Cost-effectiveness of Lutetium [^{177}Lu] oxodotreotide versus everolimus in gastroenteropancreatic neuroendocrine tumors: Responses to reviewer comments

We would like to thank the reviewers for their objective critique of our analysis. We have responded to the reviewer's concerns below and have updated the manuscript as required. For ease of review edits to the manuscript have been made in blue text.

1 Peer-review report

Reviewer #1: Dear Authors, The article is a profound study. Here are the questions/comments:

1. You take into account serious adverse events, grade 3-4, however did you consider long-term toxicity, e.g. leukemia? Bergsma et al. published some incidence data on this topic. Since it also affects the quality of life, please mention this (Why/Why not) in the discussion section.

The health-economic model used for the analyses was constructed prior to the publication of the Bergsma et al. 2018 data and the possibility of persistent hematologic dysfunctions as highlighted by Bergsma et al. were therefore not captured in the analysis. We have updated the Discussion section of the article to acknowledge that this omission is a limitation and that both the clinical and economic implications of long-term persistent hematologic dysfunction warrant consideration in future long-term cost-effectiveness analyses.

2. Your three-state partitioned survival model enables extrapolation of clinical data beyond the time frame of clinical studies. What was the time frame of extrapolation? (e.g. time outside clinical studies timeframe) and what is the time period covered by clinical studies?

The time horizon for the cost-effectiveness analyses for both Sweden and Norway is 20 years, which is mentioned in the time horizon, perspective and discount rate section of the methods, Randomization in the NETTER-1 study commenced in September 2012 and the cut-off point for the primary analysis was July 24, 2015, giving a maximum follow-up period of approximately 2 years and 11 months. The use of a time horizon of 20 years was therefore highly conservative in terms of capturing extrapolated overall survival. A conservative approach was purposely used to ensure that all long-term costs and events (with the exception of persistent hematologic dysfunctions as acknowledged above) for both the active and comparator treatment arms were captured in the analysis.

3. Why did you choose the Netter-1 study? there are studies which cover a larger clinical time period.

The rationale for using the NETTER-1 study is that was a large-scale phase III randomized controlled trial and therefore represented the most robust clinical evidence source available at the time at which the analysis was conducted in terms of both progression-free survival and overall survival data for patients treated with ^{177}Lu-Dotatate.

Reviewer #2: The authors reported a health economic research that was performed 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. This manuscript has value in that it addresses an important theme. Thank you for the opportunity to review this paper. However, I think that there are some limitations before the editors should consider it for publication. Model calculations

(modeling) are generally difficult to discuss at the level of evidence or statistical robustness. Therefore, it is desirable to clarify the preconditions and calculation process of the simulation.

Major comments. 1. Since this paper is a model analysis study (Weibull model, etc.), it is necessary to ensure the robustness of each data source to be extrapolated. In the treatment of GEP-NET with uncertainty, the validity of distributions and averages should be clarified in terms of clinical reality. Therefore, the authors should add the statistical testing (e.g., P-values) and variances of the selected sources to Table 2 or 3.

Only standard errors were available for the utility values presented in Table 2, (standard deviations were not available) and standard errors are presented in Table 2. For most of the disutility values presented in Table 3 it was conservatively assumed that the standard error was equal to the mean, this information has been added to Table 3. Uncertainty around utility values was also explored in one way sensitivity analyses in which the mean value of utilities for the progression-free and post-progression states were increased or decreased by 20%.

Reproduction of the study should be guaranteed to future researchers. The sensitivity analyses are a tool to verify the validity of the combination of indicators, and we cannot guarantee the robustness of the source data itself. 2. This study was not guided by CHEERS (health economic study). According to the statement, the content of each check item is desired to be made public. In view of the above, the authors are encouraged to provide a checklist of CHEERS whenever possible. In particular, in cost-effectiveness assessments, additional efficacy must be proven across comparative technologies (according to guidelines for multiple health economic assessments). Therefore, the statistical significance of the selected data should be explained by focusing on the "11 items: effect measurement".

In line with the reviewer's comments we have provided a completed CHEERS checklist for the analysis.

