zandee et al. are briefly summarized here to provide additional efficacy and safety data on <sup>177</sup>Lu oxodotretotide in patients with pNETs.

### Description of Studies

#### *Fröss-Baron et al. Study*

A retrospective study was conducted by Fröss-Baron et al. to determine the efficacy (PFS and OS) and safety of <sup>177</sup>Lu oxodotretotide in 102 adult patients with metastatic and/or locally advanced pNETs who have been previously treated with chemotherapy. Patients treated with <sup>177</sup>Lu oxodotretotide between 2005 and 2014 were identified using hospital records in Sweden, and medical and radiological reports were retrospectively examined. Patients received 7.4 GBq <sup>177</sup>Lu oxodotretotide per cycle with an intended 6- to 8- week interval between each cycle.

#### *Marinova et al. Study*

A retrospective study was conducted by Marinova et al. to determine the change in HRQoL and symptom burden in 68 adult patients with pNETs following treatment with <sup>177</sup>Lu oxodotretotide. Patients treated with <sup>177</sup>Lu oxodotretotide between 2007 and 2015 at a hospital in Germany were identified, and data were retrospectively analyzed. Briefly, inclusion criteria for the study were unresectable metastatic pNETs confirmed with histopathology, an ECOG PS of 0 to 2, the intended number of cycles were administered, follow-up at 3 months after the last cycle was completed, and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was completed before the first cycle and at least once after the last cycle. Patients received a mean activity of 7.6 GBq (SD = not reported [NR]) <sup>177</sup>Lu oxodotretotide per cycle. Change in HRQoL and symptom status were evaluated according to the EORTC QLQ-C30. Higher scores on the Global Health Status and functional scales indicate better function and higher scores on the symptom scales and

single items indicate significant symptomatology. Patients completed the EORTC QLQ-C30 at baseline and every 3 months following each treatment cycle for up to 12 months.

### ***Zandee et al. Study***

A retrospective study was conducted by Zandee et al. to determine the efficacy and safety of <sup>177</sup>Lu oxodotreotide in 34 adult patients with functioning pNETs who were treated with <sup>177</sup>Lu oxodotreotide between 2000 and 2017 at a centre in the Netherlands. Of these patients, 14 patients had insulinoma, 8 had glucagonoma, 7 had gastrinoma, and 5 had VIPoma. Patients received up to 4 cycles of 7.4 GBq <sup>177</sup>Lu oxodotreotide per cycle with an intended interval of 6 to 10 weeks and an intended cumulative activity of 27.8 to 29.6 GBq. Patients were admitted for clinical observation or treatment of hormonal syndrome per protocol. The study aimed to evaluate symptomatic, biochemical, and radiological response and toxicity. Hematology, kidney, and liver function tests were completed after each cycle and at follow-up visits (6 weeks, 3 months, 6 months following the last cycle, and every 6 months thereafter). CT or MRI imaging was completed within 3 months of the first cycle and at each follow-up visit. Patients completed the EORTC QLQ-C30 at all visits.

### **Efficacy Results**

#### ***Fröss-Baron et al. Study***

The median follow-up period was 34 months (range = 4 to 160), and survival data for patients in Sweden (46.1%) were based on data from the National Health Registry until 2018. PFS was calculated using the Kaplan-Meier method and based on the first date of treatment to the date of radiologically confirmed progression per RECIST 1.1 or death from any cause. OS was calculated using the Kaplan-Meier method and based on the first day of treatment with <sup>177</sup>Lu oxodotreotide to the day of death or the last day of follow-up. The median PFS was 24 months (95% CI, 17 to 28) and the median OS was 42 months (95% CI, 29 to 61). During follow-up, 63 (61.8%) patients died; tumour progression was reported as the cause of death in 60 patients. Tumour response was assessed with RECIST 1.1 criteria in 100 patients. Complete response was reported in 4 (4.0%) patients, partial response in 45 (45.0%) patients, stable disease in 44 (44.0%) patients, and progressive disease in 7 (7.0%) patients. Objective response, defined as complete or partial response, was reached by 49% of patients. The median time to best response was 14.8 months (range = 3 to 108). Disease control, which was defined as complete response, partial response, or stable disease, was reported in 91.0% of 92 patients with progressive disease at baseline.

