NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Lutetium (177lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours [ID1224]

In August 2017, an Appraisal Consultation Document (ACD) was released for consultation. The company, Advanced Accelerator Applications (AAA), requested to submit additional clinical data at this stage. This data was reviewed by the Assessment Group and a further committee meeting discussion was scheduled for April 2018. Following the April 2018 committee meeting, issues were identified that needed clarifying by the clinical experts and the company requested to submit a new value proposition for lutetium. The clinical expert responses and the new value proposition were considered at the committee meeting on 12 June 2018.

The following documents are made available to the consultees and commentators:

1. **Response to questions from Professor Juan Valle**

2. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Advanced Accelerator Applications (AAA)
   - NET Patient Foundation
   - British Nuclear Medicine Society
   - Joint response from the Royal College of Physicians

4. **Comments on the Appraisal Consultation Document from experts:**
   - Mark Zwanziger, patient expert, nominated by NET Patient Foundation

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Additional evidence from** Advanced Accelerator Applications (AAA)

7. **Assessment Group critique of company additional evidence**
   - Erratum
   - Addendum report
   - Matched adjusted indirect comparison (MAIC) results

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

From: Valle, Juan (RBV)
Sent: 08 June 2018 15:41
To: [redacted]
Subject: RE: NICE MTA - neuroendocrine tumours (metastatic, unresectable) - 177 Lu-dotatate [ID1224]

Dear Gavin

For clarity of thought let me walk you through the pathway as I see it.

Pre-progression:

- Close to all patients are likely to be receiving a somatostatin analogue (a small minority, <5% will be intolerant to the injections); this is based on the results of the PROMID study and the CLARINET study. Previously the use of SSAs was limited to patients with syndrome (approx. 40%) but after the publications of these two studies, all patients receive a SSA due to the documented anti-proliferative properties.
- The doses with documented anti-proliferative properties were octreotide LAR 30mg and lanreotide 120 mg. Given that lutetium is for patients with disease progression, it would be anticipated that patients would be receiving these maximum doses, according to the SPC, prior to lutetium therapy.
- In the absence of additional treatment options, some clinicians have used above-label dosing of SSAs (either increased the dose every 4 weeks, or reduced the injection interval to every 3 weeks or every 2 weeks). This is mainly done due to the good tolerability of the SSA but there is insufficient information on efficacy and it is outside of the marketing authorisation of these compounds. I therefore do not believe that we should be recommending that approach.

Post-progression:

- In patients with hormonal syndrome (e.g. carcinoid, approx. 40% of the population): all patients would continue SSA with the escalation of therapy
- In patients with no hormonal syndrome (approx. 60%) practice varies. In the pivotal NETTER-1 study the somatostatin analogue (octreotide LAR 30mg) was continued with lutetium in the experimental arm. In the control arm octreotide LAR 60 mg was used. The study has since shown that this was inferior in outcomes both in terms of PFS and OS.
- There is variability of opinion on whether patients should continue a SSA with lutetium. No question that I syndromic patients an SSA would be continued. For non-syndromic patients the NETTER-1 study would suggest this is continued (at doses within marketed authorisation, not above-label dosing).

The scenarios below are polarised and I believe neither are correct. The proportion of patients receiving a SSA is way too low in the AG model but neither is this 100% as there are some patients with tolerability issues (mainly the 25% who develop pancreatic enzyme insufficiency, although we are now more cognisant of this and are able to actively identify and manage this situation).

Allowing for intolerability issues, I would suggest that 95% of patients would be on a SSA at study entry (initially these may include some above-label dosing due to the lack of other treatment options, may be in about 20% of patients). If in keeping with the NETTER-1 study, all patients would continue SSA for the duration of lutetium treatment (4 cycles, each 2-3 months apart). Thereafter, it is difficult to project SSA use; some clinicians may continue the SSA until disease progression; others may use the opportunity to reduce or even stop SSA in non-syndromic patients where the disease is under control/responding. I suspect this would be in a minority of patients (estimate: 10%).

I am aware that I haven't "pinned the tail on the donkey" with respect to the scenarios below; rather I wanted to provide some clarity of thought process. Happy to follow-up over the weekend.

Best

Juan

From: [redacted]
Sent: 01 June 2018 13:19
To: Valle, Juan (RBV)
Subject: RE: NICE MTA - neuroendocrine tumours (metastatic, unresectable) - 177 Lu-dotatate [ID1224]

Dear Professor Valle,

I wanted to follow up on the below email to see if you would you be available to speak with the technical team on the week of 4 June for a 60-90 minute call, on either Wednesday, Thursday or Friday if at all possible? If so, could you please let me know what times/dates would be best for you?

I also wanted to share a summary of the issue that we wanted to discuss with you and some specific questions that require your input. At the appraisal committee meeting for lutetium in April, the committee heard from the clinical experts (including yourself) about the role of somatostatin analogues (SSAs) in treating neuroendocrine tumours (NETs). Two points on SSA use for progressed disease were discussed on the day – a). the proportion of people that have SSAs in the NHS and b). the SSA dose for these patients at this point in the pathway. However there remains some confusion about the most appropriate analysis that reflects the views of the experts and the use of SSAs in the NHS, particularly for GI NETs. Therefore we have a few questions that we require clarity on to aid the committee's discussions at the next committee meeting. A separate email will be going out shortly to stakeholders to inform them of the next committee discussion.

As a reminder, the company and assessment group presented the following in their base case for GI NETs;

Use of SSRAs in AG and Company models

Disease and stage	Strategy	Proportion using SSRAs – AG model	Proportion using SSRAs – AAA model
Whole/midgut GI NETs			
Pre-progression	BSC	1.03%(LD)	100.00%(HD)
	Active treatments	1.95%(LD)	0.00%
Post-progression 1st cycle	BSC	22.74%(LD)	100.00%(LD)
	Active treatments	29.80%(LD)	100.00%(LD)
Post-progression Subsequent cycles	BSC	1.03%(LD)	100.00%(LD)
	Active treatments	1.95%(LD)	100.00%(LD)

Key: BSC = Best Supportive Care; HD = High dose; LD = Low dose; SSRA = Somatostatin Receptor agonist.

Active treatments were Everolimus, and 177Lu-DOTATATE

The assessment group also presented 3 different scenarios for GI NETs, as follows;

- BSC scenario 1 - High dose Octreotide, 60mg, in 40% pts (pre-progression only, BSC arm)
- BSC scenario 2 - High dose Octreotide, 60mg, in 100% pts (pre-progression only, BSC arm)
- Real world scenario - Octreotide 30mg in 90% of pts pre-progression, reducing to 85% post-progression. Applied to all treatment groups in the model (BSC, 177Lu-DOTATATE and Everolimus)

Questions

1. Which of these scenarios best reflects the use of SSAs for GI NETs in the NHS – in terms of proportion of patients and SSA dose?
2. Is there an alternative scenario, not presented above, that would reflect the use of SSAs for GI NETs in the NHS – in terms of proportion of patients and SSA dose?

Your comments will be presented to the Appraisal Committee for consideration during the committee meeting. Both your comments and the committee's consideration of your comments will be discussed in the guidance document produced after the meeting.

I would be grateful if you could respond to these questions by close business on Monday 4 June, 2018. Please let me know if you are unable to respond by this date or if you have any questions.

Best wishes

[redacted]

177Lu-dotatate for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease [ID1224]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Professional organisation	NCRI-ACP-RCP-RCR	We are concerned that this recommendation will deprive patients with small intestinal neuroendocrine tumours (SINETS) from receiving arguably the most effective new treatment that has ever been developed for recurrent neuroendocrine tumours. The introduction of somatostatin analogues in the 1980s was a remarkable breakthrough in that it was able to control the life-threatening symptoms from carcinoid syndrome but at that time it was only for symptomatic relief. Subsequently it has been shown to have a minor antiproliferative effect. PRRT when compared with the unlicensed high-dose octreotide LAR has shown a truly remarkable improvement in progression free survival although no significant improvement in overall survival probably due to the fact that most patients who received high-dose LAR subsequently were able to access PRRT off label or through other mechanisms. The difference in PFS is very highly significant. This level of benefit in PFS has rarely been seen in oncology circles. Our experts are concerned that the committee has not recommended approval. Please see section 6 for comments on a possible solution. This benefit in the clinical trial was only for SINETs as no patients with pancreatic or other NETS were included. Therefore our experts are disappointed that NICE has rejected outright the use of PRRT. We would strongly urge the committee to review and revise their recommendation to allow its use in patients with SINETS until further evidence comes through to confirm the benefit in pancreatic, bronchial and other neuroendocrine tumours. There is a significant experience in other sites in Europe but this is not evidenced by randomised trials. It is commented that the NICE end-of-life criteria would not apply however at the time that the trial was conceived it would have been anticipated that most of these patients would be dead within 2-3 years at most. The remarkable improvements in the care in neuroendocrine tumours over the past decade have	Comments noted. After considering the new analyses that incorporated data from the ERASMUS study and the comments received in response to the appraisal consultation document, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD) for the committee's recommendation.

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			demonstrated that these data are now obsolete. This in itself is further confirmation of the effectiveness of new treatments in NETS which have revolutionised clinical care and given patients the chance to live with their disease.	
2	Professional organisation	NCRI-ACP-RCP-RCR	We are concerned that NICE has dismissed high-dose octreotide as the effective comparator. There is evidence of small clinical benefit from the use and there are two clinical trials which have shown that somatostatin analogues do have a minor anti-proliferative effect. However in real practice very few clinicians would use (or even be allowed to use) octreotide LAR 60 mg. Other measures would be introduced such as chemotherapy, embolisation, ablation and if possible PRRT. However if a placebo arm had been used then we can anticipate that the difference between the study arm and the control arm would have been even larger.	Comment noted. High-dose octreotide as a comparator has been considered by the committee. Please see sections 3.5 and 3.13 of the final appraisal determination (FAD) for the committee's full considerations on the use of high-dose octreotide.
3	Professional organisation	NCRI-ACP-RCP-RCR	We would recommend that further trials in neuroendocrine tumours at other sites be completed to provide the evidence to support its use	Comment noted.
4	Professional organisation	NCRI-ACP-RCP-RCR	Our experts cannot comment on the cost of treatment as this is usually independent but assume there may be some opportunity for patient access schemes to modify the cost.	Thank you for your comment. Lutetium is recommended within its marketing authorisation only if the company provides it according to the commercial arrangement. See sections 1 and 2 of the FAD.
5	Professional organisation	NCRI-ACP-RCP-RCR	Regarding the comparators, in real life practice there is a sequence of treatments that may be considered. This will vary between pancreatic, small intestinal and bronchial. If we focus purely on small intestinal NETs, then the first-line treatment is normally a somatostatin analogue and on progression much will be determined by the site of disease. When it is liver predominant metastatic disease, targeted therapies at the liver such as hepatic artery embolisation and ablation have been traditionally offered. Chemotherapy has been used but has relatively limited benefit and recently everolimus has been approved in some parts of the United Kingdom for small intestinal and bronchial NETs. However the European guidelines from ENETs and other expert bodies including NANETS and the SNMMI recommend that PRRT is used earlier in the disease process. Given the significantly higher progression free survival seen with Lutetium which far exceeds the PFS seen with everolimus and sunitinib.	Comments noted. Please see sections 3.2 and 3.3 for the committee's full considerations on comparators for lutetium. Please also note that lutetium is now recommended as a treatment option for unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), and somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours

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				(NETs) in adults (see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD)).
6	Professional organisation	NCRI-ACP-RCP-RCR	The likelihood of benefiting from PRRT can be predicted by the use of somatostatin receptor scintigraphy with either Octreoscan or where available gallium PET. Therefore the committee might also wish to consider recommending that the use of lutetium should be restricted to patients with neuroendocrine tumours of small intestinal origin which have progressed on somatostatin analogue therapy and which are shown to be somatostatin receptor scintigraphy positive. If accepted, this would identify the niche subgroup of patients most likely to benefit and where there would be the best value for money as well as clinical benefit	Comments noted. After considering the additional analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD) for the committee's recommendations.
7	Professional organisation	NCRI-ACP-RCP-RCR	The comments on day case administration need to be qualified because of the issues of geography. There are a limited number of specialist centres in the UK who treat neuroendocrine tumours but because of the special requirements with radionuclides there will be a small number of centres capable of providing this service. Our experts believe that patients in remote parts of Northwest England and the Southwest of England in particular may have considerable distances to travel for this treatment. Therefore these patients will need to be admitted overnight. Our experts are concerned that the committee has overlooked the fact that although there is low-dose radioactivity, there are special precautions required which will be individualised. Although the document is principally aimed at patients in England, in other parts of the United Kingdom even greater distances may be required to travel and attend for treatment.	Comment noted. Please see section 3.16 of the FAD for the committees consideration and conclusion on the administration costs for lutetium
1	Professional organisation	NET Patient Foundation	Thank you for the invitation to comment	Comments noted. After considering the new analyses

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			The immediate response to the proposed outcome is of disbelief and shock. The treatment under review has robust and increasing evidence to support its clinical effectiveness, as well as increasing data to show significant clinical and patient reported benefit. Whilst we acknowledge that NHS finances are finite, we believe there is significant scope to negotiate a fair and competitive price which would allow this therapy to become available, once again, through the NHS - we do not believe that such a negotiation would require 3 years to successfully complete. We understand that the current UK list price is £17k per session (£68k for all 4 treatments) - though proposed costings have been withheld from the available NICE documents so decision based costing unclear. However, we know that this therapy has previously been made available to the NHS, by the company, as a BOGOF deal (significantly reducing costs) - also an understanding and willingness amongst the clinical community to minimise administration and monitoring costs. We have learned from patient reports from the wider NET community, that it is currently available to NET patients in Europe at a cost of between £7-15k per session (variation possibly due to differences in healthcare systems, insurance and funding streams). We estimate reasonable, competitive, costs (incl administration) to total £36k If cost is the primary driver influencing decision - we fully support NICE negotiation on price, prior to final decision. The NPF is a patient centric charity, whose primary aims are to educate, inform, support and advocate for those diagnosed and living with malignant neuroendocrine tumours. As such we would also wish to comment on some of the information and statements made within the committee papers - to reflect patients concerns regarding other potential influences on decision making.	from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD) for the committee's recommendation.
2	Professional organisation	NET Patient Foundation	Understanding of the disease - NETs are a heterogenous group of tumours - as diverse as cancer itself. One treatment does not fit all - and there is concern that	Comments noted. After considering the new analyses

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			the true complexity of this group of malignancies has not been fully appreciated. One example of this is referring to NECs as Neuroendocrine Carcinoids. NEC refers to Neuroendocrine Carcinoma - a far more aggressive malignancy than carcinoid. (Carcinoid is a term utilised to describe either low-moderate Lung NETs or the syndrome associated with (primarily) small bowel NETs). Another is the reference to the variety of treatments available including transplantation (without matching them to the relevant specific NETs). There is variety, because as with cancer itself, there is variety in the types of NET and as stated one treatment does not fit all (nb transplantation is not available in the UK on the NHS at this time). Understanding the impact of the disease - 60-80% of all NETs have already metastasised at the time of diagnosis. Symptoms range from those associated with more common cancers (pain, lethargy, weight loss, tumour burden, etc) as well as those caused by excessive hormone release - which themselves range from mildly challenging to life threatening. Compounding this is the perceived lack of awareness - not just amongst the general population, but also medical establishment - limited access to timely and accurate diagnostics, restricted access to effective treatment - and a perceived assumption that somehow despite malignant nature and lack of cure NETs are 'less serious' the cancer to have, if you going to get cancer, We live WITH cancer . . . every day, never knowing if the next scan or test will show it's changed. Its cancer and you are not on chemo - are you sure its cancer? Unmet clinical need - which follows on from point 1. There is NO other systemic NHS treatment for well differentiated, low-moderate grade SSTR positive FUNCTIONAL midgut NETs that progress - beyond best supportive care +/- off label use of somatostatin analogues. NB whilst there is clinical practice experience and emerging evidence of the use of this treatment in Lung and Pancreatic NETs - we support recommendation for use in small bowel NET as per NETTER1 - at this time. For low-moderate grade, well differentiated NON functional pancreatic, midgut and lung NETs there is now Everolimus For pancreatic NETs there is Everolimus, Sunitinib and chemotherapy Inequality - UK and England is used interchangeably throughout this document - clarity is sought as to which NHS entities NICE guidance would influence.	from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD) for the committee's recommendation.

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			Currently patients living under the devolved nations NHS care have access to this treatment whilst those under NHS England care do not. Please note that those living in devolved nations have to travel to England to receive this treatment - often sitting alongside patients from England in clinic or Nuclear Medicine department. People who have been denied access following the withdrawal of this therapy from the CDF. Patients from all UK nations have expressed concern that highlighting this geographical inequality may risk people's access - i.e. they do not wish to see this therapy also withdrawn from those living within the devolved nations.	
3	Professional organisation	NET Patient Foundation	We would also like to clarify whether, in considering costs, assessment of cost of NOT treating this group of patients has been made? Given length of time to progression with or without this treatment - has additional supportive care, including hospitalisations, in the non-treated cohort been calculated - the financial model / definition is not quite clear . For example we have been involved in supporting a young woman with progressive metastatic pNET (insulinoma) – she's a young mum, who was working but off sick debilitated by symptoms which included having to eat every 2 hours to prevent coma - subsequent weight gain, experiencing extreme lethargy, hypoglycaemic episodes, confusion, nausea, etc , with repeated hospitalisations, increasing social isolation and decreasing family life interaction - all together, a profoundly compromised quality of life with life-threatening symptomatic episodes. She has just completed this treatment - and has not had a single hypoglycaemic episode or non-treatment hospitalisation since her 1st session (so reduced healthcare costs with significant QoL improvement due to treatment), has recently been able to not only go on holiday with her young family but take part in activities and consider return to work pending end of treatment scans, bloods and clinical advice. You have also heard from an expert patient, who having received this therapy went from pre-hospice admission status to running the Marathon! We have also been asked to confirm what is meant by best supportive care - does this include palliation with somatostatin analogues? Given published data and clinical practice would be a not uncommon standard of palliative care. Again	Comments noted. The committee recognised the need for effective treatment for NET (FAD, section 3.1). After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD) for the committee's recommendation.

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			this is unclear. In summary - NET patients acknowledge the financial constraints the NHS has to operate within, also that not everyone will require the same treatment - they understand the concept of appropriate treatment criteria, however, they feel let down by the lack of consideration for those living with NETs (rare/uncommon cancers requirements not addressed within National Cancer Plan), are perplexed at how World Class Outcomes can be achieved when clinically proven treatments cannot be accessed and are frustrated, frightened, disappointed and angry that more isn't being done to assertively negotiate pricing to allow, clinically appropriate candidates, NHS access to this treatment.	
1	Professional organisation	British Nuclear Medicine Society	The costing does not take into account the highly specialised nature of providing a molecular radiotherapy service. This is a multidisciplinary area requiring input from radio pharmacy, nuclear medicine, medical and clinical oncology, physics and nursing and must be costed as such. There is also a need to ensure equal geographical access to treatment, which at present is governed. Of particular note, the ionising radiation regulations, due to come into force in February 2018, mandates dosimetry-based treatment planning and verification of the absorbed doses delivered. This is yet to be evaluated or implemented, but will have an impact on the cost of delivery.	Comments noted. Please see section 3.16 of the final appraisal determination (FAD) for the committee's full considerations on all the relevant administration costs for lutetium.
2	Professional organisation	British Nuclear Medicine Society	We are concerned about this product because in over 20 years work in patients with progressive neuroendocrine tumours this is the only treatment which has consistently been able to treat the majority of patients with improvement in quality of life as well as survival, Evidence NETTER 1 trial.	Comments noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the

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				final appraisal determination (FAD) for the committee's recommendations.
3	Professional organisation	British Nuclear Medicine Society	We are concerned as this product has been the only product which has been proven to extend mean PFS over 12 months in a RCT (mean PFS for Lu-177 dotatate not reached by 30 months) Evidence NETTER 1 trial.	Comments noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD) for the committee's recommendations.
4	Professional organisation	British Nuclear Medicine Society	We are concerned as this product is much less toxic than many alternatives and is better tolerated and so reduces on costs from side effects which we have seen with chemotherapy based regimes (own observations and Khan S et al JNM 2011).	Comments noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.22 and 3.23 of the

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				final appraisal determination (FAD) for the committee's recommendations.
5	Professional organisation	British Nuclear Medicine Society	We are concerned that when available there will be a "post code lottery" of where this treatment will be available and how availability will be England wide (My concerns are that there are no centres experienced in using Lu-177 dotatate in East Midlands, Yorkshire, the North East and South West) Evidence review of provision of nuclear medicine speclalists).	Comment noted. Please note that the committee has now recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, section 1.1).
6	Professional organisation	British Nuclear Medicine Society	We are concerned that the best screening test for PRRT with Lu-177 dotatate is Ga-68 DOTATOC PET which is not currently funded by NHS England and is only available in a few centres in the England and those centres may find it difficult to scan patients under the provisions of NHS England phase II PET/CT contract roll out.(Evidence discussion with nuclear medicine and PET provider colleagues).	Comment noted. Comments from various stakeholders during the consultation of the scope indicated that diagnostic testing with radiopharmaceuticals is standard practice. Therefore this was not considered any further in the appraisal.
1	Company	Advanced Accelerator Applications UK Limited	**1.** NICE has failed to consider the full marketing authorisation for Lu-177 dotatate The Committee has issued draft guidance for only one subgroup of patients, midgut vs the broader gastroenteropancreatic neuroendocrine tumour (GEP-NET) population approved in the CHMP positive opinion and which form the basis for the marketing authorisation for Lu-177 dotatate. The Committee has not provided any justification for this despite the opinion of the clinical experts as stated in the ACD. *"The clinical experts explained that in their experience, they do not expect much difference in the efficacy of Lu-177 dotatate across the*	Comments noted. After considering the new analyses that incorporated data from the ERASMUS study and the comments received in response to the appraisal consultation document, the committee recommended lutetium for treating unresectable or metastatic,

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			different tumour sites. The committee acknowledged that Lu-177 dotatate may be equally effective across different tumour sites, but concluded that its recommendations should be guided by evidence from the clinical trial that underpins the marketing authorisation." (ACD, 3.4) (1) We would like to highlight that Lu-177 dotatate has previously been available for the treatment of patients with GEP-NETs through the Cancer Drugs Fund until just prior to the reorganisation of the fund. This decision was upheld despite an appeal by the NET Patient Foundation. We are aware that removal of Lu-177 dotatate from the fund has restricted patient access to this effective treatment, and this has been distressing for patients with GEP-NETs. The focus of the Committee only on patients with midgut NETs for this appraisal will lead to continued uncertainty for a significant proportion of the GEP-NET patient population. We detailed the results of the large single arm trial of Lu-177 dotatate (Erasmus) in our submission to NICE. This study provides significant evidence on the therapeutic benefits of Lu-177 dotatate for the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NET) patients. It formed a core part of the submission to regulatory authorities who accepted the results as providing evidence of benefit in the GEP-NET population. As the Committee heard from their clinical experts at the Committee Meeting, given the mechanism of action of Lu-177 dotatate, its efficacy is expected to be similar across the different tumour sites. The study population of patients with midgut carcinoid tumours recruited to the NETTER-1 study was selected as these NETs are broadly representative of the GEP-NET population: they are the most common type of GEP-NETs, are frequently metastatic and progressive at diagnosis (like most GEP-NETs), and have features similar to other GEP-NETs (common cell type origin, SSTR overexpression and high receptor mediated uptake of Lu-177 dotatate). Furthermore, because GEP-NET is an orphan disease and subpopulations are too small to conduct controlled trials, the midgut carcinoid tumour population was selected to reduce study heterogeneity, reduce potential bias and increase internal and external validity. We further note that the Committee concluded that it was inappropriate to distinguish between tumour sites when formulating its recommendations for the	progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.23 and 3.24 of the final appraisal determination (FAD) for the committee's recommendations.

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			gastro-intestinal NET population in its appraisal of everolimus, despite data being available for the midgut subgroup.(2) Whilst we note that NICE has a preference for data from RCTs, we also note that NICE routinely considers data from non-randomised studies. This is recognised in the NICE Guide to the Methods of Technology Appraisal as cited below. "*RCTs directly comparing the technology under appraisal with relevant comparators provide the most valid evidence of relative efficacy. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised studies may be required to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented*." (NICE Guide to the Methods of Technology Appraisal, 5.2.3) (3) We also note that NICE has previously evaluated and recommended technologies on the basis on non-randomised data. A few recent examples are: • Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451) • Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (TA446) • Bosutinib for previously treated chronic myeloid leukaemia (TA401) The NICE Decision Support Unit (DSU) Document has published guidance on the use of non-randomised data to inform estimates of treatment effect. It is unclear why this guidance has not been followed by the Assessment Group. The DSU authors also conducted a review of 110 NICE technology appraisals and identified 16 appraisals that had used non-randomised data to inform estimates of treatment effect. {R Faria, 2015 #11} It is therefore unclear why NICE has failed to consider a significant part of the evidence underpinning the marketing authorisation in this instance and why they have disregarded the testimonies of their clinical experts on this specific issue.	