3. The analysis of health care costs in this study was calculated from the official unit price of the healthcare payer and the frequency (quantity) of various interventions. As an analysis from a social standpoint, it is reasonable to use the official unit price. On the other hand, the explanation of the rationale for the frequency of intervention, which corresponds to the consumption of medical resources, is somewhat vague. The authors should further explain the baseline and reimburse system background for this number of times that they perform the sensitivity analyses.

We have assumed here that by frequency of intervention the reviewer is referring to the relative dose intensity (RDI) for ^{177}Lu-Dotatate. We have updated the methods section of the manuscript to incorporate a more comprehensive explanation of RDI. Specifically, the following text had been added.

"For ^{177}Lu-Dotatate, RDI refers to the amount of the drug that is actually administered relative to the amount that originally ordered, 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."

Minor comments. 4. The authors should further explain why chose the Weibull model. If the present study evaluates the validity by the "Weibull probability paper plot" or others, those results should be shown. Also, the conditions used for the base case analysis (such as 4-week cycle length) should be explained in more detail.

The text relating to the use of the Weibull model for extrapolation of data has been expanded. Several different functions were tested and the Weibull function was selected based on a combination of visual inspection, Akaike's Information Criterion and the Bayesian Information Criterion as well as both clinical and biological plausibility.

All details of the base case settings (cycle length, half cycle correction, discount rate, time horizon, perspective, costs and utilities) are provided in the Methods section.

5. The authors should widely collect and reflect similar research information (e.g, papers below: some adverse events associated with treatment of the gastrointestinal system). Further explanation of data collection methods (survey and selection criteria) is desired. - ^{177}Lu-DOTATATE peptide receptor radionuclide therapy versus Everolimus in advanced pancreatic neuroendocrine tumors: a systematic review and meta-analysis. Nucl Med Commun. 2019 Dec;40(12):1195-1203.

We'd like to thank the review for directing us to this valuable article, which was not initially included in the manuscript as this published after the manuscript was prepared. We have added details of the findings of this article to the Discussion section. Whilst the systematic review and meta-analysis provides valuable data, for the analysis of everolimus the authors have included studies that include both everolimus and sunitinib used in different sequences, whereas the comparison made in the current analysis is versus everolimus alone.

We would also note that in terms of the selection criteria used for the clinical data utilized in the analysis was based on the most robust data available – which is already detailed in the manuscript.

In line with comments from Reviewer 1, we have also added discussion on adverse events, in particular long-term hematologic toxicities to the Discussion section.

2 Editorial Office's comments

1) Science Editor: 1 Scientific quality: The manuscript describes a basic study of the expression of gastroenteropancreatic neuroendocrine tumors. The topic is within the scope of the WJG. (1) Classification: Grade B and Grade D; (2) Summary of the Peer-Review Report: This manuscript has value in that it addresses an important theme. The article is well written, with good methodology. However, there are some issues should be addressed. In the treatment of GEP-NET with uncertainty, the validity of distributions and averages should be clarified in terms of clinical reality. Therefore, the authors should add the statistical testing (e.g., P values) and variances of the selected sources to Tables 2 or 3.

Unfortunately, p values are not available to include for the values included in Tables 2 and 3. However, standard errors are presented now in both tables, where available. Where not available, in line with good practice for economic analysis it was assumed that the standard error was equal to the mean (Briggs A, Sculpher MJ, Claxton K. Decision Modelling for Health Economic Evaluation. Oxford: OUP; 2006).

The questions raised by the reviewers should be answered; and (3) Format: There are 5 tables and 2 figures. A total of 39 references are cited, including 9 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B and Grade B. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No animals or humans are involved in the study. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by Advanced Accelerator

Applications International. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG.

5 Issues raised: (1) I found no “Author contribution” section. Please provide the author contributions;

An author contributions section has been added.

(2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); and

No grant application was made in relation to the economic analysis performed or subsequent analysis, therefore this aspect is not applicable.

(3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

All figures are provided in PowerPoint format.

6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

2) Editorial Office Director: I have checked the comments written by the science editor.

3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Clinical Cases.