#### ***Marinova et al. Study***

The primary analysis using the EORTC QLQ-C30 scores was according to data collected at baseline and 3 months after the last cycle (follow-up). The mixed longitudinal (panel) model was used to evaluate the data and a non-parametric Skilling-Mack test was used to verify the unbalanced panel data; a value of less than 0.05 was considered to be statistically significant. An increase in the mean Global Health Status score was reported (P = 0.008); the mean score was 58.2 (95% CI, 53.1 to 63.2) at baseline and 69.3 (95% CI, 61.4 to 77.2) at follow-up. An increase in the mean social functioning score was reported (P = 0.049); the mean score was 63.9 (95% CI, 56.7 to 71.2) at baseline and 70.9 (95% CI, 61.1 to 80.7) at follow-up. A decrease in the mean fatigue symptom score was reported (P = 0.029); the mean score was 42.4 (95% CI, 36.3 to 48.4) at baseline and 32.0 (95% CI, 22.2 to 41.7) at follow-up. A decrease in the mean appetite loss symptom score was reported (P = 0.015); the mean score was 25.7 (95% CI, 19.5 to 31.9) at baseline and 11.6 (95% CI, 0.7 to 22.5) at follow-up. The difference in change from baseline in the mean scores on the remaining functional and symptom scales

were not considered statistically significant. Further, the investigators reported a significantly greater improvement (magnitude of benefit was not reported) on the diarrhea and dyspnea symptom scale scores observed in patients with functioning versus non-functioning pNETs. The subanalysis of the EORTC QLQ-C30 results was based on data collected at baseline and 3 months after the first, second, and third cycle. Changes from baseline in the EORTC QLQ-C30 scores in the subanalysis were generally consistent with those observed in the primary analysis.

### ***Zandee et al. Study***

The median follow-up period was 39.3 months (range = NR). PFS was calculated using the Kaplan-Meier method and was based on the time from the first cycle of <sup>177</sup>Lu oxodotreotide to objective disease progression, change to a new line of therapy, or death from any cause. The median PFS was 18.1 months (interquartile range = 3.3 to 35.7). A primary event was reported in 31 patients, of which 24 patients had progressive disease, 5 patients changed to a new line of therapy, and there were 2 deaths. Tumour response was evaluated with RECIST v1.1 criteria in 34 patients. Complete response was reported in 1 (2.9%) patient, partial response in 19 (55.9%) patients, stable disease in 8 (23.6%) patients, and progressive disease in 6 (17.6%) patients. Disease control, which was defined as patients with complete response, partial response, or stable disease, was reported in 18 of the 23 patients with progressive disease at baseline.

HRQoL was assessed in 22 patients using the EORTC QLQ-C30 by comparing the scores 3 months after the last cycle (follow-up) to baseline. For the comparison of continuous variables, a paired t-test and the Wilcoxon signed-rank test were used for normally distributed and non-normally distributed variables, respectively. An increase in the mean Global Health Score and Quality of Life was reported (P = 0.002); the mean score was 61.7 (95% CI, NR) at baseline and 79.5 (95% CI, NR) at follow-up. An increase in the mean physical functioning score was reported (P = 0.008); the mean score was 79.7 (95% CI, NR) at baseline and 90.0 (95% CI, NR) at follow-up. An increase in the mean role functioning score was reported (P = 0.006); the mean score was 62.7 (95% CI, NR) at baseline and 90.3 (95% CI, NR) at follow-up. An increase in the mean emotional functioning score was reported (P = 0.002); the mean score was 74.1 (95% CI, NR) at baseline and 84.5 (95% CI, NR) at follow-up. An increase in the mean social functioning score was reported (P = 0.047); the mean score was 77.3 (95% CI, NR) at baseline and 85.6 (95% CI, NR) at follow-up. A decrease in the mean fatigue symptom score was reported (P = 0.02); the mean score was 27.3 (95% CI, NR) at baseline and 17.2 (95% CI, NR) at follow-up. The difference in change from baseline in the mean scores on the remaining functional and symptom scales were not considered statistically significant.

## **Harms Results**

### ***Fröss-Baron et al. Study***

Bone marrow, liver, and kidney toxicity were defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Grade 3 or 4 bone marrow toxicity was reported in 11 (10.8%) patients. Grade 3 toxicity of white blood cells and/or granulocytes was reported in 5 (4.9%) patients, grade 3 or 4 toxicity of platelets was reported in 5 (4.9%) patients, and grade 3 toxicity of hemoglobin was reported in 2 (1.9%) patients. Grade 4 (lethal) thrombocytopenia and acute myeloid leukemia were reported in 1 (1.0%) patient each. Fatal liver toxicity was reported in 1 (1.0%) patient; the cause of death was also considered related to tumour progression. Grade 3 or 4 nephrotoxicity was not observed. Treatment discontinuations were due to the following: termination according to the dosimetry-guided protocol was applied to 51 (50.0%) patients, disease progression in 17 (16.7%) patients, bone marrow toxicity in

11 (10.8%) patients, the standard 4-cycle protocol was applied to 9 (8.8%) patients, reduced tumour load in 3 (2.9%) patients, deterioration in 2 (1.9%) patients, death was reported in 2 (1.9%) patients, and a combination of factors not specified in 7 (6.8%) patients.