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			We encourage NICE to give a thorough consideration of the important data from the Erasmus study and the opinions of the clinical experts.	
2	Company	Advanced Accelerator Applications UK Limited	**2.** Lu-177 dotatate is a cost-effective use of NHS resources We thank NICE for forwarding the updated Assessment Group (AG) model used by the Committee to inform the development of the ACD. We have significant concerns about fundamental errors that bias against Lu-177 dotatate in the AG reanalysis and the lack of transparency in the amendments made (detailed below). However, even with these biases, we believe that the updated model demonstrates that Lu-177 dotatate is a cost-effective use of NHS resources at NICE standard threshold ranges of £20,000 to £30,000 when compared with everolimus. We note that the ACD states the following "*The assessment group's base-case results, which were used in the committee's decision-making, include the confidential patient access scheme discount for everolimus*." (ACD, 3.11).(1) We acknowledge the confirmation that the basecase analysis of the AG updated model formed the basis of the Committee's decision-making. Whilst we do not have access to information on the level of discount included in the patient access scheme (PAS) for everolimus, we believe that the AG analysis demonstrates that Lu-177 dotatate is cost-effective for plausible ranges of PAS discounts. We note that recently published NICE Guidance recommends everolimus as routine treatment for patients with gastro-intestinal and pancreatic neuroendocrine tumours.(2) In addition, everolimus has been available for use by UK clinicians for several years. It can therefore be considered to be the alternative routine treatment to Lu-177 dotatate for this group of patients. In making a recommendation, the Committee concluded that "*the cost effectiveness of Lu-177 dotatate compared with everolimus and best supportive care for midgut gastrointestinal NETs and determined that in both cases, the deterministic and probabilistic ICERs were much higher than £30,000 per quality-adjusted life year (QALY) gained."* (ACD, 3.12)(1) In testing the reliability of the model sent by NICE and used to generate the results on which this decision has been made, it is impossible to reconcile the	Comments noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.22 and 3.23 of the final appraisal determination (FAD) for the committee's recommendations.

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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
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commentary provided in the appraisal committee document with the figures shown in the executable model provided by NICE.

At the list price of £17,875 per dose of treatment with Lu-177 dotatate, the total cost of treating a patient as presented in the model is £91,624 and the total QALY's accrued are 6.04. Corresponding figures for best Supportive Care (BSC) and everolimus are presented in the Table 1 below.

Table 1: Summary of AG executable base case results
<table>
<tr><th></th><th>BSC</th><th>Everolimus</th><th>Lu-177 dotatate</th><th>Incremental Lu-177 dotatate vs BSC</th><th>Incremental Lu-177 dotatate vs Everolimus</th></tr>
<tr><td colspan="6">QALYs (discounted)</td></tr>
<tr><td>Pre-progression</td><td>1.1</td><td>1.49</td><td>6.04</td><td>4.94</td><td>4.55</td></tr>
<tr><td>Post-progression</td><td>3.09</td><td>2.88</td><td>0</td><td>-3.09</td><td>-2.88</td></tr>
<tr><td>Total QALYs</td><td>4.19</td><td>4.37</td><td>6.04</td><td>1.85</td><td>1.67</td></tr>
<tr><td colspan="6">Cost (discounted)</td></tr>
<tr><td>Pre-progression</td><td>£4,194</td><td>£34,443</td><td>£88,493</td><td>£84,299</td><td>£54,050</td></tr>
<tr><td>Post-progression</td><td>£16,925</td><td>£17,627</td><td>£3,131</td><td>-£13,794</td><td>-£14,496</td></tr>
<tr><td>Total Costs</td><td>£21,119</td><td>£52,070</td><td>£91,624</td><td>£70,505</td><td>£39,554</td></tr>
<tr><td>ICER</td><td></td><td></td><td></td><td>£38,110</td><td>£23,685</td></tr>
</table>
</td><td></td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			The cost-effectiveness results for a comparison between Lu-177 dotatate versus BSC generates an incremental cost-effectiveness ratio (ICER) of approximately £38,110 per QALY. In a comparison between Lu-177 dotatate versus everolimus, the ICER generated is £23,685 per QALY. As an illustration and to highlight this possible error in the Committee's interpretation of the AG reanalysis we have detailed the AG basecase analysis including an illustrative PAS discount for everolimus. If a hypothetical PAS price discount of 30% is applied to the drug acquisition cost of everolimus, the ICER for a comparison between Lu-177 dotatate and everolimus will increase to £28,222 per QALY. For Lu-177 dotatate to have an ICER above a threshold of £30,000 compared to everolimus taking into account PPS, the PAS for everolimus would need to be at least 69%. This demonstrates that under these conditions, the ICER for Lu-177 dotatate compared to everolimus is within the range usually considered by NICE to be a cost-effective use of NHS resources. The lack of detail in the ACD and supporting information, and absence of a description of the amendments in the AG model, have severely limited our ability to understand the rationale behind the Committee's preliminary decision.	
3	Company	Advanced Accelerator Applications UK Limited	**3. The NICE analysis of overall survival is fundamentally flawed** "*The committee concluded that the evidence showed an improvement in progression-free survival with Lu-177 dotatate compared with everolimus for midgut gastrointestinal NETs, but the overall survival benefit was less clear because of the immaturity of the data*." (ACD, 3.8) We welcome the Committee's recognition that Lu-177 dotatate is effective at improving progression-free survival (PFS) for people with mid-gut NETs; however, we have concerns about the Committee's conclusion regarding the uncertainty in its benefits for overall survival in light of the evidence available. We are extremely concerned that the AG model, noted by the Committee as its basis for its decision-making, fails to reflect any survival gain beyond disease progression for Lu-177 dotatate. As shown in Table 1, the AG analysis assumes	Comments noted. In response to comments provided during consultation, the committee considered the AG's new analyses on progression-free survival and overall survival that incorporated data from the ERASMUS study. These new analyses do not assume that all patients die immediately upon disease progression and uses a lifetime horizon. Please also note that after considering the new analyses, the committee recommended lutetium as a

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			that there is no survival post-progression for patients treated with Lu-177 dotatate; that is, it assumes that all patients treated Lu-177 dotatate would die immediately upon disease progression. **3.1 The assumption that all patients die immediately upon disease progression is clinically implausible** The updated NICE AG model assigns a value of zero (with 100% certainty) to post-progression survival (PPS) in its analysis of Lu-177 dotatate. No rationale for, or account of the Committee discussion of, this is provided within the ACD. This assumption has not been made for any other comparator in the AG analysis, including everolimus and BSC. This assumption is unfair and clinically implausible. **3.2 The assumption that all patients die immediately upon disease progression is perverse in light of the evidence available to the Committee** AAA has submitted evidence on overall survival (OS) from two large studies, one of which appears to have been disregarded by the Committee in its consideration. The evidence submitted in our submission from the pivotal NETTER-1 randomised controlled trial (RCT) and now reanalysed show that of a total of 116 patients randomised to receive Lu-177 dotatate, only 17 had died compared to 31 of the 113 patients randomised to Octreotide LAR (n=87 censored) by the interim data cut-off of June 2015 (p=0.0083, hazard ratio of 0.459 (95% CI: 0.254 – 0.830). Median OS had not yet been reached at the time of the interim analysis; data from an additional year of follow-up are reported below. The final OS analysis will be carried out when 158 deaths have occurred or 5 years after the last subject is randomised. The interim and updated analyses demonstrate that patients randomised to receive treatment with Lu-177 dotatate are clearly living well beyond disease progression. **3.3 Updated data from the NETTER-1 and Erasmus studies further reduces uncertainty around the estimates of overall survival** New data from the NETTER-1 study have become available since our submission	cost-effective use of NHS resources for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.7- 3.9, 3.11, 3.22 and 3.23 of the final appraisal determination (FAD) for the committee's full considerations on the progression-free survival and overall survival analyses and recommendations.

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			was provided to NICE.(4) These data have been considered by the EMA, and form the basis of its conclusion that Lu-177 dotatate is efficacious in the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults. Since the interim OS analysis was submitted to NICE, the median OS in the octreotide LAR arm of the NETTER-1 study has been reached. At an updated data cut-off date of 30 June 2016, the median OS was 27.4 months in the octreotide LAR arm and was not reached in Lu-177 dotatate arm. The updated analysis showed a similar trend to the previous analysis with 28 deaths in the Lu-177 dotatate arm and 43 in the octreotide LAR 60 mg arm (HR of 0.536; 95% CI: 0.333 – 0.864), confirming the trend to a lower risk for an OS event under Lu-177 dotatate compared to Octreotide LAR.(4) The large difference between the median PFS (8.5 months; 95% CI: 5.8 - 9.1) and median OS (27.4 months; 95% CI: 23.1-NE) in the octreotide LAR arm of NETTER-1 demonstrates that the longevity of patients in the NETTER-1 study extends well beyond the estimates of PFS. Although median OS in the Lu-177 dotatate arm of the NETTER-1 study has not been reached, it is reasonable to assume that it will be at least as great as that observed for the octreotide LAR arm, and is likely to be greater. Further details of the updated analysis of the NETTER-1 trial are presented in Section 5 below and in Appendix 1. We were disappointed that the Committee had not considered the data submitted in our submission from the Erasmus study. This study is a large, non-randomised study of patients with GEP-NETs. Data were available from a 1214 patients, and a subset of 811 Dutch patients which form the basis of the evidence included in our submission. These data have been considered by the EMA and have directly informed the marketing authorisation and CHMP positive opinion for Lu-177 dotatate. The PFS for the GEP-NET population observed in the Erasmus study was 28.5 months (95% CI: 24.8 to 31.4) and the median OS was 61.2 (updated analysis; 95%: 54.8 to 67.4). These data provide further evidence of a survival benefit from Lu-177 dotatate survival beyond disease progression. The data from the Erasmus study are presented in more detail in Section 6 below and in Appendix 2. In summary, we consider it perverse for the Committee to assume that there is no	

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			survival beyond disease progression (PPS=0) for patients receiving Lu-177 dotatate as included in the AG economic model used by the Committee to inform their decision-making. We suggest that the Committee reconsiders its assumptions regarding overall and post-progression survival in light of the new data presented. **3.4 The Committee's approach to modelling post-progression survival does not align with recommended practice according to NICE's preferred methods and good practice guidelines** The NICE Guide to Methods of Technology Appraisal recognises that modelling is usually required beyond the clinical trial period, that the uncertainty in the extrapolation should be explored, and uncertainty around parameter estimates should be quantified. The AG model used to inform the Committee's decision has failed to adhere to these recommendations. In its analysis, the AG have assumed an estimate of 0 months PPS, with absolute certainty. *"Modelling is usually required to extrapolate costs and health benefits over an extended time horizon. Assumptions used to extrapolate the impact of treatment over the relevant time horizon should have both external and internal validity and be reported transparently. The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources such as historical cohort data sets or other relevant clinical trials." (NICE Guide to methods of Technology Appraisal, 5.7.7)(3)* *"A third source of uncertainty arises from parameter precision, once the most appropriate sources of information have been identified (that is, the uncertainty around the mean health and cost inputs in the model). Distributions should be assigned to characterise the uncertainty associated with the (precision of) mean parameter values." (NICE Guide to methods of Technology Appraisal, 5.8.7)(3)* To adhere to the recommended NICE methods, a plausible estimate of PPS should have been included in the analysis, and a distribution assigned to the parameter to characterise the uncertainty associated with that mean value.	

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			In addition, the NICE Guide to Methods of Technology Appraisals states, "*A lifetime time horizon is required when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life*." (NICE Guide to the Methods of Technology Appraisal, 5.1.16)(3) The AG analysis of Lu-177 dotatate stops at the time of disease progression, rather than taking a lifetime perspective. Statistically significant differences in PFS, and a clear trend of a difference in OS, have been demonstrated but the latter has not been reflected in their analysis. We recommend that the analysis is revised to properly take account of a lifetime horizon. Furthermore, the approach used by the AG contravenes other guidance on good practice in economic modelling. For example, guidelines on good research practices in modelling from the International Society for Pharmacoeconomic and Outcomes Research explicitly state that it is inappropriate to exclude parameters from analyses due to uncertainty. *"When there is very little information on a parameter, analysts should adopt a conservative approach such that the absence of evidence is reflected in a very broad range of possible estimates. On no account should parameters be excluded from a sensitivity analysis on the grounds that 'there is not enough information from which to estimate uncertainty'" (ISPOR Modeling Good Research Practices, recommendation VI-8).(5)* We also note that Professor Hoyle, Director of the PenTAG Assessment Group and Guarantor of the Assessment Report, has, with colleagues, previously published his own recommendations for the analysis of post-progression survival in the presence of uncertainty. The authors state: *"Therefore, we recommend that the default position is to assume equal mean times post-progression. If there is no a priori biological reason to suppose that the PPS times are likely to differ between treatments (e.g. due to differences in cross-resistance or long term*	

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			toxicities between treatments), our recommendation is that it should be assumed that the mean time in progressive disease is equal between treatment arms if any of the following apply: OS is very immature; treatments post-progression are substantially imbalanced between treatment arms; in particular, treatment switching has occurred at progression; treatments post-progression are different to those routinely given in clinical practice; only single arm trials are available. If none of the above apply, or if there are a priori reasons to suggest that ΔPPS differs from 0, then the recommendation is to model OS and PFS in the traditional way." (Hoyle et al, 2014)(6) As can be seen from the summary of AG executable model basecase results presented in Table 1 above, the PenTAG Assessment Group have taken neither a traditional approach [estimating a mean and characterising the associated uncertainty], nor the conservative approach described of assuming *the same* PPS between treatment arms. Rather they have adopted an extreme and implausible approach of assuming a PPS of 0 months for Lu-177 dotatate and estimates of 3.09 and 2.88 years for everolimus and BSC respectively. **3.5 The ICERs for Lu-177 dotatate are significantly reduced when post-progression survival is properly recognised** We urge NICE to reassess its calculation of the cost-effectiveness of Lu-177 dotatate using methods for the estimation of PPS that are clinical plausible, reflect the available evidence and adhere to good practice guidelines. To give an indication of the impact of this error in the AG model, we have re-estimated the ICERs using the updated AG model using the conservative approach of assuming equivalent PPS in treatment arms (to be further conservative we use the PPS estimates from everolimus in the analysis) as recommended by Hoyle and colleagues (6), that is mean QALYs of 2.88 and mean costs of £17,627 have been assumed. This assumption increases the total QALY's accrued by a patient receiving Lu-177 dotatate to 8.92 and a total cost of £106,120. A full breakdown of the	

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results taking this assumption into consideration are presented in

Table 2.

Table 2: Summary of executable base case results including post progression survival for Lu-177 dotatate

	BSC	Everolimus	Lu-177 dotatate	Incremental Lu-177 dotatate vs BSC	Incremental Lu-177 dotatate vs Everolimus
QALYs (discounted)					
Pre-progression	1.1	1.49	6.04	4.94	4.55
Post-progression	3.09	2.88	**2.88**	-0.21	0
Total QALYs	**4.19**	**4.37**	**8.92**	**4.73**	**4.55**
Cost (discounted)					
Pre-progression	£4,194	£34,443	£88,493	£84,299	£54,050
Post-progression	£16,925	£17,627	**£17,627**	£702	£0
Total Costs	**£21,119**	**£52,070**	**£106,120**	**£85,001**	**£54,050**

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			ICER **£17,970** **£11,879** The cost-effectiveness results of a comparison between Lu-177 dotatate versus BSC generates an ICER of approximately £17,970 per QALY. In a comparison between Lu-177 dotatate versus everolimus, the ICER generated is £11,879 per QALY. If a hypothetical PAS price discount of 30% is applied to the drug acquisition cost of everolimus, the ICER for a comparison between Lu-177 dotatate and everolimus will increase to £13,544 per QALY. Based on the results presented that take post-progression benefits and costs into consideration, Lu-177 dotatate is a cost-effective treatment option for patients when compared to BSC and everolimus.	
4	Company	Advanced Accelerator Applications UK Limited	**4. The AG analysis does not reflect the composition of BSC in UK clinical practice** Best supportive care (BSC) as defined in the analysis performed by the assessment group does not reflect treatment administered in UK clinical practice. The AG approach to BSC is based on the comparator arm of the everolimus RADIANT-4 study and comprises of a combination of lidocaine, dexamethasone, prednisone, prochlorperazine, biofermin, sacchromyces boulardii, external beam radiation therapy and standard dose somastatin analogues (SSAs) (with only 10% of patients receiving SSA as part of their treatment). The comparator arm of the RADIANT-4 study, and the approach used for BSC does not reflect UK clinical practice as corroborated by UK clinical key opinion leaders. Clinicians in the UK have had access to active treatments for many years; as such, BSC as defined by the assessment group and the RADIANT-4 study is rarely considered an option for treating patients in the UK who have progressed on SSAs. The inappropriateness of this approach to BSC for this group of patients was highlighted in our previous comments on the AG's analysis but this has not been taken into consideration.	Comment noted. Please see section 3.13 of the final appraisal determination (FAD) for the committee's full considerations on their preferred definition and analysis of BSC.

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			UK clinical practice is more aligned to the design of the NETTER-1 study. Patients who are at this stage of their disease (progressive) receive an escalated dose of SSA (between octreotide 30 to octreotide 60mg). The population considered in this appraisal are patients whose disease has progressed and will therefore receive an escalated dose of octreotide (either in the form of increased frequency or increased dosage). This was confirmed at the NICE Appraisal Committee by NICE's clinical expert who confirmed that upon disease progression patients are frequently treated by increasing dosage of SSAs or, for patients suitable, liver embolization. A recent study evaluated the benefits of octreotide LAR dose escalation in a retrospective evaluation of medical records of patients with NETs. The authors concluded that goal of improved symptom control is a common reason for dose escalation of octreotide LAR, and that escalation to above the standard dose of octreotide LAR of 30 mg every 4 weeks may result in improved symptom control.(7) Furthermore, a recent systematic review has identified that higher octreotide LAR doses are being prescribed for symptom and tumour control in NET patients.(8) Based on the incorrect assumption surrounding BSC made by the AG, the BSC drug acquisition cost per cycle of treatment used in the model is approximately £35.50. This cost greatly underestimates the true cost of BSC for these patients to the NHS. As stated previously, we would expect patients at this stage of their disease to receive a SSA dose ranging from between 30mg (single dose) to 60mg (double dose). The cost per cycle of treatment with a single of SSA as presented in the AG model is £806.42. This means the true cost of BSC to the NHS for these patients is between £806.42 (for a single dose) and £1,612.84 for a double dose of treatment. We encourage NICE to revisit their analysis of BSC as it currently does not reflect NHS resources spent on BSC for this group of patients and significantly underestimates the true cost-effectiveness of Lu-177 dotatate when compared to BSC.	

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5	Company	Advanced Accelerator Applications UK Limited	**5. NICE has failed to consider data underpinning the marketing authorisation for Lu-177 dotatate from the Erasmus study** Data submitted to NICE in our submission from the large non-controlled open-label ERASMUS study that have now been published (9), appear to have been disregarded by the Committee and no rationale has been provided for this in the ACD or accompanying documentation. These data demonstrated the effectiveness of Lu-177 dotatate in the treatment of different somatostatin receptor positive tumour types. Data from the Erasmus study form part of the core clinical evidence supporting the marketing authorisation for Lu-177 dotatate for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults and are included in the Summary of Product Characteristics. The Erasmus study was an investigator sponsored, phase I–II non-randomised single-arm study to evaluate the efficacy of Lu-177 dotatate in patients with SSTR positive histologically confirmed NETs (the majority GEP-NET), conducted at the Erasmus Medical Centre (Erasmus MC), Rotterdam, The Netherlands. This was a prospective trial retrospectively analysed. Due to early suggestion of significant clinical benefit of Lu-177 dotatate in terms of prolonged survival, patients were referred from all over the world to the Erasmus MC for treatment with Lu-177 dotatate, resulting in 67% of enrolled patients being from The Netherlands. The Dutch population (n=811) was considered the main population of relevance supporting the licence application to EMA and is reported here and in our original submission, because of the very limited loss in follow-up in this subgroup. The patient population enrolled was heterogeneous, including various SSTR-positive types. The majority consisted of NETs and most of them GEP-NET, including foregut, midgut and hindgut carcinoids of the digestive tract, the bronchus, and all types of P-NETs. Patients eligible for enrolment were treated with four intravenous administrations of 200 mCi (7.4 GBq) at 6 − 13 week intervals. The mean follow-up was 34.8 months (SD 26.7) for the Dutch population.	Comments noted. After considering the comments received in response to the appraisal consultation document, the committee fully reconsidered the data from ERASMUS study. The recommendation made in the Final Appraisal Determination (FAD, Section 1.1) is made in respect of the full evidence base.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Further details of the Erasmus study are reported in Section 4.11 of our submission. The updated data from ERASMUS has been provided in a separate document. The Erasmus study provides supporting evidence that treatment with Lu-177 dotatate offers a meaningful therapeutic benefit to GEP-NET patients, in terms of safety, tumour response, survival and QoL. This data also underpins the marketing authorisation for Lu-177 dotatate.	
6	Company	Advanced Accelerator Applications UK Limited	**6. NICE has acted unfairly in its appraisal of Lu-177 dotatate** AAA have been severely hampered in their ability to fully engage with the NICE appraisal in several ways, detailed below. In addition, we consider that the AG analysis which has formed the basis of the NICE provisional recommendations includes fundamental errors and has not followed the NICE guidelines for technology appraisal. We urge the NICE to review and amend these issues as a matter of urgency. **6.1 Lack of clarity in AG model and ACD** NICE provided AAA with the AG executable model (AG model 1) and AR prior to the Appraisal Committee Meeting. In response, we provided a detailed description of our serious concerns with the analysis in our letter to the Committee. On review of AG model 2, we noted that significant amendments had been made to the AG analysis compared to model 1. Details of the amendments made to the model were not provided, other than an addendum to the AR describing the changes made to the analysis of everolimus. One key amendment, the removal of all post-progression survival from the analysis of Lu-177 dotatate, was not described in the documentation and no clear rationale was provided. Given the significance of this amendment and our serious concerns about this approach, we have been unable to understand the basis for this amendment and have been unable to respond to the rationale for this change.	In light of the comments on the appraisal consultation document, the second appraisal committee meeting was delayed to allow the company and the assessment group sufficient time to revise their analyses based on additional data from the company. The committee have fully considered the additional evidence and revised analyses and have now recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults.

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			Furthermore, there are major discrepancies between the ACD and the AG model that have not been explained in the documentation. As noted in Section 2 of this response, there a significant difference in the ICERs included in the AG model 2 and those referred to in the ACD. The ACD clearly states that the AG model was used as its basis for decision-making. AG model 2 demonstrates that Lu-177 dotatate is a cost-effective use of NHS resources at the standard NICE threshold range when compared with the recently approved treatment, everolimus; however, the ACD statement is to the contrary. This lack of clarity has severely hindered our ability to respond to the recommendations in the ACD as it is unclear what evidence they are based upon. In addition, the recently implemented new format of the ACD, which excludes the description of the evidence considered by the Committee, has resulted in very little information being provided on the sections of the evidence base considered by the Appraisal Committee leading to a lack of transparency. **6.2 AG model provided very late in process** We would also like to note that the executable AG model 2 was provided late into the ACD consultation period to provide a thorough analysis. We requested the model from NICE upon receipt of the ACD 27th July 2017 and received this on 2nd August 2017. This hindered our ability to review the model, particularly given the lack of clarity about the amendments made to the model. **6.3 NICE has failed to consider important evidence submitted to support the therapeutic benefits of Lu-177 dotatate** Important evidence on the efficacy of Lu-177 dotatate have not been considered by NICE with no justification provided. Data from the large non-randomised trial, Erasmus, were provided to NICE in our MS but do not appear to have been reviewed by the Committee. These data formed part of the core clinical evidence supporting the marketing authorisation for Lu-177 dotatate and demonstrate its effectiveness across a range of GEP-NET tumour types. No rationale for this has been provided, and, as described in Section 1 of this document, the exclusion of these data is not compatible with the NICE Guide to Methods of Technology Appraisal, and are inconsistent with the approach taken in previous NICE appraisals. **6.4 The AG analysis is not consistent with recommended NICE methods and is**	

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			perverse The analysis of Lu-177 dotatate included in the AR was relegated to a scenario analysis and did not fully evaluate the cost-effectiveness of Lu-177 dotatate. The NICE Guide to the Methods of Technology Appraisal describes methods that AGs and companies should follow for their economic evaluations. Several of the recommendations were not followed by the PeNTAG in its analysis of the cost-effectiveness of Lu-177 dotatate. Details of these, and the relevant sections of the NICE Guide to Methods of Technology Appraisal, are noted below. "*Full documentation and justification of structural assumptions and data inputs should be provided. When there are alternative plausible assumptions and inputs, sensitivity analyses of their effects on model outputs should be undertaken."* (5.7.1) (3) Full details of the structural assumptions underpinning AG model 2 have not been provided. Despite the availability of alternative plausible assumptions (for example, PPS is greater than zero for patients treated with Lu-177 dotatate), sensitivity analysis on these have not been performed. Furthermore, as described in Section 2 of this document, we believe that the approach to the analysis of PPS in the AG analysis is perverse in light of the evidence provided and clinical plausibility. It contravenes NICE's recommended methods for modelling an appropriate time horizon and dealing with uncertainty. It also contravenes good practice guidelines and the published recommendations of a senior author of the PenTAG report. "*For a lifetime time horizon, it is often necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty. When the impact of treatment beyond the results of the clinical trials is estimated, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects using different statistical models are desirable (see section 5.7 on modelling). These should include assuming that the treatment does not provide further benefit beyond the treatment period as well as more optimistic assumptions. Analyses that limit the time horizon to periods shorter than the expected impact of treatment do not usually provide the best*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			estimates of benefits and costs." (5.1.16) (3) The AG have not explored alternative assumptions about survival, and have not tested alternative statistical models for extrapolating the survival. They have applied an exponential model to the survival, which we believe is inappropriate. We note that in their analysis of data for everolimus and sunitinib, a range of alternative statistical models were explored by the AG. It is unclear why a similar approach was not also undertaken for Lu-177 dotatate. *"It is important for the model to quantify the decision uncertainty associated with a technology (that is, the probability that a different decision would be reached if the true cost effectiveness of each technology could be ascertained before making the decision)."* (5.8.1) (3) The AG has not performed adequate sensitivity analyses on the cost-effectiveness of Lu-177 dotatate. No probabilistic sensitivity analysis has been performed.	
1	Patient expert	Mark Zwanziger	As a patient who has is because of PRRT (Y90-2011 & Lu177-2015), This negative appraisal of Lu-177 Dotatate is a major setback to the patient community that sees PRRT as their only treatment when the disease is progressing. To shelf this discussion for 3 years as stated in para 4.1 is a harsh penalty for patients needing the treatment.	Comments noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.22 and 3.23 of the final appraisal determination

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				(FAD) for the committee's recommendations.
2	Patient expert	Mark Zwanziger	I'm concerned that the appraisal was confused on the scope from the start, including Lanreotide at first, and then it didn't. Then, we waited for the EUMA statement of human use even though this drug was already in orphan status. It seemed to me that the scope was either too big or not defined enough for the PENTAG report. Over 585 pages of graphs that really never defined what ICER we should all be working off. This appraisal also covered several very different patient groups, with the main 3 being: 1-Pancreate NETS, 2-Mid&High Grade NETS, and 3 low grade NETS. Everolimus was recommended for 1 & 2, but not 3. Lu177 was presented as the only option for low grade. Sunitib for pancreatic.	Comment noted. The scope of this technology appraisal was considered to be appropriate by consultees. In line with the remit of the appraisal, the appraisal committee appraised the treatments according to their respective marketing authorisations.
3	Patient expert	Mark Zwanziger	I don't completely understand marketing authorization process or patents, but would like to see NHS consultants have "PRRT" or "Radio-labelled Somatostatin" in their arsenal. NETTER-1 from a patient view was also a huge scope. Why didn't it compare Lu-177 to Y-90. Y-90 has been the gold standard for almost 20 years in Europe. Comparing Lu-177 to Lanreotide or Everolimus seems a mistake, as Lu-177 is given in addition. (Part of what makes the ICER so confusing)	Comments noted. Please note that the committee has now recommended lutetium for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, section 1.1). Section 6.2.2 of the NICE Methods Guide indicates that when selecting the most appropriate comparator(s), the Committee consider: • established NHS practice in England • the natural history of the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator. Please see sections 3.2 and 3.3 for the committee's full considerations on appropriate comparators for lutetium.
4	Patient expert	Mark Zwanziger	I'm concerned that there was no technical expert at the appraisal that had administered PRRT. The two technical experts were excellent, but we could have used a PRRT expert. The UK is a leader in the world of treating NETS, and their work is published. I'd really recommend readdressing with someone like Professor Caplin.	Comment noted. All experts selected are from nominations provided by consultees and commentators.
5	Patient expert	Mark Zwanziger	It is very concerning that a negative decision references a ICER, but then doesn't list due to confidential pricing. The cost model seems extremely complicated. The ICERS in the PenTAG report ranged from under £10K by AAA, £24K-£40K by PenTAG, and my guess of £35K. The patients can understand denial if the ICER is over £30K, but not if the results are off ambiguous numbers.	Comments noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.22 and 3.23 of the final appraisal determination (FAD) for the committee's recommendations.
6	Patient	Mark	I'm concerned when the report cites "median overall survival was not reached"	Comments noted. After

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	expert	Zwanziger	para 3.3. The extremely high QALY of this treatment is amazing, and survival stats might not be "reached" or complete (because the patients are still alive). I was told early in my PRRT journey "trials should be quicker now, because we know what happens when you do nothing". I didn't see this data included in the PenTAG report.	considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults. Please see sections 1, 3.22 and 3.23 of the final appraisal determination (FAD) for the committee's recommendations.

Summary of comments received from members of the public

Theme	NICE Response
Disappointed not recommended as it was removed from CDF due to lack of data – that is now available through NETTER-1	Comments noted. The committee recognised the need for effective treatment for NET (FAD, section 3.1). After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, sections 1, 3.22 and 3.23)
177-Lu dotatate has become standard of care, superior to SSA's (which have low response rate) after progression	Comments noted. The committee recognised the need for effective treatment for NET (FAD, section 3.1). After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, sections 1, 3.22 and 3.23)
It is very important that this is funded for Small bowel NET since there are few other therapies. Clinical experience suggests that this	Comments noted. The committee recognised the need for effective treatment for NET (FAD, section 3.1). After considering the new analyses from the company, the

therapy is useful for pancreatic net also, hence ideally the approval would include all the licensed indications.	committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, sections 1, 3.22 and 3.23)
Likely to be effective in other NET subgroups, evidence base may not be robust enough	Comments noted. The committee recognised the need for effective treatment for NET (FAD, section 3.1). After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, sections 1, 3.22 and 3.23)
PFS benefit seen in NETTER-1 – rarely seen in oncology	Comment noted. The committee concluded that lutetium was clinically effective for people with mid-gut gastrointestinal NETs when compared with octreotide 60mg (FAD, section 3.5).
Median OS survival not reached – can be seen as positive, shows people are not dying	Comment noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, sections 1, 3.22 and 3.23).
Use of octreotide as comparator is correct – dosage	Comment noted. Octreotide as a comparator has been considered by the committee. Please see sections 3.5 and 3.13 of the final appraisal determination (FAD) for the committee's full considerations on the use of high-dose octreotide.
NETTER-1/RADIANT-4 comparison not appropriate, heterogeneous studies	Comment noted. As discussed in section 3.7 of the final appraisal determination (FAD), the committee noted that there were important differences between NETTER-1 and RADIANT-4 and therefore agreed that it would not consider the network meta-analysis with this comparison.
UK leading country within ENETS with 10 European Centres of Excellence - without 177-Lu dotatate (standard in Europe) status of UK centres affected	Comment noted. After considering the new analyses from the company, the committee recommended lutetium within its marketing authorisation, as an option for treating unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (NETs) in adults (FAD, sections 1, 3.22 and 3.23).

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24th August 2017

Dear Kate

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-dotatate [ID1224]

Thank you for the opportunity to respond the Appraisal Consultation Document (ACD). We have reviewed the documentation and have some concerns about the provisional recommendations in light of the data presented in our submission to NICE.

Please see summary responses to the questions included in the ACD. Full details of our responses are provided in the document accompanying this letter.

1. *Has all of the relevant evidence been taken into account?*

All the relevant evidence supporting the effectiveness and cost-effectiveness of Lu-177 dotatate has not been taken into account.

We submitted detailed information from a large non-randomised study (Erasmus) of Lu-177 dotatate within our submission. These important data formed part of the core clinical evidence considered by the EMA when issuing the marketing authorization for Lu-177 dotatate. The data have not been taken into account by the Appraisal Committee and insufficient information has been provided in the ACD on the rationale for excluding these data from the Committee's considerations. These data demonstrate the efficacy of Lu-177 in treating patients with progressive GEP-NETs; favourable results were shown in progression-free survival (PFS), time to disease progression and overall survival (OS).

Updated data are now available from the Erasmus and NETTER-1 studies, at the efficacy cut-off date of 24 July 2015 (date when the required number of primary end-point events

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was reached), and other analyses have been run using a more recent cut-off date (30 June 2016), as agreed with the Agencies. The updated data is provided in a separate document for your consideration.

In addition, we are unclear why the evidence from the clinical experts provided during the Committee meeting has not been taken into consideration. The experts stated that they expect the efficacy of Lu-177 dotatate to be comparable across tumour sites; however this appears to have not been taken into consideration by the Committee in their decision to focus the guidance only on patients with midgut NETs rather than the broader GEP-NET population. In addition, we note that one of NICE's clinical experts gave verbal evidence at the Committee meeting that part of standard clinical practice in the UK for the treatment of patients with progressive GEP-NETs includes increasing the dose (or frequency of administration) of somastatin analogues (SSAs). This part of the pathway of care for this group of patients has not been reflected in the analyses underpinning the Committee's provisional recommendations.

2. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*

The summaries of clinical and cost-effectiveness are not reasonable interpretations of the evidence.

We are concerned that the Committee has misunderstood standard clinical practice in the treatment of patients with progressive GEP-NETs in the UK. The Committee have relied on the comparator arm of the RADIANT-4 study as their interpretation of Best Supportive Care (BSC) in the UK, and in the economic analysis underpinning the Committee's judgement of the cost-effectiveness of Lu-177 dotatate. As reported in our submission, and in the detailed response attached, it is standard clinical practice in the UK to consider increasing the dose or the frequency of the administration of SSAs upon disease progression, which we believe is best represented by the design of the control arm in the NETTER-1 study.

We have significant concerns about the Committee's interpretation of the cost-effectiveness evidence. The revised Assessment Group model appears to contradict the statement included in the ACD that the incremental cost-effectiveness ratios (ICERs) for Lu-177 dotatate are well above the standard threshold range considered acceptable by NICE of £20,000 to £30,000 per additional QALY gained. In fact, the model provided to AAA demonstrates that the ICERs for Lu-177 dotatate are well within the standard threshold range when compared to everolimus, which has recently been approved by NICE and can be considered a standard of care for the treatment of this group of patients.

In addition, we consider there to be serious flaws in the Assessment Group's model which substantially overestimate the ICERs for Lu-177 dotatate. The approach to modelling post-progression survival assumes that all patients treated with Lu-177 dotatate die immediately upon disease progression. This approach has not been used for any of the other comparators in the analysis and therefore biases against Lu-177 dotatate. The assumption is clinically implausible and perverse in light of the evidence submitted to the Committee demonstrating favourable survival post-disease progression. The approach also contravenes recommendation on good practice in economic modelling, including NICE's own recommendations, those of international societies (e.g. ISPOR) and recommendations published by the senior author of the Assessment Group's report, Professor Martin Hoyle. We also note that the approach to modelling the costs of BSC do not reflect standard UK

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clinical practice because it ignores the practice of increasing SSA dosage for some patients whose disease has progressed as noted above.

3. *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?*

The provisional recommendations are not a sound and suitable basis for guidance to the NHS for the reasons noted above, and detailed in our accompanying response document. As outlined in our response, Lu-177 dotatate is an effective and cost-effective treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults.

Please note that the International Nonproprietary Name has now been confirmed as lutetium (177Lu) oxodotreotide.

Thank you for your consideration. We look forward to discussing these issues with you further at the next Appraisal Committee meeting.

Best regards

[redacted]

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Response to the NICE ACD for Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-dotatate [ID1224]

Advanced Accelerator Applications UK Limited

24th August 2017

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1. NICE has failed to consider the full marketing authorisation for Lu-177 dotatate

The Committee has issued draft guidance for only one subgroup of patients, midgut vs the broader gastroenteropancreatic neuroendocrine tumour (GEP-NET) population approved in the CHMP positive opinion and which form the basis for the marketing authorisation for Lu-177 dotatate. The Committee has not provided any justification for this despite the opinion of the clinical experts as stated in the ACD.

> *"The clinical experts explained that in their experience, they do not expect much difference in the efficacy of Lu-177 dotatate across the different tumour sites. The committee acknowledged that Lu-177 dotatate may be equally effective across different tumour sites, but concluded that its recommendations should be guided by evidence from the clinical trial that underpins the marketing authorisation."* (ACD, 3.4) (1)

We would like to highlight that Lu-177 dotatate has previously been available for the treatment of patients with GEP-NETs through the Cancer Drugs Fund until just prior to the reorganisation of the fund. This decision was upheld despite an appeal by the NET Patient Foundation. We are aware that removal of Lu-177 dotatate from the fund has restricted patient access to this effective treatment, and this has been distressing for patients with GEP-NETs. The focus of the Committee only on patients with midgut NETs for this appraisal will lead to continued uncertainty for a significant proportion of the GEP-NET patient population.

We detailed the results of the large single arm trial of Lu-177 dotatate (Erasmus) in our submission to NICE. This study provides significant evidence on the therapeutic benefits of Lu-177 dotatate for the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NET) patients. It formed a core part of the submission to regulatory authorities who accepted the results as providing evidence of benefit in the GEP-NET population.

As the Committee heard from their clinical experts at the Committee Meeting, given the mechanism of action of Lu-177 dotatate, its efficacy is expected to be similar across the different tumour sites. The study population of patients with midgut carcinoid tumours recruited to the NETTER-1 study was selected as these NETs are broadly representative of the GEP-NET population: they are the most common type of GEP-NETs, are frequently metastatic and progressive at diagnosis (like most GEP-NETs), and have features similar to other GEP-NETs (common cell type origin, SSTR overexpression and high receptor mediated uptake of Lu-177 dotatate). Furthermore, because GEP-NET is an orphan disease and subpopulations are too small to conduct controlled trials, the midgut carcinoid tumour population was selected to reduce study heterogeneity, reduce potential bias and increase internal and external validity.

We further note that the Committee concluded that it was inappropriate to distinguish between tumour sites when formulating its recommendations for the gastro-intestinal NET population in its appraisal of everolimus, despite data being available for the midgut subgroup.(2)

Whilst we note that NICE has a preference for data from RCTs, we also note that NICE routinely considers data from non-randomised studies. This is recognised in the NICE Guide to the Methods of Technology Appraisal as cited below.

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"*RCTs directly comparing the technology under appraisal with relevant comparators provide the most valid evidence of relative efficacy. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised studies may be required to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented*." (NICE Guide to the Methods of Technology Appraisal, 5.2.3) (3)

We also note that NICE has previously evaluated and recommended technologies on the basis on non-randomised data. A few recent examples are:

- Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (TA451)
- Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (TA446)
- Bosutinib for previously treated chronic myeloid leukaemia (TA401)

The NICE Decision Support Unit (DSU) Document has published guidance on the use of non-randomised data to inform estimates of treatment effect. It is unclear why this guidance has not been followed by the Assessment Group. The DSU authors also conducted a review of 110 NICE technology appraisals and identified 16 appraisals that had used non-randomised data to inform estimates of treatment effect. {R Faria, 2015 #11}

It is therefore unclear why NICE has failed to consider a significant part of the evidence underpinning the marketing authorisation in this instance and why they have disregarded the testimonies of their clinical experts on this specific issue. We encourage NICE to give a thorough consideration of the important data from the Erasmus study and the opinions of the clinical experts.

2. Lu-177 dotatate is a cost-effective use of NHS resources

We thank NICE for forwarding the updated Assessment Group (AG) model used by the Committee to inform the development of the ACD. We have significant concerns about fundamental errors that bias against Lu-177 dotatate in the AG reanalysis and the lack of transparency in the amendments made (detailed below). However, even with these biases, we believe that the updated model demonstrates that Lu-177 dotatate is a cost-effective use of NHS resources at NICE standard threshold ranges of £20,000 to £30,000 when compared with everolimus.

We note that the ACD states the following "*The assessment group's base-case results, which were used in the committee's decision-making, include the confidential patient access scheme discount for everolimus*." (ACD, 3.11).(1) We acknowledge the confirmation that the basecase analysis of the AG updated model formed the basis of the Committee's decision-making. Whilst we do not have access to information on the level of discount included in the patient access scheme (PAS) for everolimus, we believe that the AG analysis demonstrates that Lu-177 dotatate is cost-effective for plausible ranges of PAS discounts.

We note that recently published NICE Guidance recommends everolimus as routine treatment for patients with gastro-intestinal and pancreatic neuroendocrine tumours.(2) In

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addition, everolimus has been available for use by UK clinicians for several years. It can therefore be considered to be the alternative routine treatment to Lu-177 dotatate for this group of patients.

In making a recommendation, the Committee concluded that "*the cost effectiveness of Lu-177 dotatate compared with everolimus and best supportive care for midgut gastrointestinal NETs and determined that in both cases, the deterministic and probabilistic ICERs were much higher than £30,000 per quality-adjusted life year (QALY) gained.*" (ACD, 3.12)(1)

In testing the reliability of the model sent by NICE and used to generate the results on which this decision has been made, it is impossible to reconcile the commentary provided in the appraisal committee document with the figures shown in the executable model provided by NICE.

At the list price of £17,875 per dose of treatment with Lu-177 dotatate, the total cost of treating a patient as presented in the model is £91,624 and the total QALY's accrued are 6.04. Corresponding figures for best Supportive Care (BSC) and everolimus are presented in the Table 1 below.

Table 1: Summary of AG executable base case results

	BSC	Everolimus	Lu-177 dotatate	Incremental Lu-177 dotatate vs BSC	Incremental Lu-177 dotatate vs Everolimus
		QALYs (discounted)			
Pre-progression	1.1	1.49	6.04	4.94	4.55
Post-progression	3.09	2.88	0	-3.09	-2.88
Total QALYs	**4.19**	**4.37**	**6.04**	**1.85**	**1.67**
		Cost (discounted)			
Pre-progression	£4,194	£34,443	£88,493	£84,299	£54,050
Post-progression	£16,925	£17,627	£3,131	-£13,794	-£14,496
Total Costs	£21,119	£52,070	£91,624	£70,505	£39,554
ICER				**£38,110**	**£23,685**

The cost-effectiveness results for a comparison between Lu-177 dotatate versus BSC generates an incremental cost-effectiveness ratio (ICER) of approximately £38,110 per QALY. In a comparison between Lu-177 dotatate versus everolimus, the ICER generated is £23,685 per QALY.

As an illustration and to highlight this possible error in the Committee's interpretation of the AG reanalysis we have detailed the AG basecase analysis including an illustrative PAS

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discount for everolimus. If a hypothetical PAS price discount of 30% is applied to the drug acquisition cost of everolimus, the ICER for a comparison between Lu-177 dotatate and everolimus will increase to £28,222 per QALY. For Lu-177 dotatate to have an ICER above a threshold of £30,000 compared to everolimus taking into account PPS, the PAS for everolimus would need to be at least 69%. This demonstrates that under these conditions, the ICER for Lu-177 dotatate compared to everolimus is within the range usually considered by NICE to be a cost-effective use of NHS resources.

The lack of detail in the ACD and supporting information, and absence of a description of the amendments in the AG model, have severely limited our ability to understand the rationale behind the Committee's preliminary decision.

3. The NICE analysis of overall survival is fundamentally flawed

> "*The committee concluded that the evidence showed an improvement in progression-free survival with Lu-177 dotatate compared with everolimus for midgut gastrointestinal NETs, but the overall survival benefit was less clear because of the immaturity of the data*." (ACD, 3.8)

We welcome the Committee's recognition that Lu-177 dotatate is effective at improving progression-free survival (PFS) for people with mid-gut NETs; however, we have concerns about the Committee's conclusion regarding the uncertainty in its benefits for overall survival in light of the evidence available. We are extremely concerned that the AG model, noted by the Committee as its basis for its decision-making, fails to reflect any survival gain beyond disease progression for Lu-177 dotatate. As shown in Table 1, the AG analysis assumes that there is no survival post-progression for patients treated with Lu-177 dotatate; that is, it assumes that all patients treated Lu-177 dotatate would die immediately upon disease progression.

3.1 The assumption that all patients die immediately upon disease progression is clinically implausible

The updated NICE AG model assigns a value of zero (with 100% certainty) to post-progression survival (PPS) in its analysis of Lu-177 dotatate. No rationale for, or account of the Committee discussion of, this is provided within the ACD. This assumption has not been made for any other comparator in the AG analysis, including everolimus and BSC.

This assumption is unfair and clinically implausible.

3.2 The assumption that all patients die immediately upon disease progression is perverse in light of the evidence available to the Committee

AAA has submitted evidence on overall survival (OS) from two large studies, one of which appears to have been disregarded by the Committee in its consideration.

The evidence submitted in our submission from the pivotal NETTER-1 randomised controlled trial (RCT) and now reanalysed show that of a total of 116 patients randomised to receive Lu-177 dotatate, only 17 had died compared to 31 of the 113 patients randomised to Octreotide LAR (n=87 censored) by the interim data cut-off of June 2015 (p=0.0083, hazard ratio of 0.459 (95% CI: 0.254 – 0.830). Median OS had not yet been reached at the time of the interim analysis; data from an additional year of follow-up are reported below.

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The final OS analysis will be carried out when 158 deaths have occurred or 5 years after the last subject is randomised.

The interim and updated analyses demonstrate that patients randomised to receive treatment with Lu-177 dotatate are clearly living well beyond disease progression.

3.3 Updated data from the NETTER-1 and Erasmus studies further reduces uncertainty around the estimates of overall survival

New data from the NETTER-1 study have become available since our submission was provided to NICE.(4) These data have been considered by the EMA, and form the basis of its conclusion that Lu-177 dotatate is efficacious in the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults.

Since the interim OS analysis was submitted to NICE, the median OS in the octreotide LAR arm of the NETTER-1 study has been reached. At an updated data cut-off date of 30 June 2016, the median OS was 27.4 months in the octreotide LAR arm and was not reached in Lu-177 dotatate arm. The updated analysis showed a similar trend to the previous analysis with 28 deaths in the Lu-177 dotatate arm and 43 in the octreotide LAR 60 mg arm (HR of 0.536; 95% CI: 0.333 – 0.864), confirming the trend to a lower risk for an OS event under Lu-177 dotatate compared to Octreotide LAR.(4)

The large difference between the median PFS (8.5 months; 95% CI: 5.8 - 9.1) and median OS (27.4 months; 95% CI: 23.1-NE) in the octreotide LAR arm of NETTER-1 demonstrates that the longevity of patients in the NETTER-1 study extends well beyond the estimates of PFS. Although median OS in the Lu-177 dotatate arm of the NETTER-1 study has not been reached, it is reasonable to assume that it will be at least as great as that observed for the octreotide LAR arm, and is likely to be greater. Further details of the updated analysis of the NETTER-1 trial are presented in Section 5 below and in Appendix 1.

We were disappointed that the Committee had not considered the data submitted in our submission from the Erasmus study. This study is a large, non-randomised study of patients with GEP-NETs. Data were available from a 1214 patients, and a subset of 811 Dutch patients which form the basis of the evidence included in our submission. These data have been considered by the EMA and have directly informed the marketing authorisation and CHMP positive opinion for Lu-177 dotatate. The PFS for the GEP-NET population observed in the Erasmus study was 28.5 months (95% CI: 24.8 to 31.4) and the median OS was 61.2 (updated analysis; 95%: 54.8 to 67.4). These data provide further evidence of a survival benefit from Lu-177 dotatate survival beyond disease progression. The data from the Erasmus study are presented in more detail in Section 6 below and in Appendix 2.

In summary, we consider it perverse for the Committee to assume that there is no survival beyond disease progression (PPS=0) for patients receiving Lu-177 dotatate as included in the AG economic model used by the Committee to inform their decision-making.

We suggest that the Committee reconsiders its assumptions regarding overall and post-progression survival in light of the new data presented.

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3.4 The Committee's approach to modelling post-progression survival does not align with recommended practice according to NICE's preferred methods and good practice guidelines

The NICE Guide to Methods of Technology Appraisal recognises that modelling is usually required beyond the clinical trial period, that the uncertainty in the extrapolation should be explored, and uncertainty around parameter estimates should be quantified. The AG model used to inform the Committee's decision has failed to adhere to these recommendations. In its analysis, the AG have assumed an estimate of 0 months PPS, with absolute certainty.

> *"Modelling is usually required to extrapolate costs and health benefits over an extended time horizon. Assumptions used to extrapolate the impact of treatment over the relevant time horizon should have both external and internal validity and be reported transparently. The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources such as historical cohort data sets or other relevant clinical trials." (NICE Guide to methods of Technology Appraisal, 5.7.7)(3)*

> *"A third source of uncertainty arises from parameter precision, once the most appropriate sources of information have been identified (that is, the uncertainty around the mean health and cost inputs in the model). Distributions should be assigned to characterise the uncertainty associated with the (precision of) mean parameter values." (NICE Guide to methods of Technology Appraisal, 5.8.7)(3)*

To adhere to the recommended NICE methods, a plausible estimate of PPS should have been included in the analysis, and a distribution assigned to the parameter to characterise the uncertainty associated with that mean value.

In addition, the NICE Guide to Methods of Technology Appraisals states,

> "*A lifetime time horizon is required when alternative technologies lead to differences in survival or benefits that persist for the remainder of a person's life*." (NICE Guide to the Methods of Technology Appraisal, 5.1.16)(3)

The AG analysis of Lu-177 dotatate stops at the time of disease progression, rather than taking a lifetime perspective. Statistically significant differences in PFS, and a clear trend of a difference in OS, have been demonstrated but the latter has not been reflected in their analysis. We recommend that the analysis is revised to properly take account of a lifetime horizon.

Furthermore, the approach used by the AG contravenes other guidance on good practice in economic modelling. For example, guidelines on good research practices in modelling from the International Society for Pharmacoeconomic and Outcomes Research explicitly state that it is inappropriate to exclude parameters from analyses due to uncertainty.