### ***Marinova et al. Study***

No analyses for harms were conducted.

### ***Zandee et al. Study***

Nausea, vomiting, and pain were reported in 22 (17.6%), 6 (4.8%), and 10 (8.0%) of the 125 cycles administered in total, respectively. Toxicity was defined according to the CTCAE 4.03 criteria. Grade 3 anemia and grade 3 thrombocytopenia were reported in 1 (2.9%) patient each, and grade 3 leukopenia was reported in 3 (8.8%) patients. Hormonal crisis, which was defined as an acute complication of hormonal secretion following treatment with <sup>177</sup>Lu oxodotreotide that required medical care, was reported in 3 (8.8%) patients, and late toxicity with myelodysplastic syndrome (MDS) was reported in 1 (2.9%) patient. Reasons for not having received the intended cumulative activity of 29.6 GBq <sup>177</sup>Lu oxodotreotide included a reduced cumulative activity ranging from 18.5 to 25.9 GBq <sup>177</sup>Lu oxodotreotide was administered in 5 (14.7%) patients due to hepatotoxicity; only 1 cycle was administered in 3 (8.8%) patients each due to noncompliance, unexplained progressive cognitive decline, and patient withdrawal; only 3 cycles were provided to 1 (2.9%) patient due to clinical progression; and the last patient case was not reported.

### **Critical Appraisal**

In the absence of an active comparator or placebo group, the interpretation of the efficacy and safety results from the 3 non-comparative observational studies is limited. The interpretation of treatment benefit is further limited by the retrospective non-randomized study design and relatively small sample size. This is compounded by the relatively large number of patients who were excluded from the analysis due to their incomplete questionnaires, as indicated in the study conducted by Marinova et al. However, the clinical experts consulted by CADTH indicated patients with NETs in general were rare, and Zandee et al. also indicated pNETs were rare. Although treatment with <sup>177</sup>Lu oxodotreotide can be ascertained by the use of hospital records, data were sourced from 1 hospital in either Sweden, Germany, or the Netherlands and were retrospectively analyzed. The use of a single source for the recruitment of patients may introduce the risk of selection bias because patients under the care of 1 team may share common characteristics, including treatment history, disease severity, and level of supportive care, which can bias the estimation of treatment effect and limit the external validity of the results. Notably, the place of <sup>177</sup>Lu oxodotreotide in the treatment sequence varied within the cohort and was preceded by various therapies, which the clinical experts suggested can bias the median OS. It should also be noted that Marinova et al. indicated the validated German version of EORTC QLQ-C30 was used in the study but did not identify a clinically meaningful difference; Zandee et al. also did not identify a clinically meaningful difference. Although it was indicated that patients did not undergo further therapies after treatment with <sup>177</sup>Lu oxodotreotide and follow-up, it was unclear if patients received any concomitant therapy that could bias the reporting on the HRQoL questionnaire.

A number of baseline characteristics of the cohorts in the studies, specifically the mean age, proportion of patients with liver metastases, and the proportion of patients with an ECOG PS of 0, were similar to the NETTER-R study, which the clinical experts consulted by CADTH suggested were representative of patients seen in clinical practice in Canada (refer to the Systematic Review section for a detailed description of the patient population in NETTER-R).