> *"When there is very little information on a parameter, analysts should adopt a conservative approach such that the absence of evidence is reflected in a very broad range of possible estimates. On no account should parameters be excluded from a sensitivity analysis on the grounds that 'there is not enough information from which to estimate uncertainty'" (ISPOR Modeling Good Research Practices, recommendation VI-8).(5)*

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We also note that Professor Hoyle, Director of the PenTAG Assessment Group and Guarantor of the Assessment Report, has, with colleagues, previously published his own recommendations for the analysis of post-progression survival in the presence of uncertainty. The authors state:

> *"Therefore, we recommend that the default position is to assume equal mean times post-progression. If there is no a priori biological reason to suppose that the PPS times are likely to differ between treatments (e.g. due to differences in cross-resistance or long term toxicities between treatments), our recommendation is that it should be assumed that the mean time in progressive disease is equal between treatment arms if any of the following apply: OS is very immature; treatments post-progression are substantially imbalanced between treatment arms; in particular, treatment switching has occurred at progression; treatments post-progression are different to those routinely given in clinical practice; only single arm trials are available. If none of the above apply, or if there are a priori reasons to suggest that ΔPPS differs from 0, then the recommendation is to model OS and PFS in the traditional way." (Hoyle et al, 2014)(6)*

As can be seen from the summary of AG executable model basecase results presented in Table 1 above, the PenTAG Assessment Group have taken neither a traditional approach [estimating a mean and characterising the associated uncertainty], nor the conservative approach described of assuming *the same* PPS between treatment arms. Rather they have adopted an extreme and implausible approach of assuming a PPS of 0 months for Lu-177 dotatate and estimates of 3.09 and 2.88 years for everolimus and BSC respectively.

3.5 The ICERs for Lu-177 dotatate are significantly reduced when post-progression survival is properly recognised

We urge NICE to reassess its calculation of the cost-effectiveness of Lu-177 dotatate using methods for the estimation of PPS that are clinical plausible, reflect the available evidence and adhere to good practice guidelines.

To give an indication of the impact of this error in the AG model, we have re-estimated the ICERs using the updated AG model using the conservative approach of assuming equivalent PPS in treatment arms (to be further conservative we use the PPS estimates from everolimus in the analysis) as recommended by Hoyle and colleagues (6), that is mean QALYs of 2.88 and mean costs of £17,627 have been assumed. This assumption increases the total QALY's accrued by a patient receiving Lu-177 dotatate to 8.92 and a total cost of £106,120. A full breakdown of the results taking this assumption into consideration are presented in

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Table 2.

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Table 2: Summary of executable base case results including post progression survival for Lu-177 dotatate

	BSC	Everolimus	Lu-177 dotatate	Incremental Lu-177 dotatate vs BSC	Incremental Lu-177 dotatate vs Everolimus
		QALYs (discounted)			
Pre-progression	1.1	1.49	6.04	4.94	4.55
Post-progression	3.09	2.88	**2.88**	-0.21	0
Total QALYs	**4.19**	**4.37**	**8.92**	**4.73**	**4.55**
		Cost (discounted)			
Pre-progression	£4,194	£34,443	£88,493	£84,299	£54,050
Post-progression	£16,925	£17,627	**£17,627**	£702	£0
Total Costs	**£21,119**	**£52,070**	**£106,120**	**£85,001**	**£54,050**
ICER				**£17,970**	**£11,879**

The cost-effectiveness results of a comparison between Lu-177 dotatate versus BSC generates an ICER of approximately £17,970 per QALY. In a comparison between Lu-177 dotatate versus everolimus, the ICER generated is £11,879 per QALY.

If a hypothetical PAS price discount of 30% is applied to the drug acquisition cost of everolimus, the ICER for a comparison between Lu-177 dotatate and everolimus will increase to £13,544 per QALY.

Based on the results presented that take post-progression benefits and costs into consideration, Lu-177 dotatate is a cost-effective treatment option for patients when compared to BSC and everolimus.

4. The AG analysis does not reflect the composition of BSC in UK clinical practice

Best supportive care (BSC) as defined in the analysis performed by the assessment group does not reflect treatment administered in UK clinical practice. The AG approach to BSC is based on the comparator arm of the everolimus RADIANT-4 study and comprises of a combination of lidocaine, dexamethasone, prednisone, prochlorperazine, biofermin, sacchromyces boulardii, external beam radiation therapy and standard dose somastatin

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analogues (SSAs) (with only 10% of patients receiving SSA as part of their treatment). The comparator arm of the RADIANT-4 study, and the approach used for BSC does not reflect UK clinical practice as corroborated by UK clinical key opinion leaders.

Clinicians in the UK have had access to active treatments for many years; as such, BSC as defined by the assessment group and the RADIANT-4 study is rarely considered an option for treating patients in the UK who have progressed on SSAs. The inappropriateness of this approach to BSC for this group of patients was highlighted in our previous comments on the AG's analysis but this has not been taken into consideration.

UK clinical practice is more aligned to the design of the NETTER-1 study. Patients who are at this stage of their disease (progressive) receive an escalated dose of SSA (between octreotide 30 to octreotide 60mg). The population considered in this appraisal are patients whose disease has progressed and will therefore receive an escalated dose of octreotide (either in the form of increased frequency or increased dosage). This was confirmed at the NICE Appraisal Committee by NICE's clinical expert who confirmed that upon disease progression patients are frequently treated by increasing dosage of SSAs or, for patients suitable, liver embolization.

A recent study evaluated the benefits of octreotide LAR dose escalation in a retrospective evaluation of medical records of patients with NETs. The authors concluded that goal of improved symptom control is a common reason for dose escalation of octreotide LAR, and that escalation to above the standard dose of octreotide LAR of 30 mg every 4 weeks may result in improved symptom control.(7) Furthermore, a recent systematic review has identified that higher octreotide LAR doses are being prescribed for symptom and tumour control in NET patients.(8)

Based on the incorrect assumption surrounding BSC made by the AG, the BSC drug acquisition cost per cycle of treatment used in the model is approximately £35.50. This cost greatly underestimates the true cost of BSC for these patients to the NHS.

As stated previously, we would expect patients at this stage of their disease to receive a SSA dose ranging from between 30mg (single dose) to 60mg (double dose). The cost per cycle of treatment with a single of SSA as presented in the AG model is £806.42. This means the true cost of BSC to the NHS for these patients is between £806.42 (for a single dose) and £1,612.84 for a double dose of treatment.

We encourage NICE to revisit their analysis of BSC as it currently does not reflect NHS resources spent on BSC for this group of patients and significantly underestimates the true cost-effectiveness of Lu-177 dotatate when compared to BSC.

5. NICE has failed to consider data underpinning the marketing authorisation for Lu-177 dotatate from the Erasmus study

Data submitted to NICE in our submission from the large non-controlled open-label ERASMUS study that have now been published (9), appear to have been disregarded by the Committee and no rationale has been provided for this in the ACD or accompanying documentation. These data demonstrated the effectiveness of Lu-177 dotatate in the treatment of different somatostatin receptor positive tumour types.

Data from the Erasmus study form part of the core clinical evidence supporting the marketing authorisation for Lu-177 dotatate for the treatment of unresectable or metastatic,

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progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults and are included in the Summary of Product Characteristics.

The Erasmus study was an investigator sponsored, phase I–II non-randomised single-arm study to evaluate the efficacy of Lu-177 dotatate in patients with SSTR positive histologically confirmed NETs (the majority GEP-NET), conducted at the Erasmus Medical Centre (Erasmus MC), Rotterdam, The Netherlands. This was a prospective trial retrospectively analysed.

Due to early suggestion of significant clinical benefit of Lu-177 dotatate in terms of prolonged survival, patients were referred from all over the world to the Erasmus MC for treatment with Lu-177 dotatate, resulting in 67% of enrolled patients being from The Netherlands. The Dutch population (n=811) was considered the main population of relevance supporting the licence application to EMA and is reported here and in our original submission, because of the very limited loss in follow-up in this subgroup.

The patient population enrolled was heterogeneous, including various SSTR-positive types. The majority consisted of NETs and most of them GEP-NET, including foregut, midgut and hindgut carcinoids of the digestive tract, the bronchus, and all types of P-NETs. Patients eligible for enrolment were treated with four intravenous administrations of 200 mCi (7.4 GBq) at 6 − 13 week intervals. The mean follow-up was 34.8 months (SD 26.7) for the Dutch population.

Further details of the Erasmus study are reported in Section 4.11 of our submission. The updated data from ERASMUS has been provided in a separate document.

The Erasmus study provides supporting evidence that treatment with Lu-177 dotatate offers a meaningful therapeutic benefit to GEP-NET patients, in terms of safety, tumour response, survival and QoL. This data also underpins the marketing authorisation for Lu-177 dotatate.

6. NICE has acted unfairly in its appraisal of Lu-177 dotatate

AAA have been severely hampered in their ability to fully engage with the NICE appraisal in several ways, detailed below. In addition, we consider that the AG analysis which has formed the basis of the NICE provisional recommendations includes fundamental errors and has not followed the NICE guidelines for technology appraisal. We urge the NICE to review and amend these issues as a matter of urgency.

6.1 Lack of clarity in AG model and ACD

NICE provided AAA with the AG executable model (AG model 1) and AR prior to the Appraisal Committee Meeting. In response, we provided a detailed description of our serious concerns with the analysis in our letter to the Committee.

On review of AG model 2, we noted that significant amendments had been made to the AG analysis compared to model 1. Details of the amendments made to the model were not provided, other than an addendum to the AR describing the changes made to the analysis of everolimus.

One key amendment, the removal of all post-progression survival from the analysis of Lu-177 dotatate, was not described in the documentation and no clear rationale was provided. Given the significance of this amendment and our serious concerns about this approach, we

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have been unable to understand the basis for this amendment and have been unable to respond to the rationale for this change.

Furthermore, there are major discrepancies between the ACD and the AG model that have not been explained in the documentation. As noted in Section 2 of this response, there a significant difference in the ICERs included in the AG model 2 and those referred to in the ACD. The ACD clearly states that the AG model was used as its basis for decision-making. AG model 2 demonstrates that Lu-177 dotatate is a cost-effective use of NHS resources at the standard NICE threshold range when compared with the recently approved treatment, everolimus; however, the ACD statement is to the contrary. This lack of clarity has severely hindered our ability to respond to the recommendations in the ACD as it is unclear what evidence they are based upon. In addition, the recently implemented new format of the ACD, which excludes the description of the evidence considered by the Committee, has resulted in very little information being provided on the sections of the evidence base considered by the Appraisal Committee leading to a lack of transparency.

6.2 AG model provided very late in process

We would also like to note that the executable AG model 2 was provided late into the ACD consultation period to provide a thorough analysis. We requested the model from NICE upon receipt of the ACD 27th July 2017 and received this on 2nd August 2017. This hindered our ability to review the model, particularly given the lack of clarity about the amendments made to the model.

6.3 NICE has failed to consider important evidence submitted to support the therapeutic benefits of Lu-177 dotatate

Important evidence on the efficacy of Lu-177 dotatate have not been considered by NICE with no justification provided. Data from the large non-randomised trial, Erasmus, were provided to NICE in our MS but do not appear to have been reviewed by the Committee. These data formed part of the core clinical evidence supporting the marketing authorisation for Lu-177 dotatate and demonstrate its effectiveness across a range of GEP-NET tumour types. No rationale for this has been provided, and, as described in Section 1 of this document, the exclusion of these data is not compatible with the NICE Guide to Methods of Technology Appraisal, and are inconsistent with the approach taken in previous NICE appraisals.

6.4 The AG analysis is not consistent with recommended NICE methods and is perverse

The analysis of Lu-177 dotatate included in the AR was relegated to a scenario analysis and did not fully evaluate the cost-effectiveness of Lu-177 dotatate. The NICE Guide to the Methods of Technology Appraisal describes methods that AGs and companies should follow for their economic evaluations. Several of the recommendations were not followed by the PeNTAG in its analysis of the cost-effectiveness of Lu-177 dotatate. Details of these, and the relevant sections of the NICE Guide to Methods of Technology Appraisal, are noted below.

> "*Full documentation and justification of structural assumptions and data inputs should be provided. When there are alternative plausible assumptions and inputs, sensitivity analyses of their effects on model outputs should be undertaken."* (5.7.1) (3)

Full details of the structural assumptions underpinning AG model 2 have not been provided. Despite the availability of alternative plausible assumptions (for example, PPS is greater

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than zero for patients treated with Lu-177 dotatate), sensitivity analysis on these have not been performed. Furthermore, as described in Section 2 of this document, we believe that the approach to the analysis of PPS in the AG analysis is perverse in light of the evidence provided and clinical plausibility. It contravenes NICE's recommended methods for modelling an appropriate time horizon and dealing with uncertainty. It also contravenes good practice guidelines and the published recommendations of a senior author of the PenTAG report.

> "*For a lifetime time horizon, it is often necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty. When the impact of treatment beyond the results of the clinical trials is estimated, analyses that compare several alternative scenarios reflecting different assumptions about future treatment effects using different statistical models are desirable (see section 5.7 on modelling). These should include assuming that the treatment does not provide further benefit beyond the treatment period as well as more optimistic assumptions. Analyses that limit the time horizon to periods shorter than the expected impact of treatment do not usually provide the best estimates of benefits and costs."* (5.1.16) (3)

The AG have not explored alternative assumptions about survival, and have not tested alternative statistical models for extrapolating the survival. They have applied an exponential model to the survival, which we believe is inappropriate. We note that in their analysis of data for everolimus and sunitinib, a range of alternative statistical models were explored by the AG. It is unclear why a similar approach was not also undertaken for Lu-177 dotatate.

> *"It is important for the model to quantify the decision uncertainty associated with a technology (that is, the probability that a different decision would be reached if the true cost effectiveness of each technology could be ascertained before making the decision)."* (5.8.1) (3)

The AG has not performed adequate sensitivity analyses on the cost-effectiveness of Lu-177 dotatate. No probabilistic sensitivity analysis has been performed.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression [ID858]

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by Peninsula Technology Assessment Group (PenTAG). It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

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The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

Please upload and submit your response via NICE Docs/Appraisals. Any responses that are not sent via NICE Docs/Appraisals will not be accepted. No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

May 2017

Issue 1 Lutathera post-progression survival benefits have not been taken into consideration

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Post-progression survival benefits and cost associated with Lu-177 dotatate have not been taken to consideration in the model.	The analysis performed by the assessment group (AG) does not take post-progression survival benefits and cost for Lu-177 dotatate into consideration. In the current analysis, the post progression survival benefits and cost are set to zero. An explanation in to why this has been done has not been provided by the AG and we do not see any justifiable reason for this assumption to be made. Worryingly, the same assumptions have not been applied to the other treatments (everolimus and BSC) that Lu-177 dotatate is being compared against.	If the post progression survival benefits and cost are taken into consideration, the expectation is that the new ICER's generated will come in below the NICE willingness to pay threshold of £20,000 to £30,000 per QALY.

Issue 2 Best supportive care as used in the model does not reflect UK clinical practise

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Best supportive care (BSC) as used in the analysis by the assessment group does not reflect UK clinical practise.	The AG's approach to BSC is based on the comparator arm of the everolimus RADIANT-4 study and comprises of a combination of Lidocaine, dexamethasone, prednisone, prochlorperazine, biofermin, sacchromyces boulardii, external beam radiation therapy and SSA (with only 10% of patients receiving SSA as part of their treatment). The comparator arm of the RADIANT-4 study, and the AG approach used for BSC does not reflect UK clinical practise as corroborated by UK clinical key opinion leaders. Clinicians in the UK have had access to active treatment for a long time, as such BSC as defined by the assessment group and the RADIANT-4 study is rarely considered an option for treating patients in the UK who have progressed on SSA's.	If the cost of BSC is increased in line with UK clinical practise, the expectation is that the new ICER's generated for a comparison between Lu-177 dotatate and either BSC or everolimus will come in below the NICE willingness to pay threshold of £20,000 to £30,000 per QALY.

	The inappropriateness of this approach to BSC for this group of patients was highlighted in our previous comments on the AG's analysis but this has not been taken into consideration. UK clinical practice is more aligned to the design of the NETTER-1 study. Patients who are at this stage of their disease (progressive) receive an escalated dose of SSA (treatment anywhere between Octreotide 30 to octreotide 60mg). Based on the incorrect assumption surrounding BSC made by the AG, the BSC drug acquisition cost per cycle of treatment used in the model is approximately £35.50. This cost greatly underestimates the true cost of BSC for these patients to the NHS. We would expect patients at this stage of their disease to receive a SSA dose ranging from between 30mg (single dose) to 60mg (double dose). The cost per cycle of treatment with a single of SSA as presented in the AG model is £806.42. This means the true cost of BSC to the NHS for these patients is between £806.42 (for a single dose) and £1,612.84 for a double dose of treatment.	

Issue 3 Choice of parametric survival model used for extrapolation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Justification for the exponential model as the choice of best fitting parametric survival distribution.	The executable model sent through by the AG shows that while the lognormal, weibull and exponential parametric survival models were fitted to GI/lung NET's and P-NETs, only the exponential parametric survival model has been fitted to the midgut NET data for the analysis. The AG offers no explanation to the unfairness and disparity in the manner in	If the model is amended to include either a lognormal/ Weibull model for the midgut patient population, the ICERs are expected to improve as more survival benefits will be accrued.

	which the best fitting parametric survival models for the different subpopulations has been chosen. There are no goodness of fit analysis results presented that show justify the choice of the exponential distribution as the best fitting curve. Based on the natural history of midgut NETs and the very good results of treatment as shown in the NETTER-1 study, the choice of an exponential model is not a clinically plausible choice as patients with this condition who receive treatment with lutathera live for an incredibly long period of time.	

Issue 4 Lack of probabilistic sensitivity analysis around comparisons including lutathera

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Probabilistic sensitivity analysis have not been carried out in analysis involving Lu-177 dotatate	The model built by the AG does not perform a PSA analysis that involve a comparison with Lu-177 dotatate	There is no conclusive evidence that there is uncertainty in the ICER results for Lu-177 dotatate. The conclusion in the ACD stating that there is uncertainty in the ICER results for lutathera is therefore inaccurate because these analysis have not been carried out.

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177Lu-dotatate for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease [ID1224]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NET Patient Foundation
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Thank you for the invitation to comment The immediate response to the proposed outcome is of disbelief and shock. The treatment under review has robust and increasing evidence to support its clinical effectiveness, as well as increasing data to show significant clinical and patient reported benefit. Whilst we acknowledge that NHS finances are finite, we believe there is significant scope to negotiate a fair and competitive price which would allow this therapy to become available, once again, through the NHS - we do not believe that such a negotiation would require 3 years to successfully complete. We understand that the current UK list price is £17k per session (£68k for all 4 treatments) - though proposed costings have been withheld from the available NICE documents so decision based costing unclear. However, we know that this therapy has previously been made available to the NHS, by the company, as a BOGOF deal (significantly reducing costs) - also an understanding and willingness amongst the clinical community to minimise administration and monitoring costs. We have learned from patient reports from the wider NET community, that it is currently available to NET patients in Europe at a cost of between £7-15k per session (variation possibly due to differences in healthcare systems, insurance and funding streams). We estimate reasonable, competitive, costs (incl administration) to total £36k If cost is the primary driver influencing decision - we fully support NICE negotiation on price, prior to final decision. The NPF is a patient centric charity, whose primary aims are to educate, inform, support and advocate for those diagnosed and living with malignant neuroendocrine tumours. As such we would also wish to comment on some of the information and statements made within the committee papers - to reflect patients concerns regarding other potential

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	influences on decision making.
2	1. Understanding of the disease - NETs are a heterogenous group of tumours - as diverse as cancer itself. One treatment does not fit all - and there is concern that the true complexity of this group of malignancies has not been fully appreciated. One example of this is referring to NECs as Neuroendocrine Carcinoids. NEC refers to Neuroendocrine Carcinoma - a far more aggressive malignancy than carcinoid. (Carcinoid is a term utilised to describe either low-moderate Lung NETs or the syndrome associated with (primarily) small bowel NETs). Another is the reference to the variety of treatments available including transplantation (without matching them to the relevant specific NETs). There is variety, because as with cancer itself, there is variety in the types of NET and as stated one treatment does not fit all (nb transplantation is not available in the UK on the NHS at this time). 2. Understanding the impact of the disease - 60-80% of all NETs have already metastasised at the time of diagnosis. Symptoms range from those associated with more common cancers (pain, lethargy, weight loss, tumour burden, etc) as well as those caused by excessive hormone release - which themselves range from mildly challenging to life threatening. Compounding this is the perceived lack of awareness - not just amongst the general population, but also medical establishment - limited access to timely and accurate diagnostics, restricted access to effective treatment - and a perceived assumption that somehow despite malignant nature and lack of cure NETs are 'less serious' the cancer to have, if you going to get cancer, We live WITH cancer . . . every day, never knowing if the next scan or test will show it's changed. Its cancer and your not on chemo - are you sure its cancer ? 3. Unmet clinical need - which follows on from point 1. There is NO other systemic NHS treatment for well differentiated, low-moderate grade SSTR positive FUNCTIONAL midgut NETs that progress - beyond best supportive care +/- off label use of somatostatin analogues. NB whilst there is clinical practice experience and emerging evidence of the use of this treatment in Lung and Pancreatic NETs - we support recommendation for use in small bowel NET as per NETTER1 - at this time. For low-moderate grade, well differentiated NON functional pancreatic, midgut and lung NETs there is now Everolimus For pancreatic NETs there is Everolimus, Sunitinib and chemotherapy 4. Inequality - UK and England is used interchangeably throughout this document - clarity is sought as to which NHS entities NICE guidance would influence. Currently patients living under the devolved nations NHS care have access to this treatment whilst those under NHS England care do not. Please note that those living in devolved nations have to travel to England to receive this treatment - often sitting alongside patients from England in clinic or Nuclear Medicine department. People who have been denied access following the withdrawal of this therapy from the CDF. Patients from all UK nations have expressed concern that highlighting this geographical inequality may risk people's access - i.e. they do not wish to see this therapy also withdrawn from those living within the devolved nations.
3	We would also like to clarify whether, in considering costs, assessment of cost of NOT

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	treating this group of patients has been made? Given length of time to progression with or without this treatment - has additional supportive care, including hospitalisations, in the non-treated cohort been calculated - the financial model / definition is not quite clear For example we have been involved in supporting a young woman with progressive metastatic pNET (insulinoma) – she's a young mum, who was working but off sick debilitated by symptoms which included having to eat every 2 hours to prevent coma - subsequent weight gain, experiencing extreme lethargy, hypoglycaemic episodes, confusion, nausea, etc , with repeated hospitalisations, increasing social isolation and decreasing family life interaction - all together, a profoundly compromised quality of life with life-threatening symptomatic episodes . She has just completed this treatment - and has not had a single hypoglycaemic episode or non-treatment hospitalisation since her 1st session (so reduced healthcare costs with significant QoL improvement due to treatment), has recently been able to not only go on holiday with her young family but take part in activities and consider return to work pending end of treatment scans, bloods and clinical advice. You have also heard from an expert patient, who having received this therapy went from pre-hospice admission status to running the Marathon! We have also been asked to confirm what is meant by best supportive care - does this include palliation with somatostatin analogues? Given published data and clinical practice would be a not uncommon standard of palliative care. Again this is unclear. In summary - NET patients acknowledge the financial constraints the NHS has to operate within, also that not everyone will require the same treatment - they understand the concept of appropriate treatment criteria, however, they feel let down by the lack of consideration for those living with NETs (rare/uncommon cancers requirements not addressed within National Cancer Plan), are perplexed at how World Class Outcomes can be achieved when clinically proven treatments cannot be accessed and are frustrated, frightened, disappointed and angry that more isn't being done to assertively negotiate pricing to allow, clinically appropriate candidates, NHS access to this treatment.
4	
5	
6	

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Nuclear Medicine Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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1	The costing does not take into account the highly specialised nature of providing a molecular radiotherapy service. This is a multidisciplinary area requiring input from radiopharmacy, nuclear medicine, medical and clinical oncology, physics and nursing and must be costed as such. There is also a need to ensure equal geographical access to treatment, which at present is governed. Of particular note, the ionising radiation regulations, due to come into force in February 2018, mandates dosimetry-based treatment planning and verification of the absorbed doses delivered. This is yet to be evaluated or implemented, but will have an impact on the cost of delivery.
2	We are concerned about this product because in over 20 years work in patients with progressive neuroendocrine tumours this is the only treatment which has consistently been able to treat the majority of patients with improvement in quality of life as well as survival, Evidence NETTER 1 trial
3	We are concerned as this product has been the only product which has been proven to extend mean PFS over 12 months in a RCT (mean PFS for Lu-177 dotatate not reached by 30 months) Evidence NETTER 1 trial
4	We are concerned as this product is much less toxic than many alternatives and is better tolerated and so reduces on costs from side effects which we have seen with chemotherapy based regimes (own observations and Khan S et al JNM 2011)
5	We are concerned that when available there will be a “post code lottery” of where this treatment will be available and how availability will be England wide (My concerns are that there are no centres experienced in using Lu-177 dotatate in East Midlands, Yorkshire, the North East and South West) Evidence review of provision of nuclear medicine speclalists)
6	We are concerned that the best screening test for PRRT with Lu-177 dotatate is Ga-68 DOTATOC PET which is not currently funded by NHS England and is only available in a few centres in the England and those centres may find it difficult to scan patients under the provisions of NHS England phase II PET/CT contract roll out.(Evidence discussion with nuclear medicine and PET provider colleagues).

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	One of our experts has carried out clinical trials involving PRRT with Lutetium, and everolimus, and also received travel bursary from Novartis to attend clinical conferences. One of our experts has attended advisory board convened by Novartis and AAA/IEL

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1	We are concerned that this recommendation will deprive patients with small intestinal neuroendocrine tumours (SINETS) from receiving arguably the most effective new treatment that has ever been developed for recurrent neuroendocrine tumours. The introduction of somatostatin analogues in the 1980s was a remarkable breakthrough in that it was able to control the life-threatening symptoms from carcinoid syndrome but at that time it was only for symptomatic relief. Subsequently it has been shown to have a minor antiproliferative effect. PRRT when compared with the unlicensed high-dose octreotide LAR has shown a truly remarkable improvement in progression free survival although no significant improvement in overall survival probably due to the fact that most patients who received high-dose LAR subsequently were able to access PRRT off label or through other mechanisms. The difference in PFS is very highly significant. This level of benefit in PFS has rarely been seen in oncology circles. Our experts are concerned that the committee has not recommended approval. Please see section 6 for comments on a possible solution. This benefit in the clinical trial was only for SINETs as no patients with pancreatic or other NETS were included. Therefore our experts are disappointed that NICE has rejected outright the use of PRRT. We would strongly urge the committee to review and revise their recommendation to allow its use in patients with SINETS until further evidence comes through to confirm the benefit in pancreatic, bronchial and other neuroendocrine tumours. There is a significant experience in other sites in Europe but this is not evidenced by randomised trials. It is commented that the NICE end-of-life criteria would not apply however at the time that the trial was conceived it would have been anticipated that most of these patients would be dead within 2-3 years at most. The remarkable improvements in the care in neuroendocrine tumours over the past decade have demonstrated that these data are now obsolete. This in itself is further confirmation of the effectiveness of new treatments in NETS which have revolutionised clinical care and given patients the chance to live with their disease.
2	We are concerned that NICE has dismissed high-dose octreotide as the effective comparator. There is evidence of small clinical benefit from the use and there are two clinical trials which have shown that somatostatin analogues do have a minor antiproliferative effect. However in real practice very few clinicians would use (or even be allowed to use) octreotide LAR 60 mg. Other measures would be introduced such as chemotherapy, embolisation, ablation and if possible PR RT. However if a placebo arm had been used then we can anticipate that the difference between the study arm and the control arm would have been even larger. Above-label (high dose) octreotide does have clinical efficacy. It is also established clinical practice internationally, particularly in patients with syndrome of hormonal over-secretion and disease progression.3 Patients with functional midgut NET would need to remain on a somatostatin analogue

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	in any case; therefore, the use of a SSA at above-label dose was an appropriate comparator for the NETTER-1 study. Moreover, the effectiveness of Lu-177 dotatate may have been under-estimated and may be even more effective than reported. [1] Strosberg *et al* The Oncologist 2014;19:930–936 [2] Broder *et al* World J Gastroenterol 2015;21(6):1945-1955 [3] Anthony et al Journal of Clinical Oncology 22, no. 14suppl (July 2004) 4274
3	We would recommend that further trials in neuroendocrine tumours at other sites be completed to provide the evidence to support its use
4	Our experts cannot comment on the cost of treatment as this is usually independent but assume there may be some opportunity for patient access schemes to modify the cost.
5	Regarding the comparators, in real life practice there is a sequence of treatments that may be considered. This will vary between pancreatic, small intestinal and bronchial. If we focus purely on small intestinal NETs, then the first-line treatment is normally a somatostatin analogue and on progression much will be determined by the site of disease. When it is liver predominant metastatic disease, targeted therapies at the liver such as hepatic artery embolisation and ablation have been traditionally offered. Chemotherapy has been used but has relatively limited benefit and recently everolimus has been approved in some parts of the United Kingdom for small intestinal and bronchial NETs. However the European guidelines from ENETs and other expert bodies including NANETS and the SNMMI recommend that PRRT is used earlier in the disease process. Given the significantly higher progression free survival seen with Lutetium which far exceeds the PFS seen with everolimus and sunitinib.
6	The likelihood of benefiting from PRRT can be predicted by the use of somatostatin receptor scintigraphy with either Octreoscan or where available gallium PET. Therefore the committee might also wish to consider recommending that the use of lutetium should be restricted to patients with neuroendocrine tumours of small intestinal origin which have progressed on somatostatin analogue therapy and which are shown to be somatostatin receptor scintigraphy positive. If accepted, this would identify the niche subgroup of patients most likely to benefit and where there would be the best value for money as well as clinical benefit
7	The comments on day case administration need to be qualified because of the issues of geography. There are a limited number of specialist centres in the UK who treat neuroendocrine tumours but because of the special requirements with radionuclides there will be a small number of centres capable of providing this service. Our experts believe that patients in remote parts of Northwest England and the Southwest of England in particular may have considerable distances to travel for this treatment. Therefore these patients will need to be admitted overnight. Our experts are concerned that the committee has overlooked the fact that although there is low-dose radioactivity, there are special precautions required which will be individualised. Although the document is principally aimed at patients in England, in other parts of the United Kingdom even greater distances may be required to travel and attend for treatment.
8	We acknowledge that the licensed indication is broader than the level-1 evidence base; the committee state 'that its recommendations should be guided by the evidence from the clinical trial

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	that underpins the marketing authorisation (paragraph 3.4)'. We agree with this and contend that at a minimum, NICE should approve Lu-177 dotatate for patients with progressive somatostatin-receptor-positive midgut NETs, as acknowledged by the committee in the papers.
9	Although likely to be effective in other NET subgroups, we accept that the evidence base available to date for NICE to evaluate Lu-177 dotatate is not as robust (i.e. the non-NETTER-1 population). However, the data submitted in these other patient cohorts was considered adequate for the regulators in the EU and USA, reflected in the broad licensed indication.
10	The magnitude of benefit from Lu-177 dotatate in patients with midgut NETs is one of the most dramatic ever seen in the field of oncology (progression-free survival [PFS] hazard ratio = 0.21); this constitutes a step-change in the therapy of NETs (acknowledged in paragraph 3.13). Sight appears to have been lost of this when considering other data from Lu-177 dotatate to treat NETs arising from all (midgut and non-midgut) primary sites.
11	The improvement in the primary end-point (PFS) from Lu-177 dotatate, acknowledged by the committee as 'clinically effective' (paragraph 3.3), translated into an OS advantage (with 60% reduction in risk of death); this highlights the lack of effective salvage treatment options on progression and the unmet need in this patient population. Moreover, the fact that the OS was not reached in the NETTER-1 study is a testament to the high level of effectiveness of the therapy, which reduces the mortality (and hence the number overall survival events [deaths]).
12	The patient cohorts in NETTER-1 (functional and non-functional somatostatin receptor-positive midgut NETs) and RADIANT-4 (non-functional, somatostatin receptor-agnostic intestinal NETs); a direct comparison (i.e. overlap) with everolimus (only now available) is therefore only appropriate for patients with non-functional somatostatin-receptor-positive intestinal NETs. Given that NETTER-1 and RADIANT-4 are such heterogeneous studies, we challenge this comparison.
13	In addition to any financial discussions with the manufacturer, the clinical community wishes to inform NICE that it commits to keeping the costs to therapy as low as possible (for example treating patients as day cases and treating more than 1 patient on a given treatment day, thereby improving the economies of scale).
14	The UK has been acknowledged as a leader in the field of NETs with the largest number of ENETS Centres of Excellence accredited by the European Neuroendocrine Tumour Society. Failure to allow patients' access to Lutetium will not only disadvantage patients from receiving an effective treatment, but will result in reputational damage internationally (including in the research arena). There is already a history of patients travelling to other centres in Europe and successfully challenging decisions regarding funding. Moreover, there is an equity of access issue affecting the devolved nations; for example Scottish patients referred under the Shared Risk Programme may be treated in London, however, London patients cannot be treated.
15	The proposed date for review of the guidance is too long (3 years); this should be no more than 1 year, given that this is a rapidly-evolving field of research (e.g. publication of updated survival data from NETTER-1 and the Australian randomised phase II CONTROL-NET study [clinicaltrials.gov study number NCT02358356]).

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- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

177Lu-dotatate for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease [ID1224]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 August 2017
Email: TACommD@nice.org.uk

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Patient Expert – nominated by the NET Patient Foundation – Mark Zwanziger)**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**No links of investment or funding to AAA or any drug companies or healthcare providers)**]

Please return to: **TACommD@nice.org.uk or through NICE Docs**

NICE National Institute for Health and Care Excellence

177Lu-dotatate for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease [ID1224]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 August 2017
Email: TACommD@nice.org.uk

Name of commentator person completing form:	Mark Zwanziger
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	As a patient who has is because of PRRT (Y90-2011 & Lu177-2015), This negative appraisal of Lu-177 Dotatate is a major setback to the patient community that sees PRRT as their only treatment when the disease is progressing. To shelf this discussion for 3 years as stated in para 4.1 is a harsh penalty for patients needing the treatment.
2	I'm concerned that the appraisal was confused on the scope from the start, including Lanreotide at first, and then it didn't. Then, we waited for the EUMA statement of human use even though this drug was already in orphan status. It seemed to me that the scope was either too big or not defined enough for the PENTAG report. Over 585 pages of graphs that really never defined what ICER we should all be working off. This appraisal also covered several very different patient groups, with the main 3 being: 1-Pancreate NETS, 2-Mid&High Grade NETS, and 3 low grade NETS. Everolimus was recommended for 1 & 2, but not 3. Lu177 was presented as the only option for low grade. Sunitib for pancreatic.
3	I don't completely understand marketing authorization process or patents, but would like to see NHS consultants have "PRRT" or "Radio-labelled Somatostatin" in their arsenal. NETTER-1 from a patient view was also a huge scope. Why didn't it compare Lu-177 to Y-90. Y-90 has been the gold standard for almost 20 years in Europe. Comparing Lu-177 to Lanreotide or Everolimus seems a mistake, as Lu-177 is given in addition. (Part of what makes the ICER so confusing)
4	I'm concerned that there was no technical expert at the appraisal that had administered PRRT. The two technical experts were excellent, but we could have used a PRRT expert. The UK is a leader in the world of treating NETS, and their work is published. I'd really recommend readdressing with someone like Professor Caplin.
5	It is very concerning that a negative decision references a ICER, but then doesn't list due to confidential pricing. The cost model seems extremely complicated. The ICERS in the PenTAG report ranged from under £10K by AAA, £24K-£40K by PenTAG, and my guess of £35K. The patients can understand denial if the ICER is over £30K, but not if the results are off ambiguous numbers.
6	I'm concerned when the report cites "median overall survival was not reached" para 3.3. The extremely high QALY of this treatment is amazing, and survival stats might not be "reached" or complete (because the patients are still alive). I was told early in my PRRT journey "trials should be quicker now, because we know what happens when you do nothing". I didn't see this data included in the PenTAG report.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more

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NICE National Institute for Health and Care Excellence

177Lu-dotatate for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease [ID1224]

Consultation on the appraisal consultation document – deadline for comments 5pm on 24 August 2017
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than 1 set of comments from each organisation.

- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
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Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	UK and Ireland Neuroendocrine Tumour Society
Comments:	
	[redacted] The comments are on behalf of the executive of UKINETS which represents all clinicians and Allied Health professionals managing NET patients in UK. 1 The licensed indication is for more sites of disease than the level-1 evidence base; the committee states its recommendations should be guided by the evidence from the clinical trial that underpins the marketing authorisation (paragraph 3.4). We agree with this and suggest that NICE approve Lu-177 dotatate for patients with progressive somatostatin-receptor-positive midgut NETs as acknowledged by the committee. It is very important that this is funded for Small bowel NET since there are few other therapies. Clinical experience suggests that this therapy is useful for pancreatic net also, hence ideally the approval would include all the licensed indications. 2 Although likely to be effective in other NET subgroups, we accept that the evidence base to date may not be robust enough for NICE to approve Lu-177 dotatate in the non-NETTER-1 population. 3 The magnitude of benefit from Lu-177 dotatate in patients with midgut NETs is the most dramatic ever seen in oncology (PFS hazard ratio 0.21); this is a step-change in the therapy of NETs (acknowledged in paragraph 3.13) and to have funding withdrawn from this therapy (when it has been used in UK for many years) would be a disaster for this patient group. 4 The improvement in the primary end-point (PFS) from Lu-177 dotatate, acknowledged by the committee as 'clinically effective' (paragraph 3.3), translated into an OS advantage (with 60% reduction in risk of death); this highlights the lack of effective salvage treatment options on progression and the unmet need in this patient population. Median survival has not been reached which appears in the document to be a negative but in fact is a big positive factor, since the patients on therapy are not dying. This seems to have been overlooked. 5 Comparator (octreotide LAR) was appropriate at the time; although the assumption has been made that this is equivalent to BSC, above-label dosing of SSA do have clinical activity (reviewed in Broder et al World J Gastroenterol

	2015;21(6):1945-1955). The clinical view from the executive is that above-label doses are commonly used for patients that have high hormone secretion and that there is modest benefit in this group, above standard dosing. Consequently the effectiveness of Lu-177 dotatate may have been under-estimated when compared to trials using placebo or supportive care only. 6 The patient cohorts in NETTER-1 (functional and non-functional somatostatin receptor-positive midgut NETs) and RADIANT-4 (non-functional, somatostatin receptor-agnostic intestinal NETs) are clearly different; a direct comparison (i.e. overlap) with everolimus (only now available) is therefore only appropriate for patients with non-functional somatostatin-receptor-positive intestinal NETs. Given that NETTER-1 and RADIANT-4 are such heterogeneous studies, we challenge the supposition that a comparison can be made between them. 7 In addition to any financial discussions with the manufacturer, there may be scope to optimise cost-effectiveness within the NHS (e.g. day case use, treatment of more than 1 patient on a given treatment day, limiting treatment with economies of scale, etc.) This will limit add-on costs and UKINETS is keen to work with centres in UK to achieve this. 8 The UK has been acknowledged as a leader in the field of NETs and is the country with the largest number of ENETS Centres of Excellence accredited by the European Neuroendocrine Tumour Society. Failure to allow patients access to Lutetium will not only disadvantage patients from receiving an effective treatment, but will result in reputational damage internationally (including in the research arena). Many patients may seek therapy in Europe and attempt to recharge the NHS for this (for which there is a precedent of the NHS paying after legal representation). In addition some patients from Scotland have had their therapy funded from Scotland and delivered by centres in London, leading to the situation where Scottish patients can access therapy in London but London patients cannot. This is clearly unacceptable. 9 The proposed date for review of the guidance is too long (3 years); this should be 1 year, given that this is a rapidly-evolving field of research. More data is coming in from follow-up of the NETTER trial, and further randomised trials worldwide are in progress and may report shortly.

Name	[redacted]
Role	Patient
Notes	I've been urged by members of my 5000 strong patient community to submit a comment.
Comments:	

	As a patient, I was extremely disappointed and angry to see that NICE is not recommending 177 Lu-dotatate (Lutathera). Particularly after NHS England removed it from the Cancer Drugs Fund in 2015 citing a lack of clinical data as the reason, and now that clinical data is available (which is described by some physicians as a clinically important and statistically significant increase in progression-free survival), you now cite cost grounds. Are you aware that this treatment has been used in Europe for over 10 years with great success? Take Rotterdam for example, they treat 100 patients per week many from overseas. Are you aware that many private US patients come to Europe for this treatment, many to London. (at their own expense), although there is a huge expanded access program now available in USA pending FDA approval. May of my non-UK patient and patient advocate contacts are both perplexed and totally astonished by your announcement, given the esteem in which they held the UK Health System. It seems like the UK is now falling some way behind other nations in provision of this treatment for Neuroendocrine Tumour patients. For many metastatic Neuroendocrine Tumour patients (including myself), Lu-177 is the tool they will need should their tumours destabilise and become progressive. Many patients are progressive now and are waiting on this approval. I do hope this comment and others will persuade you to reverse this decision.

Name	[redacted]
Role	Patient
Comments:	
	There remains a huge unmet need for proven, successful and long term treatment for metastatic NETS. The evidence supporting the effectiveness of PRRT is excellent (i.e. NETTER study) and is improving month on month worldwide, but this document appears to demonstrate that the cost/price of PRRT delivery is the single most important factor hindering approval - rather than effectiveness of treatment and patient quality of life. Please reconsider and instead, recommend PRRT as an option for all NETS patients with metastatic disease - without price as it's most important issue. Thank you.

Name	[redacted]
Comments:	
	I have neuroendocrine tumours. I had extensive two-part surgery in February and June 2013 and have been treated with Sandostatin LAR since then. However, I have progressive disease and have been advised that PRRT may be a useful treatment. There are no other treatment options as I have functioning NETs. I find it depressing that this option is not being approved by NICE as for many of us it is our only hope. Despite the extent of my disease I returned to work after surgery and lead a fulfilling life - it is disappointing that NICE does not accept that this is a useful treatment. My understanding is that the NETTER1 trial hasn't yet been

	completed so I would hope that NICE would be able to re-think this decision. Having said that, I appreciate that these drugs must be being offered at a ridiculously high price and maybe the way forward would be negotiation with the drug companies.

Name	[redacted]
Role	[redacted]
Comments:	
1	Lutetium-177 DOTA Octreotate is an important part of the therapeutic algorithm for GEP NET patients in Europe. The past multiple phase II studies and randomised phase III NETTER-1 study (NEJM 2017) demonstrate clear therapeutic benefit and sustained response. The UK is a leading country within ENETS with 10 European Centers of Excellence and not having this therapy which is seen as a standard in Europe affects the status of UK centers.
2	The NETTER-1 Study needed to use Octreotide LAR as a comparator as many patients had carcinoid syndrome. We feel the design of this study was entirely appropriate in regard of the cohort of patients included.
3	The median overall survival even after a further year of follow-up has yet to be reached and demonstrates favourable long term efficacy.
4	The low toxicity, clear efficacy and longevity of response we respectfully suggest is a clear rationale for NICE approval of this treatment

Name	[redacted]
Comments:	
1	I am concerned that this recommendation will leave no effective therapeutic options for patients with midgut tumours and pancreatic neuroendocrine tumous (pNETs) following failure of somatostatin analogues (SSAs). SSAs have a low response rate and there is now very good evidence from NETTER-1 that they are clearly inferior to Lutetium therapy. Having treated over 60 patients with NETs with Lutetium, I can clearly state that the therapy is very well tolerated, resulting in markedly improved survival in lines with the published data. Importantly, as this cancer impacts on patients of a younger age, most of my patients who have had Lutetium have been able to return to work.
2	SSAs themselves are expensive. In the real world setting, as there are no other therapies, clinicians often continue SSA beyond disease progression.

Name	[redacted]
Organisation	[redacted]
Comments:	
1	Lutetium-177 DOTA Octreotate has been a standard of our care for our NET patients over the last 3 years (having previously successfully treated patients with Yttrium-90 DOTA Octreotate). The Lu-dotatate is better tolerated than other forms of PRRT

	and the randomised NETTER-1 study (NEJM 2017) has demonstrated excellent tolerability and efficacy.
2	For patients particularly midgut (ileo-jejunal NET) who have progressed after somatostatin analogue Lu-dotatate is the best option and undoubtedly superior as an anti-tumour agent to Everolimus which has just been endorsed by NICE. Lu-dotatate has shown perhaps excellent efficacy in other GEP NETs based on our experience and phase II data, even when used as 3rd or 4th line agent. We keep prospective data and this has been (and continues to be) presented at international meetings in addition we are in the process of writing for peer review publication. The availability of Lu-dotatate is also important as a recognised ENETS Center of Excellence.
3	The use of Octreotide LAR as the comparator in the NETTER-1 study was appropriate and was necessary as the protocol included patients with carcinoid syndrome. This was the cleanest study design. There is also a rationale as the higher the dose of SSTA the greater the anti-tumour response hence the choice of Octreotide LAR at 60mg in patients who had progressed on standard dose SSTA. (NETTER-1 PFS for Octreotide LAR 60mg was 8.4mths)
4	It would have been inappropriate to use Everolimus as a comparator because at the time of study design there was no robust evidence of efficacy in midgut NETs and of course everolimus does not treat carcinoid syndrome. PFS for Everolimus is significantly less than for Lu-dotatate.
4	The additional 1 year follow-up data has not met median overall survival thus demonstrating the long term efficacy and tolerability of Lu-dotatate
5	Post Lu-dotatate the impressive feature is the longevity of response compared to all other therapies
6	The proposed date for review of the guidance is too long and should be one year

Name	[redacted]
Role	**Consultant Clinical Oncologist**
Comments:	
1	The failure to approve this will leave an unmet need
2	I have experience of using in patients with gastroenteropancreatic tumours, bronchial carcinoids and medullary thyroid cancer patients. Have seen good symptomatic responses and tumour control. Often allowing patients to reduce analgesia and increase activities- particularly returning to employment and carer roles.
3	BSC is not a reliable comparison, as there is significant cost burden related to BSC in these patients- both economic and social.

[redacted]

Ms Kate Moore
Technology Appraisals Project Manager - Committee D
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza
Manchester M1 4BT | United Kingdom

[Date]

Dear Kate

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-dotatate [ID1224]

Please find enclosed additional analyses for the above appraisal, as agreed with Helen Knight on [add date]. An amended economic model (MS Excel) is also provided. We will be happy to answer any queries you or the Assessment group may have regarding the analyses.

Yours…..

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-dotatate [ID1224]

Advanced Accelerator Applications UK Limited

8 December 2017

Contents

List of tables and figures

1. Introduction

1.1 Background

We are pleased that NICE has recognised the importance of considering the full marketing authorisation (gastroenteropancreatic neuroendocrine tumours [GEP-NETs]) and data from the ERASMUS study following the consultation on the Appraisal Consultation Document (ACD). AAA are happy to assist in the Committee's deliberations by providing revised analyses for Lutathera® (lutetium (177Lu) oxodotreotide) for the treatment of unresectable or metastatic neuroendocrine tumours in people with progressive disease.

To accommodate NICE's request we have provided an amended economic model demonstrating the cost-effectiveness of treatment with Lutathera for patients with pancreatic neuroendocrine tumours (P-NETs) compared to Best Supportive Care (BSC), everolimus and sunitinib. The amendments reflect suggestions made by NICE and the Assessment Group to include a matching adjusted indirect comparison to replace the network meta-analysis previously provided.

In addition, we have amended the economic model for the gastro-intestinal neuroendocrine tumours (GI-NETs) population to address the Committee's comments reflected in the ACD. Furthermore, we have provided an analysis of the NETTER-1 study adjusting for cross-over in the comparator arm of the trial, which provides a better representation of the effectiveness of Lutathera.

1.2 Unmet need for GEP-NET patients

Lutathera is a peptide receptor radionuclide therapy (PRRT) and has Orphan Drug status from FDA and EMA for treatment of GEP-NETs. Lutathera has received a marketing authorisation from the EMA based on the NETTER-1 and ERASMUS studies.

There is a significant unmet medical need for patients with inoperable GEP-NETs. Few treatments are available for patients with advanced GEP-NETs progressing under SSAs, and no routinely approved effective treatments are available for a significant proportion of these patients, specifically those with functioning GI-NETs and those whose primary tumour site is the ileum.

The NETTER-1 study has shown that Lutathera provides a major therapeutic benefit for this patient population with a 79% reduction in the risk of disease progression/death [PFS (not reached with Lutathera versus 8.5 months, $p<0.0001$)] and significant difference in overall response rate [ORR (15% versus 4%, $p=0.0141$)]. Interim analysis suggests increased OS in comparator arm (17 versus 31 deaths; $p=0.0083$); to be confirmed by the final analysis.

Lutathera has a particularly favourable safety profile in comparison with the chemotherapy regimens and targeted agents currently used to treat GEP-NETs: the phase I–III studies revealed no clinically relevant toxicity findings including in relation to haematological, renal and hepatic parameters. This is because delivery of the anti-tumour agent (i.e. cytotoxic radiation) is targeted selectively to the tumour tissue via SSA-peptides to receptors expressed by the tumour, minimising the effect on healthy tissue.

PRRT is already in the guidelines for the treatment of NETs (orphan disease) as a second-line treatment option in GI-NET and P-NET; this place in therapy aligns with the positioning in this submission (ENETs guidelines (2017) (Hicks et al., 2017), ESMO guidelines (2010) (Oberg et al., 2010) and NANETs guidelines (2011) (Kulke et al., 2010).

Thus, Lutathera's innovative mechanism of action brings benefit to patients as an effective treatment with fewer side-effects than conventional therapies in a disease area where there are few treatment options available for patients progressing under SSAs and where up to 84% have reported the need for new treatment options. Lutathera has a major therapeutic benefit for this patient population, and its innovative mechanism of action in an orphan disease is difficult to capture in the quality-adjusted life year (QALY) framework.

Lutathera is licensed across all GEP-NET tumour sub-types

Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults. Its licence is not restricted by location of the primary origin nor by functional status (i.e. functional or non-functional). The rationale behind this is based on the patient populations included in NETTER-1 and ERASMUS MC studies which included a range of primary tumour sites at baseline (Table 1 and Table 2). In the NETTER-1 trial, the majority of patients in the full analysis set had the ileum diagnosed as the primary tumour site (n=86). In the ERASMUS trial, the majority of patients in the Dutch population had pancreatic (n=133) and midgut NETs (n=183).

Table 1. Primary tumour site, Full analysis set (N=229) - NETTER-1

	Lutathera n (%)	Octreotide LAR n (%)
Primary tumour site		
Jejunum	6 (5.2)	9 (8.0)
Ileum	86 (74.1)	82 (72.6)
Appendix	1 (0.9)	2 (1.8)
Right colon	3 (2.6)	1 (0.9)
Other	20 (17.2)	19 (16.8)

N, number of patients; n, number of patients per treatment group.