The retrospective studies included patients with experience with various treatment histories, thereby placing <sup>177</sup>Lu oxodotretotide at various lines in the treatment sequence and preceded by different therapies. Only 56.9%, 36.8%, and 64.7% of patients received a somatostatin analogue before treatment with <sup>177</sup>Lu oxodotretotide in the study conducted by Fröss-Baron et al., Marinova et al., and Zandee et al., respectively, and thus would match the reimbursement request for this review. Further, the number of cycles administered and the intervals between the cycles varied between studies, such as the application of the dosimetry-guided protocol and the use of 3-month intervals. Finally, Zandee et al. included patients with functioning pNETs, specifically patients with insulinoma, glucagonoma, gastrinoma, and VIPoma, but did not include patients with non-functioning pNETs.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Partitioned-survival model Cost-utility analysis
Target population	Adult patients with unresectable or metastatic, well-differentiated, somatostatin receptor-positive pancreatic neuroendocrine tumours whose disease has progressed after treatment with a somatostatin analogue
Treatment	Lutetium ( <sup>177</sup> Lu) oxodotretotide
Submitted price	<sup>177</sup> Lu oxodotretotide, 7.4 GBq (200 mCi): \$35,000 per pack
Treatment cost	\$23,333 per month
Comparators	<ul style="list-style-type: none"> <li>• Sunitinib</li> <li>• Everolimus</li> </ul>
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	20 years
Key data sources	<ul style="list-style-type: none"> <li>• PFS and OS for <sup>177</sup>Lu oxodotretotide: NETTER-R study</li> <li>• PFS and OS for <sup>177</sup>Lu oxodotretotide vs. everolimus: MAIC based on the NETTER-R and RADIANT-3 trial</li> <li>• PFS and OS for <sup>177</sup>Lu oxodotretotide vs. sunitinib: MAIC based on the NETTER-R and NCT00428597</li> </ul>
Key limitations	<ul style="list-style-type: none"> <li>• Comparative efficacy of <sup>177</sup>Lu oxodotretotide and everolimus or sunitinib was highly uncertain due to the lack of robust direct clinical evidence for <sup>177</sup>Lu oxodotretotide and limitations of the submitted ITCs. The sponsor used joint parametric survival functions for treatments and constant HRs to represent the treatment benefits of <sup>177</sup>Lu oxodotretotide. It was deemed highly uncertain whether the treatment benefits of <sup>177</sup>Lu oxodotretotide would be sustained and constant over the 20-year model time horizon.</li> <li>• Predicted long-term treatment benefits of <sup>177</sup>Lu oxodotretotide was associated with high uncertainty. The sponsor used the best fitted survival models to predict long-term PFS and OS data for <sup>177</sup>Lu oxodotretotide and comparators, but the survival models appeared to not fit PFS and OS data well when interpolated.</li> <li>• Total costs and QALYs of <sup>177</sup>Lu oxodotretotide and comparators were incorrectly estimated. Due to the</li> </ul>

Component	Description
	<p>underestimation of the use of long-acting octreotide, expert feedback indicated that treatment duration for each comparator was expected to be shorter than the time to progression.</p> <ul style="list-style-type: none"> <li>The sponsor assumed different utility values with different elicitation techniques for the comparisons of <sup>177</sup>Lu oxodotretotide and everolimus and <sup>177</sup>Lu oxodotretotide and sunitinib. Clinical experts indicated that quality of life depends on disease progression and should not vary by treatment.</li> </ul>
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>CADTH could not address several key limitations associated with the sponsor's economic evaluation, primarily the lack of robust evidence on the comparative efficacy for <sup>177</sup>Lu oxodotretotide; therefore, all reanalyses undertaken by CADTH are considered exploratory.</li> <li>In CADTH's reanalyses, the following revisions were made: correcting drug cost calculations, assuming the same proportion of patients requiring long-acting octreotide, selecting 1 set of health utility values across both comparators, using median treatment duration to calculate drug and AE costs and QALY decrements, and using alternate approaches for OS prediction.</li> <li>In CADTH's reanalyses, <sup>177</sup>Lu oxodotretotide was associated with an ICER of:               <ul style="list-style-type: none"> <li>\$120,931 per QALY compared with everolimus (incremental costs: \$94,549 and incremental QALYs: 0.78). A price reduction of at least 41% would be needed for <sup>177</sup>Lu oxodotretotide to be cost-effective at a WTP threshold of \$50,000 per QALY.</li> <li>\$466,632 per QALY compared with sunitinib (incremental costs: \$91,871 and incremental QALYs: 0.20). A price reduction of at least 63% would be needed for <sup>177</sup>Lu oxodotretotide to be cost-effective at a WTP threshold of \$50,000 per QALY.</li> </ul> </li> <li>The cost-effectiveness of <sup>177</sup>Lu oxodotretotide was highly sensitive to assumptions on costing (RDI and treatment duration), treatment waning, and health utility values.</li> </ul>

HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; QALY = quality-adjusted life-year; OS = overall survival; PFS = progression-free survival; RDI = relative dose intensity; WTP = willingness to pay.

## Budget Impact

CADTH identified a key limitation with the sponsor's analysis. The use of relative dose intensity to estimate actual drug costs was not appropriate. In CADTH reanalysis, a dose intensity of 100% was assumed for <sup>177</sup>Lu oxodotretotide and comparators, which decreased the 3-year total budget impact of reimbursing <sup>177</sup>Lu oxodotretotide to \$7,934,115 (\$1,420,013 in year 1, \$2,875,197 in year 2, and \$3,638,906 in year 3).

## pERC Information

### Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

**Meeting date:** August 10, 2022

**Regrets:** 3 expert committee members did not attend

**Conflicts of interest:** None