Table 2. ERASMUS phase I/II study in Dutch patients with GEP and bronchial NETs – (FAS, N=360)

Tumour type	n
GEP-NET*	360
Bronchial	19
Pancreatic	133
Foregut†	12
Midgut	183
Hindgut	13

*Includes foregut, midgut and hindgut; pancreatic and bronchial; †Foregut NETs other than bronchial and pancreatic

In the ERASMUS study, the functional status of patients was recorded at baseline. Analyses stratified by functioning and non-functioning P-NETs were also performed for PFS, TTP and OS (Table 3). The functional status of patients in the NETTER-1 trial was not recorded at baseline.

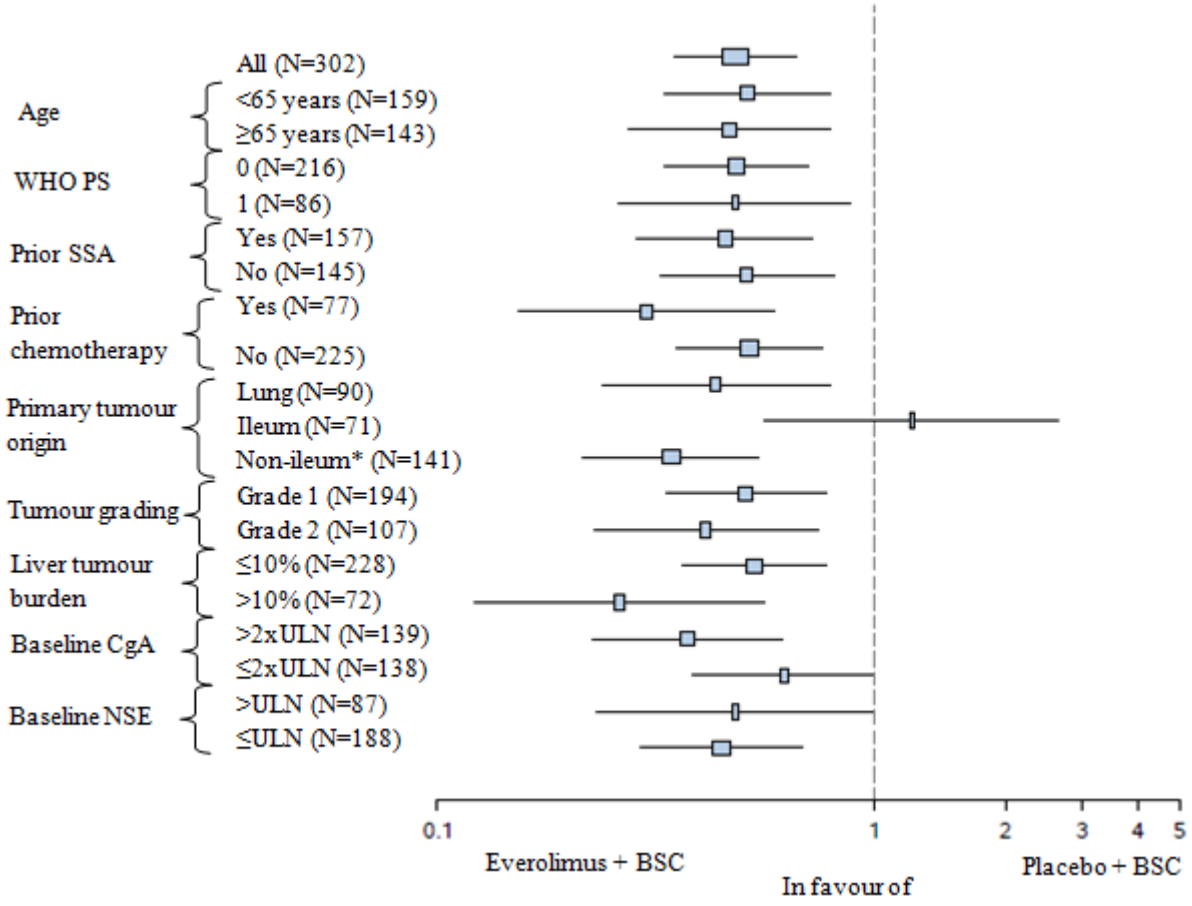
Table 3. Progression-free survival (PFS), time-to-progression (TTP) and overall survival (OS) for Dutch population according to functional status of P-NET (n=113) in ERASMUS FAS

Tumour type	PFS			TTP			OS		
	% events	Median (months)	95% CI	% events	Median (months)	95% CI	% events	Median (months)	95% CI
Functioning P-NET (n=20)	55.00	32.7	23.7 - NA	45	32.7	23.7	35.0	57.2	41.9- NA
Non-functioning P-NET (n=113)	63.72	30.3	24.3- 36.3	59.29	31.0	25.1- 37.2	44.25	66.4	57.9- 80.9

In contrast with the indication for Lutathera, everolimus is indicated for the treatment of adult patients with progressive, well-differentiated, non-functional, neuroendocrine tumours (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease. This licence was based on the RADIANT-4 trial, which enrolled patients with unresectable, locally advanced or metastatic, well-differentiated (low or intermediate grade), non-functional (no current or prior history of carcinoid symptoms), NETs of GI or lung origin. An earlier trial for everolimus, RADIANT-2, recruited both functional and non-functional patients; despite this, everolimus is not licenced to treat patients with functional tumours in any indication.

The RADIANT-4 trial demonstrated that everolimus was effective in all subgroups with the exception of the subgroup of patients with ileum as primary site of tumour origin (Ileum: HR=1.22 [95% CI: 0.56 to 2.65]; Non-ileum: HR=0.34 [95% CI: 0.22 to 0.54]; Lung: HR=0.43 [95% CI: 0.24 to 0.79]) (Figure 1) (Everolimus SPC, 2017).

Figure 1. RADIANT-4 – Progression free survival results by pre-specified patient subgroup (independent radiological review) (Everolimus SPC, 2017)



Therefore, there is a significant group of patients with GEP-NETs for whom there are no routinely approved effective treatments available: patients with functioning tumours and those whose primary tumour origin is the ileum. Lutathera has been approved by the EMA as an efficacious treatment for these important groups of patients.

1.3 Heterogeneity in clinical trials

AAA previously submitted a network meta-analysis (NMA) for the GI-NET population including 3 clinical trials: NETTER-1, RADIANT-2 and RADIANT-4. The Assessment Group only included two of these trials: NETTER-1 and RADIANT-4. The ACD states that the 'committee did not accept the

company's indirect comparison because it introduced further uncertainty in addition to that identified in the assessment group's indirect comparison'. Whereas, the RADIANT-4 trial only included patients with non-functional tumours, the RADIANT-2 trial included patients with both functional and non-functional tumours (proportions at baseline not reported) and therefore better matches the population included in the NETTER-1 study.

We note that the Committee concluded that the NETTER-1 and RADIANT-4 trials are not fully comparable and agree with this assessment. There is considerable heterogeneity amongst all 3 trials, which makes any MTC analysis subject to significant uncertainty. We have conducted a new MTC including the updated data from the NETTER-1 study and using the Committee's preferred assumptions (i.e. excluding the RADIANT-2 study). However, we consider that the results should be interpreted with caution due to the heterogeneity in the included studies.

In the economic model we therefore present results from the head-to-head NETTER-1 trial as a base case analysis for GI-NET patients and include data from the MTC as a scenario analysis. This analysis also reflects that there is currently no approved effective treatment for a significant proportion of patients with GI-NETs.

2. Overview of clinical effectiveness data for Lutathera

2.1 GI-NET effectiveness data utilised in cost-effectiveness analysis

The NETTER-1 study is a multicentre, stratified, open, randomised, comparator-controlled, parallel group phase III study comparing treatment with Lutathera plus best supportive care (30 mg octreotide LAR) to octreotide LAR (60 mg) in patients with inoperable, progressive, somatostatin receptor positive midgut neuroendocrine tumours (see clinical trial section for more details). Data from this trial were used to compare the cost-effectiveness of Lutathera against BSC. Individual patient level data were used to replicate the non-parametric Kaplan-Meier (KM) survival curves. The replicated PFS and OS curves are presented in Figure 2 and Figure 3.

Figure 2. PFS KM curves for octreotide LAR vs Lutathera

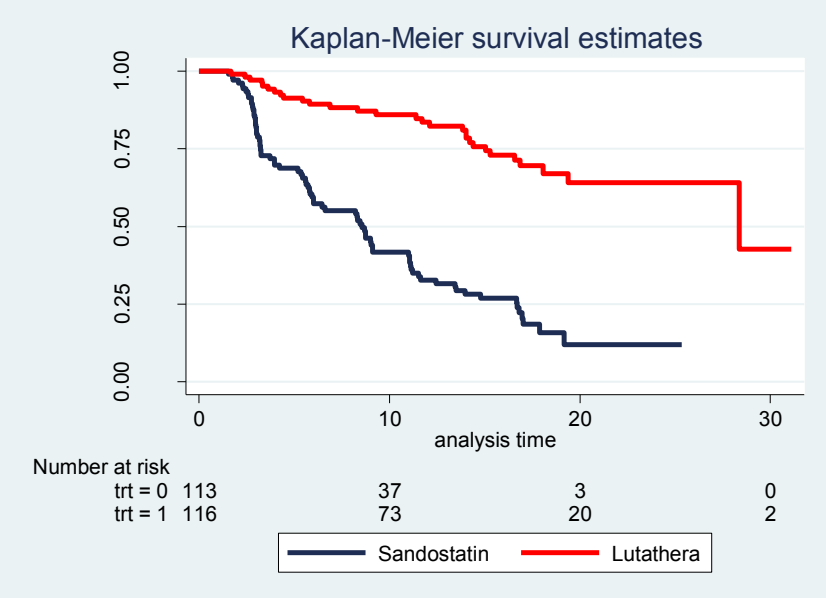
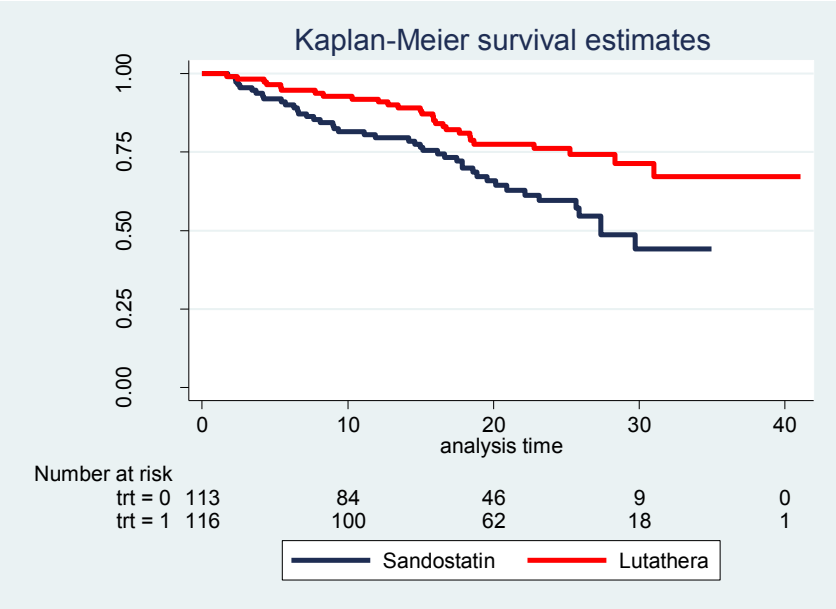


Figure 3. OS KM curves for octreotide LAR vs. Lutathera



The NETTER-1 data used in the analysis shows that when compared to octreotide LAR 60mg, Lutathera reduced the PFS risk by 79% (hazard ration [HR] = 0.21; 95% confidence interval [CI] = 0.13, 0.33), p=0.001. The overall survival risk for patients on Lutathera was reduced by 48% when compared to patients who received the octreotide LAR 60mg (hazard ratio [HR] = 0.54; 95% confidence interval [CI] = 0.33, 0.86), p=0.007. Median PFS (28.35 months) has now also been reached.

The median PFS for patients on octreotide LAR 60mg was 8.54 months (95% CI = 5.78, 9.1), and median OS was 27.37 months (95% CI = 23.13, N/R). Median OS has not yet been reached for Lutathera patients.

Summary survival results are presented in Table 4 and Table 5.

Table 4. PFS median survival estimates (GI-NET)

Comparator	Median PFS (weeks)	95% Confidence interval	Hazard ratio (95% CI)
Octreotide	8.54	5.81 – 11.0	0.21 (0.14 - 0.33)
Lutathera	28.35	28.35 – N/R	

PFS, progression free survival; N/R, not reached

Table 5. OS median survival estimates (GI-NET)

Comparator	Median OS (weeks)	95% Confidence interval	Hazard ratio (95% CI)
Octreotide	27.37	23.13 – N/R	0.54 (0.33 – 0.86)
Lutathera	N/R	N/R	

OS, overall survival; N/R, not reached

Scenario analysis based on MTC, including everolimus

For additional analyses comparing Lutathera to everolimus, a mixed treatment comparison (MTC) was necessary. Patient-level survival data for patients from the octreotide LAR arm of the NETTER-1 study was used in the survival modelling to generate a baseline risk curve for GI-NET patients. Hazard ratios from the MTC for Lutathera and everolimus were used to compare against BSC.

2.2 P-NET: ERASMUS study utilised in cost-effectiveness analysis

The ERASMUS study is an investigator-sponsored phase I/II clinical study, evaluating the efficacy of Lutathera administered intravenously to patients with somatostatin receptor-positive tumours as determined by somatostatin receptor scintigraphy.

Patient-level data from the progressive P-NET Dutch population of this study have been used to compare with BSC, sunitinib and an additional analysis comparing against everolimus. The replicated PFS and OS curves are presented in Figure 4 and Figure 5.

Figure 4. PFS curves for progressive P-NET patients

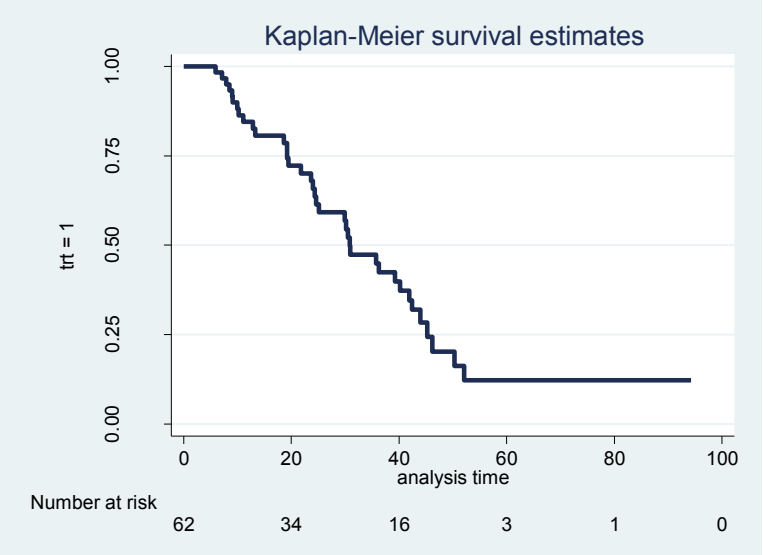
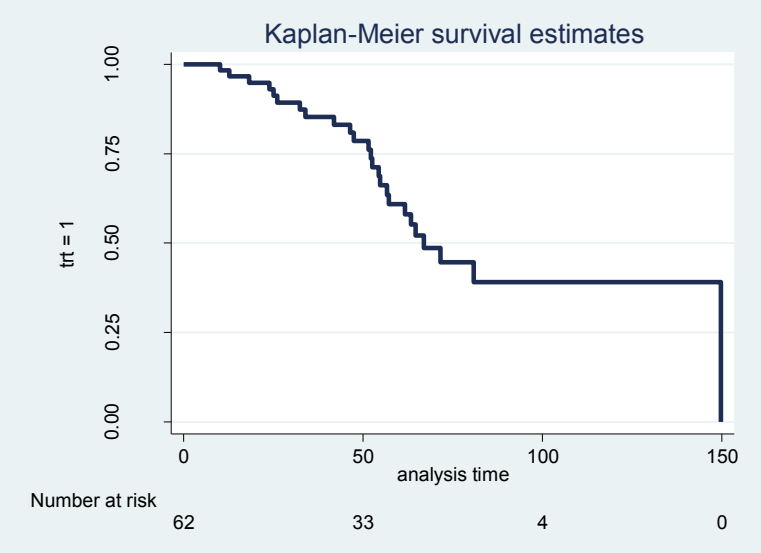


Figure 5. OS KM curves for progressive P-NET patients



The median PFS for P-NET patients was 30.88 months (95% CI = 24.31, 49.89) and the median OS was 66.92 months (95% CI = 56.74, NR). Summary survival results for PFS and OS are presented in Table 6 and Table 7.

Table 6. PFS median survival estimates (P-NET)

Regimen	Median PFS (months)	95% Confidence interval
Lutathera	30.88	24.31 – 41.89

PFS, progression-free survival

Table 7. OS median survival estimates (P-NET)

Regimen	Median OS (months)	95% Confidence interval
Lutathera	66.92	56.74 – N/R

OS, overall survival; N/R, not reached

ERASMUS is the best source of outcomes for P-NETs patients receiving Lutathera, however as a single arm study it does not give estimates of relative effectiveness against comparators. Results from different trials could be naively compared, but differences in patient population are likely to be a source of bias. As such, additional methods were necessary. Lutathera was compared to BSC, sunitinib and everolimus using the ERASMUS data to perform matching adjusted-indirect comparisons (MAIC) as described in Section 2. The patient level data from ERASMUS were reweighted based on prognostic factors and effect modifiers identified through engagement with clinicians, published literature and empirical investigation of the relationships in the PLD, to produce survival data based on a population aligned with the comparators trials.

3. Indirect treatment comparisons

3.1 GI-NET Network Meta-Analysis

Analysis

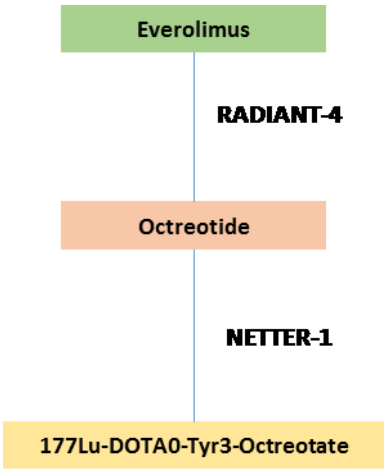
We have conducted a revised network meta-analysis (NMA) in response to comments from the Appraisal Committee and Assessment Group. The analysis includes data from two RCTs: NETTER-1 and RADIANT-4.

The methods of the NMA are as previously reported in our original submission with two amendments:

- Data from the updated analysis of the NETTER-1 study are included (database lock 30 June 2016; submitted to NICE August 2017)
- The RADIANT-2 trial has been excluded from the analysis.

The network of included studies for PFS and OS is shown in Figure 6.

Figure 6. GI-NET MTC, Network of included studies – progression-free survival and overall survival



The eligibility criteria for the NETTER-1 and RADIANT-4 trials is shown in Table 8. All patients in the NETTER-1 and RADIANT-4 trial had progressive disease. However, patients with functional GI-NET or lung NETs were excluded from the RADIANT-4 trial, whereas both functional and non-functional patients were included in the NETTER-1 trial.

Table 8. Eligibility criteria for trials included in GI-MTC

NETTER-1	RADIANT-4
Inclusion criteria	**Inclusion criteria**
1. Presence of metastasised or locally advanced, inoperable (curative intent) at enrolment time, histologically proven, midgut carcinoid tumour (to be centrally confirmed). 2. Ki67 index ≤ 20% (to be centrally confirmed). 3. Patients on Octreotide LAR at a fixed dose of 20 mg or 30 mg at 3-4 weeks intervals for at least 12 weeks prior to randomisation in the study. 4. Patients ≥18 years of age. 5. Patients must have progressive disease based on RECIST Criteria, Version 1.1 while receiving an uninterrupted fixed dose of Octreotide LAR (20-30 mg/3-4 weeks). 6. Confirmed presence of somatostatin receptors on all target lesions documented by CT/MRI scans, based on positive OctreoScan® imaging within 24 weeks prior to randomisation in the study (to be centrally confirmed). 7. The tumour uptake observed in each target lesion using OctreoScan® must be ≥ normal liver uptake observed on planar imaging (to be centrally confirmed). 8. Karnofsky Performance Score (KPS) ≥60. 9. Presence of at least 1 measurable site of disease. 10. [Applicable only for France] All patients included in the trial must be affiliated with a social security regime or be a beneficiary of the same in order to be included in the study.	1. Pathologically confirmed, well differentiated (G1 or G2), advanced (unresectable or metastatic), neuroendocrine tumour of GI or lung origin 2. No history of and no active symptoms related to carcinoid syndrome 3. In addition to treatment-naive patients, patients previously treated with SSA, Interferon (IFN), one prior line of chemotherapy, and/or PRRT are allowed into the study. Pretreated patients must have progressed on or after the last treatment 4. Radiological documented disease progression within 6 months prior to randomisation 5. Measurable disease 6. WHO performance status ≤1 7. Adequate bone marrow, liver and renal function
Exclusion criteria	**Exclusion criteria**
1. Either serum creatinine >150 µmol/L (>1.7 mg/dL), or creatinine clearance <50 mL/min. 2. Hb concentration <5.0 mmol/L (<8.0 g/dL); WBC <2x109/L (2000/mm3); platelets <75x109/L (75x103/mm3). 3. Total bilirubin >3 x ULN. 4. Serum albumin <3.0 g/dL unless prothrombin time is within the normal range. 5. Pregnancy or lactation. 6. For female patients of childbearing potential and male patients, who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception. 7. Treatment with >30 mg Octreotide LAR at 3-4 weeks intervals within 12 weeks prior to randomisation in the study. 8. Peptide receptor radionuclide therapy (PRRT) at any time prior to randomisation in the study. 9. Any surgery, radioembolisation, chemoembolisation, chemotherapy and radiofrequency ablation within 12 weeks prior to randomisation in the study.	1. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, pancreatic islet cell carcinoma, insulinoma, glucagonoma, gastrinoma, goblet cell carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma 2. Patients with pancreatic NET or NET of origins other than GI or Lung 3. Patients with history of or active symptoms of carcinoid syndrome (e.g. flushing, diarrhoea) 4. Patients with more than one line of prior chemotherapy 5. Prior targeted therapy 6. Hepatic locoregional therapy within the last 6 months 7. Prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, deforolimus) 8. Known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus)

10. Interferons, Everolimus (mTOR-inhibitors) or other systemic therapies within 4 weeks prior to randomisation in the study. 11. Known brain metastases, unless these metastases have been treated and stabilised for at least 24 weeks, prior to enrolment in the study. 12. Uncontrolled congestive heart failure (NYHA II, III, IV). 13. Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN. 14. Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 h before and 24 h after the administration of Lutathera, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of Lutathera, unless the tumour uptake on target lesions observed by OctreoScan® imaging during continued Octreotide LAR treatment is at least as high as normal liver uptake observed by planar imaging. 15. Patients with any other significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with the completion of the study.	9. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus 10. Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy 11. Patients who have any severe and/or uncontrolled medical conditions such as: o unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to randomisation, serious uncontrolled cardiac arrhythmia o active or uncontrolled severe infection o liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA) 12. Chronic treatment with corticosteroids or other immunosuppressive agents 13. Known history of HIV seropositivity 14. Pregnant or nursing (lactating) women

Assumptions

It has been necessary to make a series of assumptions in order to link the trials into a network to perform the NMA. These are detailed below.

The somatostatin receptor status of patients was not reported RADIANT-4 trial. As no sub-group analyses in somatostatin receptor-positive or negative patients were reported, the difference in relative treatment effect between these two patient populations in these trials is unknown. This is not in alignment with the NETTER-1 trial, in which all patients were somatostatin receptor-positive. Taking into account that somatostatin receptor 2 positivity has been reported in most GI-NETS (>90%) (Reubi, 2003), the assumption was made that the relative treatment effect of everolimus in the RADIANT-4 trial did not differ between somatostatin receptor-positive and negative patients.

All patients in the RADIANT-4 trial had non-functional tumours. Patients were eligible to participate in the NETTER-1 trial if they had functional or non-functional tumours. It was assumed that the relative treatment effect of everolimus and Lutathera does not differ between functional and non-functional patients.

The patient populations used in PFS and OS GI-NET MTC analyses are shown in Table 9. The RADIANT-4 trials reported PFS data for sub-groups of patients that were considered to be in close alignment with the NETTER-1 trial patient population. However, as OS data were not reported for these sub-groups, the MTC analysis was performed using OS data from the overall lung and GI-NET population in the RADIANT-4 trial.

Table 9. Patient populations: GI-NET

Trial name	GI-NET PFS analysis	GI-NET OS analysis
NETTER-1	Midgut-NETs	Midgut-NETs
RADIANT-4	GI-NETs	Lung and GI-NETs

GI-NET, gastrointestinal neuroendocrine tumour; NET, neuroendocrine tumour; OS, overall survival; PFS, progression-free survival.

Data included in the GI-NET PFS and GI-NET OS network are shown in Table 10 and Table 11, respectively.

Table 10. Data included in the GI-NET PFS MTC

Study (Trial no.)	Intervention/comparator (s)	Label for MTC	PFS update					
			Analysis population	Patient number (n)	Hazard ratio	Lower CI	Upper CI	P value
(Advanced Accelerator Applications, 2017a) **(NCT01578239 - NETTER-1)**	Lutathera 29.6 GBq	Lutathera	ITT (Midgut NET)	117	0.214	0.139	0.331	<0.0001
	Octreotide LAR (60 mg)	Octreotide	ITT (Midgut NET)	114	NA	NA	NA	NA
(Yao et al., 2016a) **(NCT01524783 - RADIANT-4)**	Everolimus (10 mg) + BSC	Everolimus	sub-analysis ITT (GI-NET)	118	0.56	0.37	0.84	NR
	Placebo + BSC	Placebo	sub-analysis ITT (GI-NET)	57	NA	NA	NA	NA

BSC, best supportive care; CI, confidence interval; GI-NET, gastrointestinal neuroendocrine tumour; ITT, intent-to-treat; LAR, long-acting release; MTC, mixed treatment comparison; NA, not applicable; NET, neuroendocrine tumour; NR, not reported; PFS, progression-free survival.

Table 11. Data included in the GI-NET OS

Study (Trial no.)	Intervention/comparator (s)	Label for MTC	OS update					
			Analysis population	Patient number (n)	Hazard ratio	Lower CI	Upper CI	P value
Advanced Accelerator Applications 2017 (Advanced Accelerator Applications, 2017a) **(NCT01578239 - NETTER-1)**	Lutathera 29.6 GBq	Lutathera	ITT (Midgut NET)	117	0.536	0.333	0.864	0.0094
	Octreotide LAR (60 mg)	Octreotide	ITT (Midgut NET)	114	NA	NA	NA	NA
Yao et al., 2015 (Yao et al., 2016a) **(NCT01524783 - RADIANT-4)**	Everolimus (10 mg) + BSC	Everolimus	ITT (FAS) (lung and GI-NETs)	205	0.64	0.4	1.05	0.037
	Placebo + BSC	Placebo	ITT (FAS) (lung and GI-NET)	97	NA	NA	NA	NA

BSC, best supportive care; CI, confidence interval; FAS, full analysis population; GI-NET, gastrointestinal neuroendocrine tumour; ITT, intent-to-treat; LAR, long-acting release; NA, not applicable; NET, neuroendocrine tumour; OS, overall survival.

Methodology for the GI-NET MTC

To correctly incorporate data from every trial, a Bayesian MTC model was used to combine the (log) hazard ratios. Fixed effects and random effects approaches were evaluated.

In order to identify the most appropriate model and test assumptions (i.e. fixed or random effects models) given the evidence base, the goodness-of-fit of model predictions to the observed data can be measured. The deviance information criterion (DIC) was used to compare different models and helped in the model choice.

There were no networks with a 'closed loop', so consistency could not be tested. In order to avoid prior beliefs influencing the results of the model, non-informative prior distributions were used.

All analyses were performed in R. (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). The MTCs analysis was implemented within a fully Bayesian framework using Markov chain Monte Carlo (MCMC) methods following those of Lu and Ades, (2004) and Dias et al., (2013). The R package gemtc was used for this (Van Valkenhoef and Kuiper, 2016).

Results

Forest plots showing results from the random effects Poisson distribution model for PFS are shown in Figure 7 and OS in Figure 8. A hazard ratio lower than 1 (left) favours the intervention, a hazard ratio greater than 1 (right) favours the comparator. When the treatments are ranked on the probability of being best Lutathera is ranked as first for both PFS and OS, suggesting it is the most effective treatment in progressive GI-NET patients (Table 12 and Table 13); however, the differences are not statistically significant.

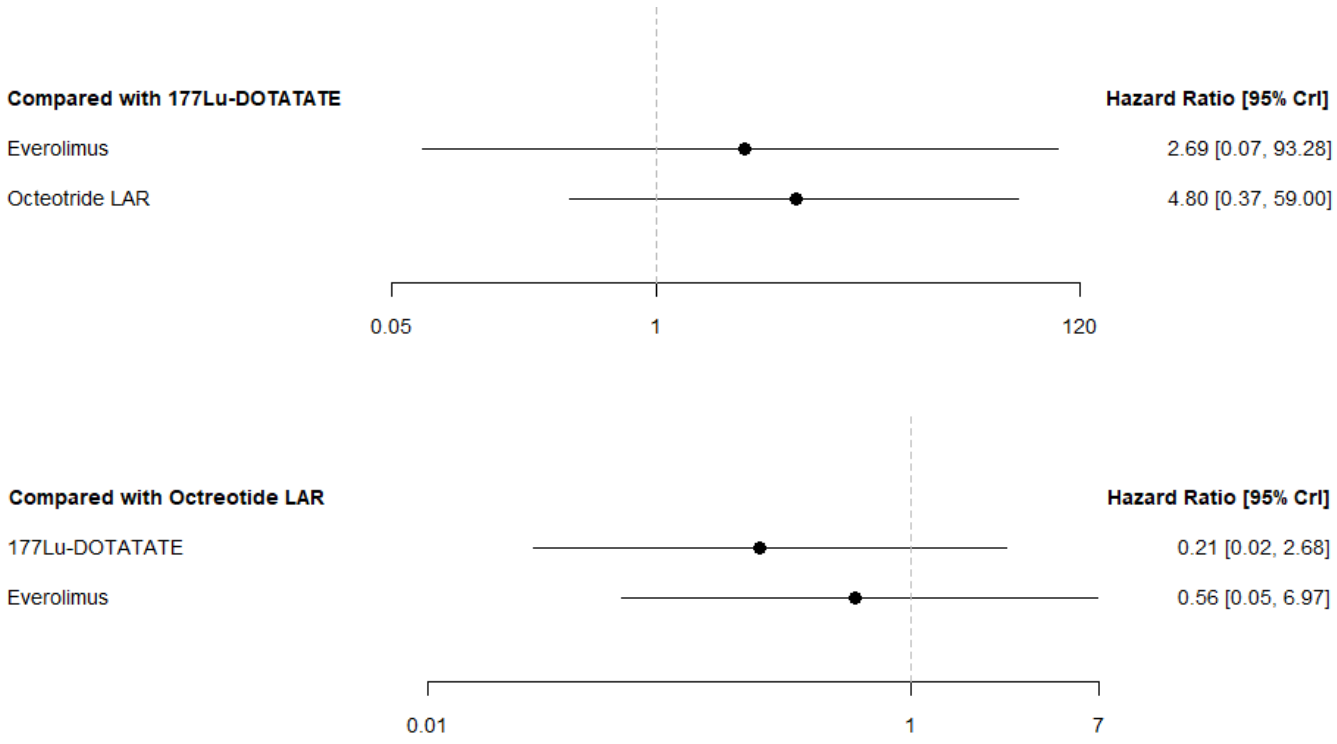


Figure 7. Forest plots showing comparative PFS results for progressive GI-NET patients using: Lutathera as a comparator and octreotide LAR as a comparator

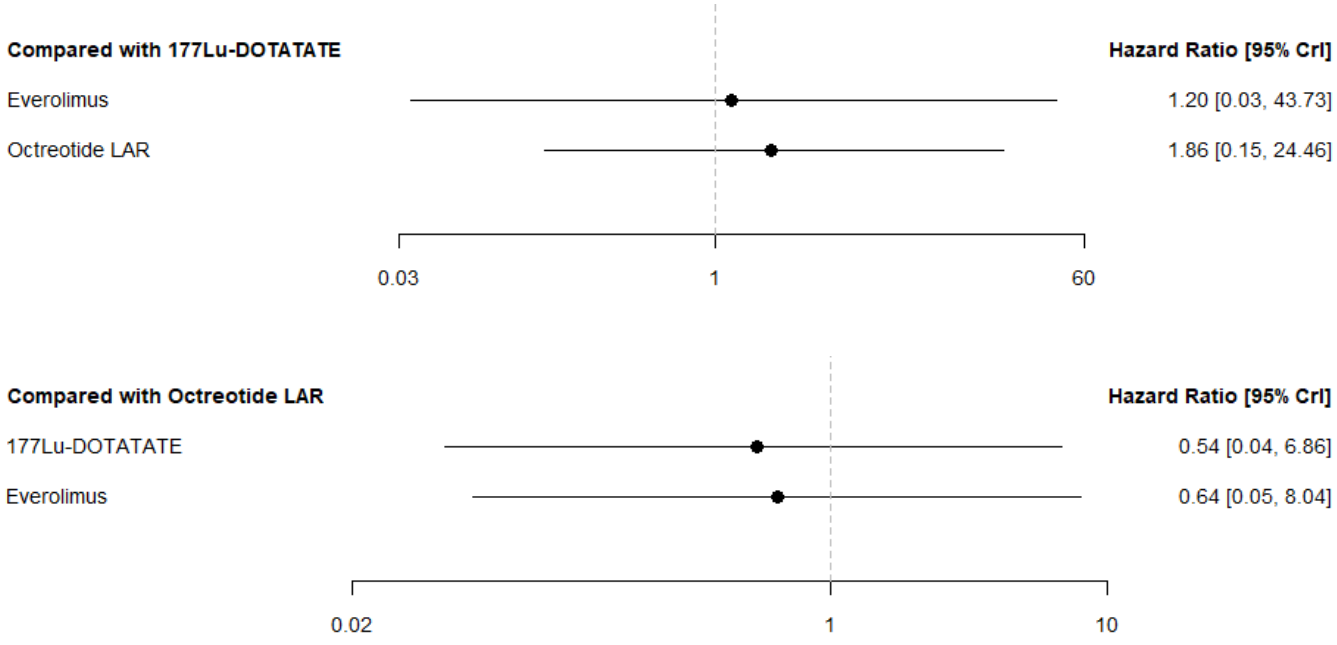


Figure 8. Forest plots showing comparative OS results for scenario 1 using: Lutathera as a comparator and octreotide LAR as a comparator

Table 12. NMA results for PFS for progressive GI-NET patients using Lutathera as a comparator and octreotide LAR as a comparator (2016 data-cut)

Compared with Lutathera			
Intervention	**HR (95% CrI)**	**Probability best**	**Rank**
Lutathera	1	77.7%	1
Everolimus	2.69 (0.07 – 93.28)	19.5%	2
Octreotide	4.80 (0.37 – 59.00)	2.8%	3
Compared with octreotide LAR			
Intervention	**HR (95% CrI)**	**Probability best**	**Rank**
Lutathera	0.21 (0.02 – 2.68)	77.7%	1
Everolimus	0.56 (0.05 – 6.97)	19.5%	2
Octreotide	1	2.8%	3

Table 13. Summary of OS results for progressive GI-NET patients using: Lutathera as a comparator and octreotide LAR as a comparator (2016 data-cut)

Compared with Lutathera			
Intervention	**HR (95% CrI)**	**Probability best**	**Rank**
Lutathera	1	52.7%	1
Everolimus	1.20 (0.03 – 43.73)	39.1%	2
Octreotide LAR	1.86 (0.15 – 24.46)	8.2%	3
Compared with octreotide LAR			
Intervention	**HR (95% CrI)**	**Probability best**	**Rank**
Lutathera	0.54 (0.04 – 6.86)	52.7%	1
Everolimus	0.64 (0.05 – 8.04)	39.1%	2
Octreotide LAR	1	8.2%	3

3.2 P-NET Matching Adjusted Indirect Comparison

Following communication with NICE following the ACD consultation, we have conducted a matching adjusted indirect comparison (MAIC) to compare Lutathera with BSC, everolimus and sunitinib in the PNET patient population.

Trial eligibility criteria

Three clinical trials met the inclusion criteria for inclusion in the MAIC (details of the review provided in original submission): ERASMUS; RADIANT-3 and NCT00428597. For Lutathera, the ERASMUS study was used (Advanced Accelerator Applications, 2017b). For everolimus and BSC, the RADIANT-3 study (Yao et al., 2011, 2016b) provides the data, and NCT00428597 (Raymond et al., 2011; Faivre et al., 2017) is used for the sunitinib data (although it also has a BSC arm that was smaller than the RADIANT-3 study). Kaplan-Meier data for OS and PFS was available in RADIANT-3 (Yao et al., 2011, 2016b) and NCT00428597 (Raymond et al., 2011; Faivre et al., 2017).

To be eligible for the ERASMUS study (Advanced Accelerator Applications, 2017b), presence of somatostatin receptors detected within six months of the start of treatment was required. A life expectancy of greater than 12 weeks, Karnofsky Performance Score of 50 or greater, serum creatine ≤ 150 µmol/L, Hb concentration of ≥ 5.5 mol/L, serum albumin > 30 g/L and total bilirubin ≤ 3 times the upper limit of normal were also listed as inclusion criteria. Those who had encountered surgery, radiotherapy, chemotherapy or other investigational therapy within three months of the start of treatment, those with brain metastases untreated in the six months previous to the start of study and those with uncontrolled congestive heart failure were all excluded from the study, along with pregnant women, those who could potentially be cured with surgery, those with any other significant medical, psychiatric or surgical condition uncontrolled by treatment and patients receiving therapy with short-acting somatostatin analogues. The updated Clinical Study Report (31 May 2017) previously provided to NICE forms the dataset used in the analysis.

The RADIANT-3 trial included patients no younger than 18 years of age with unresectable or metastatic pancreatic neuroendocrine tumours and radiologic documentation of disease progression in the 12 months preceding randomisation. A WHO performance status of 2 or less and the presence of measurable disease as assessed by RECIST version 1.0 were also key eligibility criteria, along with adequate bone marrow, hepatic and renal function, and adequately controlled lipid and glucose concentrations. Patients were excluded if they had undergone hepatic-artery embolisation in the six months preceding enrolment, or cryoablation or radiofrequency ablation of hepatic metastasis within two months of enrolment. Those with any severe or uncontrolled medical conditions, those who had received therapy with an mTOR inhibitor and those who were receiving long-term treatment with glucocorticoids or other immunosuppressive agents were excluded from the study.

NCT00428597 also considered patients with pathologically confirmed, advanced or metastatic pancreatic endocrine tumours, with documented disease progression assessed by RECIST within previous 12 months. A WHO performance status of 2 or less and adequate hematologic, hepatic and renal function were also inclusion criteria. Excluded from the trial were patients with poorly differentiated pancreatic neuroendocrine tumours, cardiac arrest or pulmonary embolism in the twelve months prior to randomisation, previous tyrosine kinase or VEGF inhibitor treatment, ongoing cardiac dysrhythmias or a prolonged QT interval corrected for heart rate, symptomatic brain metastases, or a left ventricular ejection fraction of 50% or less.

A comparison was carried out where patient-level data (PLD) was available for Lutathera, and summary data was available for the comparators. The key covariates reported by the trials indicated a good overlap between study populations. The base-case analysis was performed as shown in Table 14.

Table 14. MAIC base-case analysis

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Comparison	Outcome	Method	Lutathera data		Comparator data	
			Study	Data type	Study	Data type
Lutathera versus BSC	OS	MAIC	ERASMUS	PLD	RADIANT-3	KM
Lutathera versus BSC	OS	MAIC	ERASMUS	PLD	NCT00428597	KM
Lutathera vs everolimus	OS	MAIC	ERASMUS	PLD	RADIANT-3	KM
Lutathera vs sunitinib	OS	MAIC	ERASMUS	PLD	NCT00428597	KM
Lutathera vs BSC	PFS	MAIC	ERASMUS	PLD	RADIANT-3	KM
Lutathera vs BSC	PFS	MAIC	ERASMUS	PLD	NCT00428597	KM
Lutathera vs everolimus	PFS	MAIC	ERASMUS	PLD	RADIANT-3	KM
Lutathera vs sunitinib	PFS	MAIC	ERASMUS	PLD	NCT00428597	KM

PFS, Progression free survival; PLD, Patient level data; KM, Kaplan-Meier; MAIC, Matching adjusted indirect comparison; OS, Overall survival

For studies where Kaplan-Meier curves were available, but patient-level data (PLD) was not, digitised Kaplan-Meier curves were used. The Guyot method was used to reconstruct individual event times and censoring times from the digitised Kaplan-Meier curves (Guyot et al., 2012).

All analyses were conducted using R version 3.3.2 or above. The analysis was conducted by one statistician, and checked by a second statistician.

Covariates

To conduct an unanchored MAIC, all important covariates that determine patient outcomes must be identified to include in modelling. A shortlist of potential key prognostic factors and effect modifiers to include in the MAIC was derived from discussion with 2 clinicians with extensive experience in treating GEP-NET patients.

A full list of the shortlisted covariates obtained from the ERASMUS (Advanced Accelerator Applications, 2017b), RADIANT-3 (Yao et al., 2011, 2016b) and NCT00428597 (Raymond et al., 2011; Faivre et al., 2017) trials are shown in Table 15. These are similar to those listed in a previously published MAIC using the RADIANT-3 and NCT00428597 trials (Signorovitch et al., 2013), and broadly the same between both comparator trials. There was good overlap in most of the covariates, however, status of tumour and time from progression to randomisation do not match particularly closely. This may be due to the assumption made that tumour burden and histologic status of tumour are the same, with extensive burden assumed to be well differentiated, and moderate burden assigned as moderately differentiated. Likewise, limited tumour burden was taken as limited histological status.

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Table 15. Summary of key covariates across the trials

	ERASMUS	RADIANT-3	RADIANT-3	NCT00428597
	Lutathera	Everolimus	BSC	Sunitinib
N	62	207	203	86
Age mean, median (range) years	58.45, 58.5 (33-81)	NA, 58 (23-87)	NA, 57 (20-82)	NA, 56 (25-84)
Sex	Male: 28 (45%) Female: 34 (55%)	Male: 110 (53%) Female: 97 (47%)	Male: 117 (58%) Female: 86 (42%)	Male: 42 (49%) Female: 44 (51%)
ECOG performance status	0: 48 (77%) 1: 13 (21%) 2: 1 (1%)	0: 139 (67%) 1: 62 (30%) 2:6 (3%)	0: 133 (66%) 1: 64 (32%) 2:6 (3%)	0: 53 (62%) 1: 33 (38%) 2: 0 (0%)
Organ involved	Liver: 28 (45%) Kidneys: 34 (55%)	Liver: 190 (92%) Pancreas: 92 (44%) Lymph nodes: 68 (33%) Lung: 28 (14%) Bone: 13 (6%)	Liver: 187 (92%) Pancreas: 84 (41%) Lymph nodes: 73 (36%) Lung: 30 (15%) Bone: 29 (14%)	NA
Time from initial diagnosis	≤ 6 months: 11 (18%) >6 months to ≤2 yrs: 25 (40%) >2 yrs to ≤5 yrs: 15 (24%) >5 yrs: 10 (16%) NR: 1 (1%) Median: 1.24 years (0.37-30.78)	≤ 6 months: 24 (12%) >6 months to ≤2 yrs: 65 (31%) >2 yrs to ≤5 yrs: 54 (26%) >5 yrs: 64 (31%)	≤ 6 months: 33 (16%) >6 months to ≤2 yrs: 43 (21%) >2 yrs to ≤5 yrs: 81 (40%) >5 yrs: 46 (23%)	Median: 2.4 years (0.1-25.6)
Time from disease progression to randomisation	≤1 month: 1 (2%) >1 mo to ≤2 mo: 0 (0%) >2 mo to ≤3 mo: 3 (5%) >3 mo to ≤12 mo: 26 (42%) >12 months: 26 (42%) NR: 6 (10%)	≤1 month: 73 (35%) >1 mo to ≤2 mo: 43 (21%) >2 mo to ≤3 mo: 30 (14%) >3 mo to ≤12 mo: 58 (28%) >12 months: 3 (1%)	≤1 month: 61 (30%) >1 mo to ≤2 mo: 53 (26%) >2 mo to ≤3 mo: 29 (14%) >3 mo to ≤12 mo: 54 (27%) >12 months: 1 (<1%)	NA
Tumour functionality[3]	Gastrinoma: 2 (3%) Glucagonoma: 5 (8%) Insulinoma: 3 (5%) VIPoma: 2 (3%) Carcinoid: 1 (2%) Nonfunctioning: 30 (48%)	NA	NA	Gastrinoma: 9 (10%) Glucagonoma: 3 (3%) Insulinoma: 2 (2%) VIPoma: 0 (0%) Somatostatinoma: 1(1%) Other/unknown: 29 (34%) Nonfunctioning: 42 (49%)
Previous treatment	Surgery: 28 (45%)	Radiotherapy: 23%	Radiotherapy: 20% Chemotherapy: 50%	Surgery: 76 (88%)

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	Radiation therapy: 2 (3%) Chemoembolisation: 8 (13%)	Chemotherapy: 50% Somatostatin analogue therapy: 49%	Somatostatin analogue therapy: 50%	Radiation therapy: 9 (10%) Chemoembolisation: 7 (8%) Radiofrequency ablation: 3 (3%) Percutaneous ethanol injection: 1 (1%) Somatostatin analogues: 30 (35%)

The RADIANT-3 trial reports combined results for some variables for patients treated with everolimus and BSC, which we cannot separate. These include [1]geographical region, with a combined 185 (45%) patients from America, 156 (38%) from Europe and 69 (17%) from Asia; [2]race, with 322 (79%) white patients and 74 (21%) Asian patients involved in the study; and [3] 98 (24%) of patients had gastrinoma, glucagonoma, VIPoma, insulinoma or somatostatinoma.

To investigate the relationships between the covariates and OS and PFS, univariate analyses were carried out within each study with PLD (ERASMUS). For categorical covariates, the log-rank test was used. For continuous covariates, Cox proportional hazards models were used. Kaplan-Meier plots and log-cumulative hazard plots were used to visualise the results. Covariates were included in the MAIC if they were significant, or close to significance, at the 0.2 level (Table 16).

Table 16. MAIC covariate p-values

Covariate	ERASMUS (PFS) P-value	ERASMUS (OS) P-value	Included in PFS	Included in OS
Age mean, median (range) years	<0.001	<0.01	X	X
Sex	0.83	0.54		
ECOG performance status	<0.05	<0.01	X	X
Organ involved	0.53	0.27		
Time from initial diagnosis	0.30	0.33		
Time from disease progression to randomisation	0.73	0.76		
Tumour functionality	0.99	0.57		
Previous chemotherapy	0.19	<0.001	X	X
Previous radiotherapy	0.25	<0.001	X	X
Previous surgery	0.54	0.70		

For comparisons where a Kaplan-Meier curve was available in the second study, PLD was reconstructed for the second study. Standard errors were estimated using a robust sandwich estimator (Phillippo et al., 2016). The effective sample size (ESS) was also calculated.

The individual data was reweighted so that the reweighted mean covariate values (and variances if available) for continuous covariates, and the frequencies for categorical covariates, for the ERASMUS study balanced the corresponding values in the second study. The choice of covariates for the re-weighting was based on the results of the identification process and univariate analyses. The aim was to limit the number of covariates to avoid extreme weighting values. The post matching balance is shown in Table 17 to Table 20.

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Table 17. Post matching balance NCT00428597 (BSC)

Covariate	Result	ERASMUS (pre-match)	ERASMUS (post-match)	NCT00428597 (BSC)
	N (ESS)	62	62 (36)	85
Age	Mean	58.45	57.00	57
ECOG	0	0.77	0.48	0.48
	1 or 2	0.23	0.52	0.52
Previous radiotherapy	Yes	0.03	0.14	0.14
	No	0.97	0.86	0.86
	Unknown	0.00	0.00	0.00
Previous chemotherapy	Yes	0.13	0.16	0.16
	No	0.87	0.84	0.84
	Unknown	0.00	0.00	0.00
Weights	Mean		1.00	
	Range		0.13 – 6.95	
	No. of patients with near 0 weight		0	

Table 18. Post matching balance NCT00428597 (Sunitinib)

Covariate	Result	ERASMUS (pre-match)	ERASMUS (post-match)	NCT00428597 (Sunitinib)
	N (ESS)	62	62 (31)	86
Age	Mean	58.45	56.04	56
ECOG	0	0.77	0.62	0.62
	1 or 2	0.23	0.38	0.38
Previous radiotherapy	Yes	0.03	0.09	0.10
	No	0.97	0.91	0.90
	Unknown	0.00	0.00	0.00
Previous chemotherapy	Yes	0.13	0.09	0.08
	No	0.87	0. 91	0.92
	Unknown	0.00	0.00	0.00
Weights	Mean		1.00	
	Range		0.00 – 5.32	
	No. of patients with near 0 weight		6	

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Table 19. Post matching balance RADIANT-3 (BSC)

Covariate	Result	ERASMUS (pre-match)	ERASMUS (post-match)	RADIANT-3 (BSC)
	N (ESS)	62	62 (18)	203
Age	Mean	58.45	57.00	57
ECOG	0	0.77	0.66	0.66
	1 or 2	0.23	0.34	0.34
Previous radiotherapy	Yes	0.03	0.20	0.20
	No	0.97	0.80	0.80
	Unknown	0.00	0.00	0.00
Previous chemotherapy	Yes	0.13	0.50	0.50
	No	0.87	0.50	0.50
	Unknown	0.00	0.00	0.00
Weights	Mean		1.00	
	Range		0.31 – 11.22	
	No. of patients with near 0 weight		0	

Table 20. Post matching balance RADIANT-3 (everolimus)

Covariate	Result	ERASMUS (pre-match)	ERASMUS (post-match)	RADIANT-3 (everolimus)
	N (ESS)	62	62 (17)	207
Age	Mean	58.45	58.00	58
ECOG	0	0.77	0.67	0.67
	1 or 2	0.23	0.33	0.33
Previous radiotherapy	Yes	0.03	0.23	0.23
	No	0.97	0.77	0.77
	Unknown	0.00	0.00	0.00
Previous chemotherapy	Yes	0.13	0.50	0.50
	No	0.87	0.500	0.50
	Unknown	0.00	0.00	0.00
Weights	Mean		1.00	
	Range		0.39 – 12.23	
	No. of patients with near 0 weight		0	

Kaplan-Meier survival curves are presented for each MAIC, showing Lutathera survival after the reweighting procedure and the respective comparators, in Figure 9 to Figure 16.

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Figure 9. Kaplan-Meier survival curves after reweighting - BSC (Yao, 2016) (PFS)

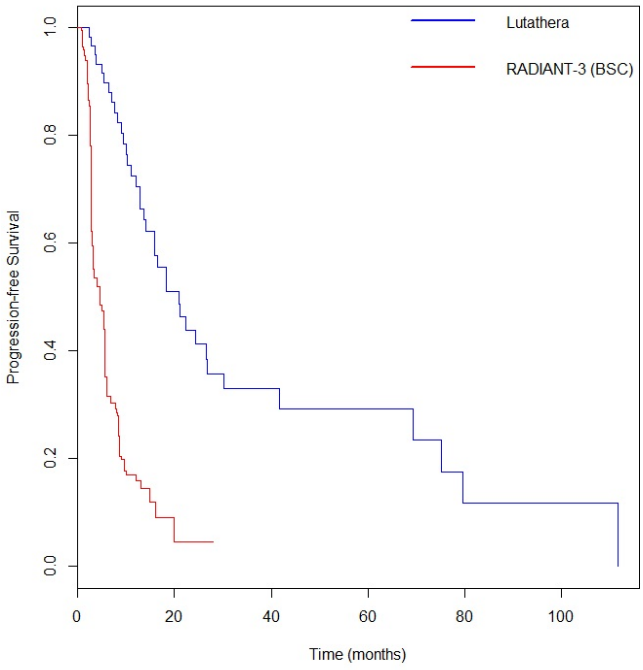

Figure 10. Kaplan-Meier survival curves after reweighting - BSC (Yao, 2016) (OS)

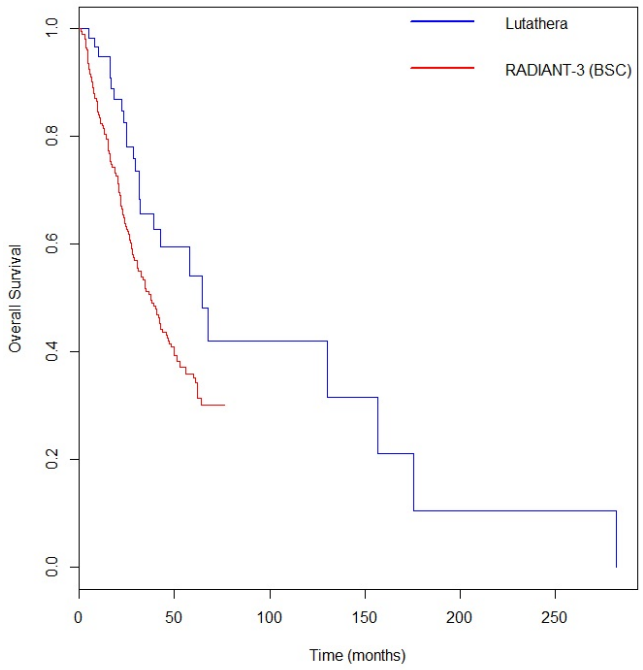

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Figure 11. Kaplan-Meier survival curves after reweighting - BSC (Faivre, 2016) (PFS)

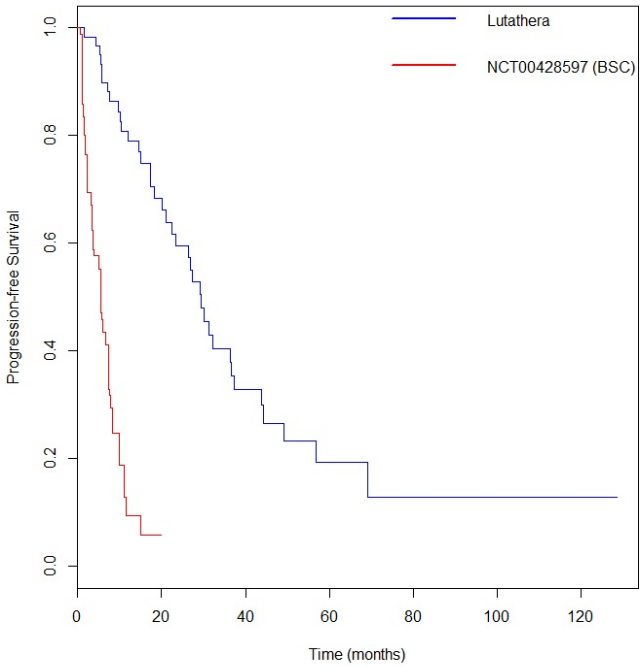

Figure 12. Kaplan-Meier survival curves after reweighting - BSC (Faivre, 2016) (OS)

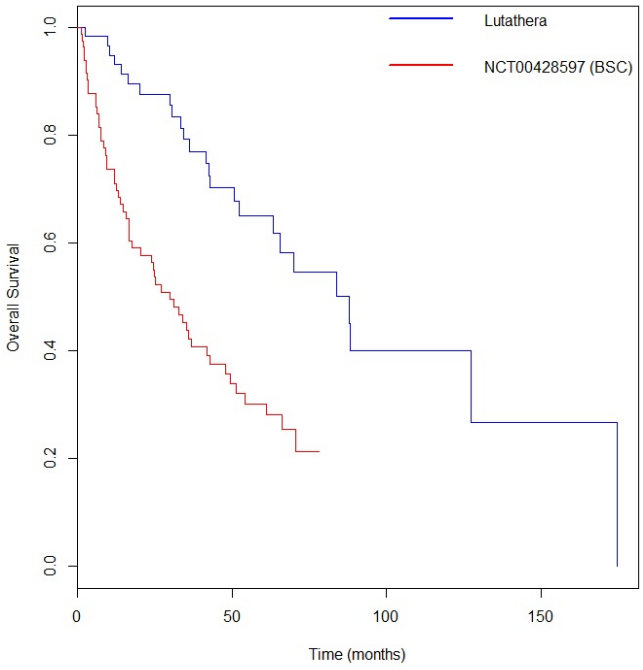

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Figure 13. Kaplan-Meier survival curves after reweighting - Everolimus (PFS)

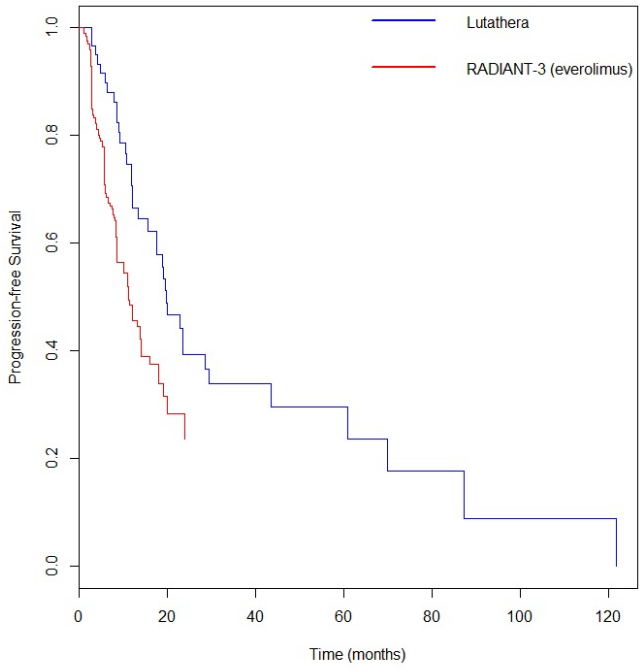

Figure 14. Kaplan-Meier survival curves after reweighting - Everolimus (OS)

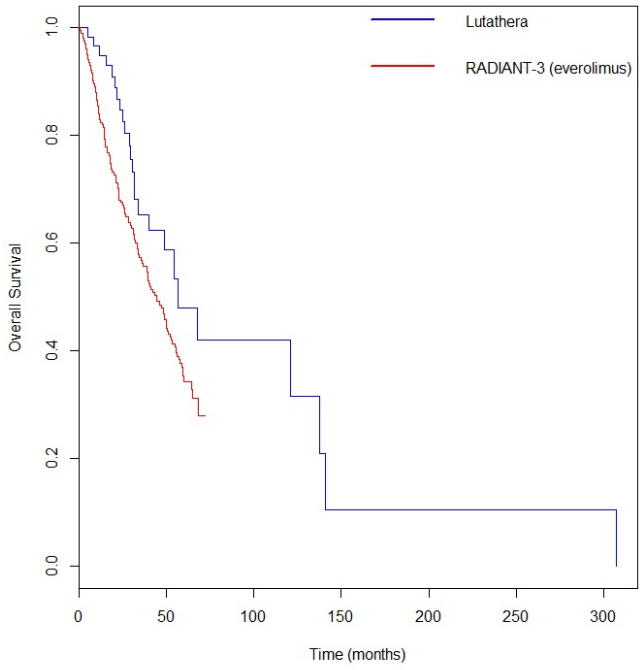

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Figure 15. Kaplan-Meier survival curves after reweighting - Sunitinib (PFS)

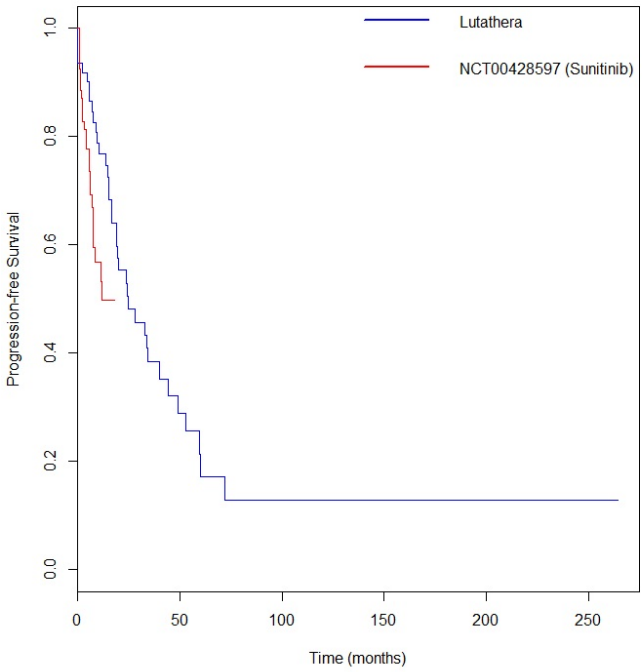
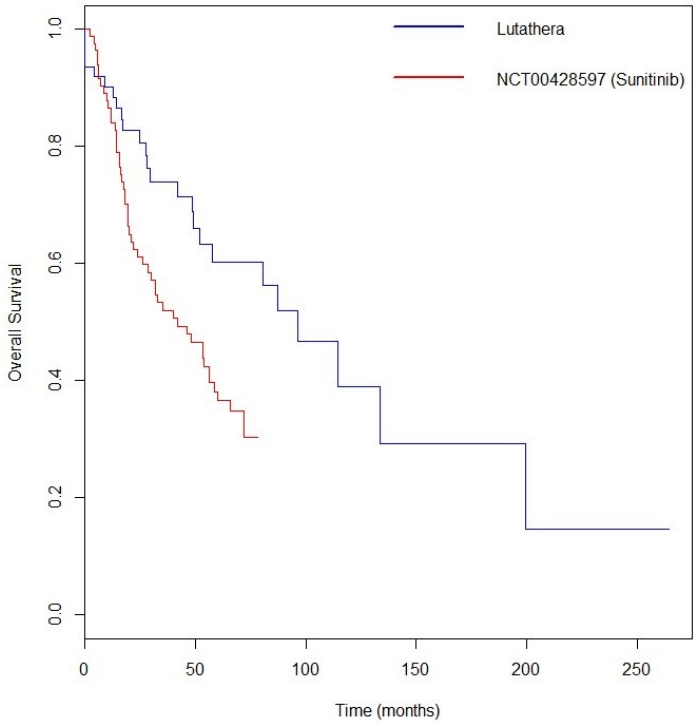


Figure 16. Kaplan-Meier survival curves after reweighting - Sunitinib (OS)



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Cox proportional hazard models were fitted to the adjusted Lutathera PFS and OS data from Erasmus, and respective reconstructed PLD for comparators, to estimate hazard ratios. These results are shown in Table 21.

Table 21. Hazard ratios estimated from Matching Adjusted Indirect Comparisons

Comparator	Hazard ratio PFS [95% CI]	Hazard ratio OS [95% CI]
Lutathera versus. NCT00428597 (Sunitinib)	0.47 [0.25, 0.88]	0.50 [0.29, 0.84]
Lutathera versus. NCT00428597 (BSC)	0.12 [0.07, 0.21]	0.33 [0.20, 0.56]
Lutathera versus. RADIANT-3 (everolimus)	0.52 [0.34, 0.79]	0.61 [0.39, 0.98]
Lutathera versus. RADIANT-3 (BSC)	0.21 [0.13, 0.32]	0.56 [0.36, 0.90]

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Table 22. Relevant GI-NET trials

Study (Trial no.)	Intervention 1	Intervention 2	Intervention 3	Population	Objective	Primary study references
Advanced Accelerator Applications 2017a (NCT01578239 - NETTER-1)	**Lutathera + octreotide** • Lutathera 29.6 GBq • Dosing: 4 administrations of 7.4 GBq (8 week intervals) • Route: IV • Octreotide 30 mg (Sandostatin® LAR Depot) • Dosing: At least 4 h after Lutathera infusion • Route: IM	**Octreotide LAR** • Octreotide 60 mg (Sandostatin® LAR Depot) • Dosing: every four weeks • Route: IM	**NA**	• Patients with locally advance, inoperable midgut carcinoid tumours (ITT (FAS) - 229) • Karnofsky Performance Score ≥60. • Progressive disease (100%) • Functional and non-functional (100%) • Somatostatin receptor positive (100%) • Received prior therapy (Octreotide LAR) (100%)	The primary objective of the study was to compare Progression Free Survival (PFS) after treatment with Lutathera plus best supportive care (30 mg octreotide LAR) to treatment with high dose (60 mg) octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, well-differentiated neuroendocrine tumours of the small bowel (midgut carcinoid tumours.	• (Advanced Accelerator Applications, 2017a) • (Advanced Accelerator Applications & Pierrel Research Europe GmbH, 2015) • (Strosberg et al., 2017)
Yao et al., 2015 (NCT01524783 - RADIANT-4)	**Everolimus plus BSC** • Everolimus 10 mg • Dosing: daily until disease progression • Route: oral *N.B. BSC included*	**Placebo plus BSC** • Matching placebo • Dosing: daily • Route: oral *N.B. BSC included treatment deemed necessary by the physician except anti-tumour agents*	NA	• Patients with advanced (unresectable or metastatic), non-functional, well-differentiated (grade 1 or 2 according to the 2010 WHO classification) neuroendocrine tumours of lung or	To assess the efficacy and safety of everolimus compared with placebo in patients with advanced, progressive neuroendocrine tumours of the lung or gastrointestinal tract	• (Yao et al., 2016a)

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Study (Trial no.)	Intervention 1	Intervention 2	Intervention 3	Population	Objective	Primary study references
	treatment deemed necessary by the physician except anti-tumour agents like somatostatin analogues, interferons, tumour ablative procedures, radiation, and concurrent chemotherapy.	*like somatostatin analogues, interferons, tumour ablative procedures, radiation, and concurrent chemotherapy.*		gastrointestinal origin (ITT = 302) • WHO performance score ≤ 2 • Progressive disease (100%) • Non-functional (100%) • Somatostatin receptor status not reported • Received prior therapy (100%) Relevant NET subgroups reported • GI-NET (n = 175)		
Castellano et al., 2013 (NCT00412061 - RADIANT-2)	**Everolimus + octreotide LAR** • Everolimus 10 mg • Dosing: daily until disease progression • Route**:** oral • Octreotide LAR 30 mg • Dosing: every 28 days**.** Route: IM	**Placebo + octreotide LAR** • Matching placebo • Dosing: daily until disease progression • Route: oral • Octreotide LAR 30 mg • Dosing: every 28 days**.** Route: IM	**NA**	• Patients with low or intermediate-grade advanced, unresectable or metastatic NETs with a history of secretory symptoms (ITT = 429) • WHO performance score ≤ 2 • Progressive disease (100%) • Functionality not reported • Somatostatin receptor status not reported • Prior therapies reported (unknown if all patients received prior therapy)	A post hoc analysis of the efficacy and tolerability of everolimus plus octreotide LAR was conducted in patients with colorectal NETs enrolled in the phase III RAD001 in Advanced Neuroendocrine Tumours, Second Trial (RADIANT-2) study.	• (Castellano et al., 2013) • (Strosberg et al., 2015) • (Pavel et al., 2011)

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Study (Trial no.)	Intervention 1	Intervention 2	Intervention 3	Population	Objective	Primary study references
				Relevant NET subgroups reported: • Colorectal (n = 39) • Small intestine (n = 224) • Colon (n = 28)		

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; GI-NET, gastrointestinal neuroendocrine tumour; IM, intramuscular; IV, intravenous; ITT, intent-to-treat; LAR, long-acting release; NA, not applicable; NET, neuroendocrine tumour; SC, subcutaneous WHO, World Health Organisation.

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Table 23. Relevant P-NET trials

Study (Trial no.)	Intervention 1	Intervention 2	Intervention 3	Population	Objective	Primary study references
Raymond et al., 2011 (NCT00428597)	**Sunitinib** • Sunitinib 37.5 mg • Dosing: daily until disease progression • Route: oral	**Placebo** • Matching placebo • Dosing: daily until disease progression • Route: oral	NA	• Patients with well-differentiated pancreatic endocrine tumours that were advanced, metastatic, or both, and they were not candidates for surgery (ITT = 171) • ECOG performance score ≤ 2 • Progressive disease (100%) • Functional (26.9%) • Non-functional (50.3%) • Somatostatin receptor status not reported • Prior therapies reported (unknown if all patients received prior therapy)	To assess the efficacy and safety of continuous daily administration of sunitinib at a dose of 37.5 mg per day in patients with advanced pancreatic neuroendocrine tumours.	• (Raymond et al., 2011) • (Faivre et al., 2017) • (Vinik et al., 2016)
Yao et al., 2011 **(NCT00510068 - RADIANT-3)**	**Everolimus plus BSC** • Everolimus 10 mg • Dosing: daily until disease progression • Route: oral *N.B. Best supportive care included the use of somatostatin analogue therapy in approximately 40% of the patients.*	**Placebo plus BSC** • Matching placebo • Dosing: daily • Route: oral • *N.B. Best supportive care included the use of somatostatin analogue therapy in approximately*	NA	• Advanced (unresectable or metastatic) pancreatic neuroendocrine tumour patients (ITT = 410) • WHO performance score ≤ 2 • Progressive disease (100%) • Functionality not reported • Somatostatin receptor status not reported • Prior therapies reported (unknown if all patients received prior therapy)	To determine whether everolimus, at a dose of 10 mg per day, as compared with placebo, would prolong progression-free survival among patients with advanced pancreatic neuroendocrine tumours	• (Yao et al., 2011) • (Ito et al., 2012) • (Lombard-Bohas et al., 2015) • (Novartis Pharmaceuticals, 2010) • (Yao et al., 2016b)

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Study (Trial no.)	Intervention 1	Intervention 2	Intervention 3	Population	Objective	Primary study references
		40% of the patients.				

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; GI-NET, gastrointestinal neuroendocrine tumour; IM, intramuscular; IV, intravenous; ITT, intent-to-treat; LAR, long-acting release; NA, not applicable; NET, neuroendocrine tumour; SC, subcutaneous WHO, World Health Organisation.

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4. Economic analysis – Methods

4.1 Overview of amendments

The economic model has previously been described in the original submission document.

GI-NET Analysis

In the GI-NET patient population, the model compares Lutathera to;

- Octreotide LAR (BSC) – base case analysis
- Everolimus – scenario analysis

A series of amendments have been made to the economic model originally submitted following the ACD consultation: These amendments are:

- Inclusion of updated data from NETTER-1 in the base case analysis
- Inclusion of relative dose intensity for everolimus in the base case analysis
- Inclusion of data from an analysis of the NETTER-1 RCT which adjusts for cross-over in a scenario analysis
- Inclusion of data from the revised MTC in a scenario analysis.

P-NET Analysis

A revised economic model for the P-NET population has been conducted. In the P-NET patient population, the model compares Lutathera to;

- Octreotide LAR (BSC)
- Everolimus
- Sunitinib

A series of amendments have been made to the economic model originally submitted following the ACD consultation: These amendments are:

- Inclusion of updated data from the ERASMUS study
- Inclusion of data on relative effectiveness from a MAIC analysis (see Section 2)
- Inclusion of relative dose intensity for everolimus and sunitinib in the base case analysis

4.2 Survival curve modelling

General approach

Parametric survival modelling was required to extrapolate observed PFS and OS of Lutathera and comparators. This enabled cost-effectiveness analyses to be performed over an appropriate time horizon. The estimates of entire survival distributions were used to ensure that the mean impacts on time to events (PFS and OS) were estimated.

Given that there are multiple comparators in the GI-NET scenario including everolimus and P-NETs analysis examined in separate RCTs, various methods were used to derive absolute and relative treatment effects. With this in mind and to establish a unified method for characterising treatment effects in the cost-effectiveness model across analyses, the proportional hazards modelling approach using hazard ratios was adopted. Under this approach a HR has been applied to a baseline survival curve to compare the experimental treatments to octreotide LAR (in the case of GI-NETs) and Lutathera (in the case of P-NETs) so that all treatments can be compared to a common comparator. In P-NETs it is important to note that the MAIC translates outcomes in the ERASMUS population to those that would have been observed in the sunitinib, octreotide and everolimus population respectively and so are not strictly comparable across studies.

Extrapolation was achieved by fitting parametric models to the time to event (survival) data from the trials. This is the preferred method for incorporating survival data into health economic models

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(Latimer, 2011). Only certain parametric models are concordant with proportional hazards, but other model fits were examined to ascertain the appropriateness of the approach. One parametric model has been fitted to the entire dataset, with treatment group included as a covariate in the model and proportional hazards were assumed. An assumption that treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape is necessary. This approach is in line with the survival model selection process algorithm set out in NICE DSU 14 (Latimer, 2011).

Parametric model fits

A wide range of parametric models are available, each with their own characteristics making them suitable for different data. A series of parametric survival functions were fitted to individual patient-level data for the NETTER-1 and reweighted ERASMUS studies. The exponential, Weibull, Gompertz, log logistic and log-normal models were considered (log based models cannot be fitted with proportional hazards). In P-NETs, where a MAIC, was performed, published aggregate Kaplan-Meier data was used to reconstruct PLD and fit parametric curves.

A variety of methods were used to assess the suitability of each fitted model to the data set. Assessing the suitability of each fitted survival model was important in determining the appropriateness of the model; defined by whether the model provided a good fit to the observed data and whether the extrapolated curve was clinically and biologically plausible. Visual inspection, Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) tests and clinical and biological plausibility were used as the criteria for determining best fit.

Consideration was given to how well the parametric models fitted the clinical data by visually examining how closely the models follow the Kaplan Meier curves. This provided a simple means by which one model could be chosen over another. Visual results of fitted models to Kaplan-Meier curves for octreotide LAR versus Lutathera are shown in Figure 17 and Figure 18.

GI-NET parametric curves (NETTER-1 study)

Figure 17. KM and fitted models for PFS curves

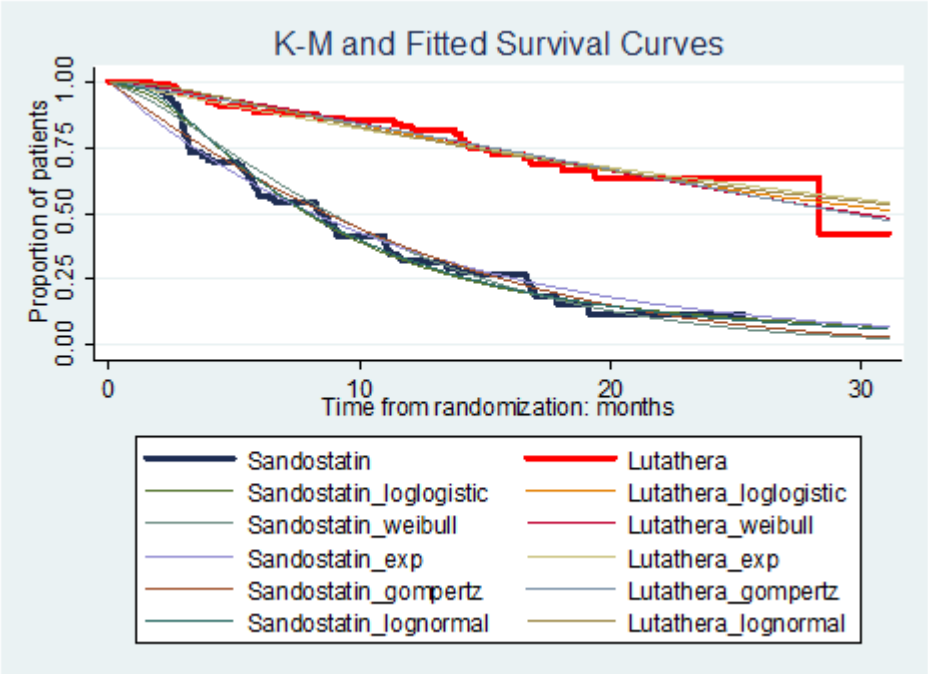

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Figure 18. KM and fitted models for OS curves

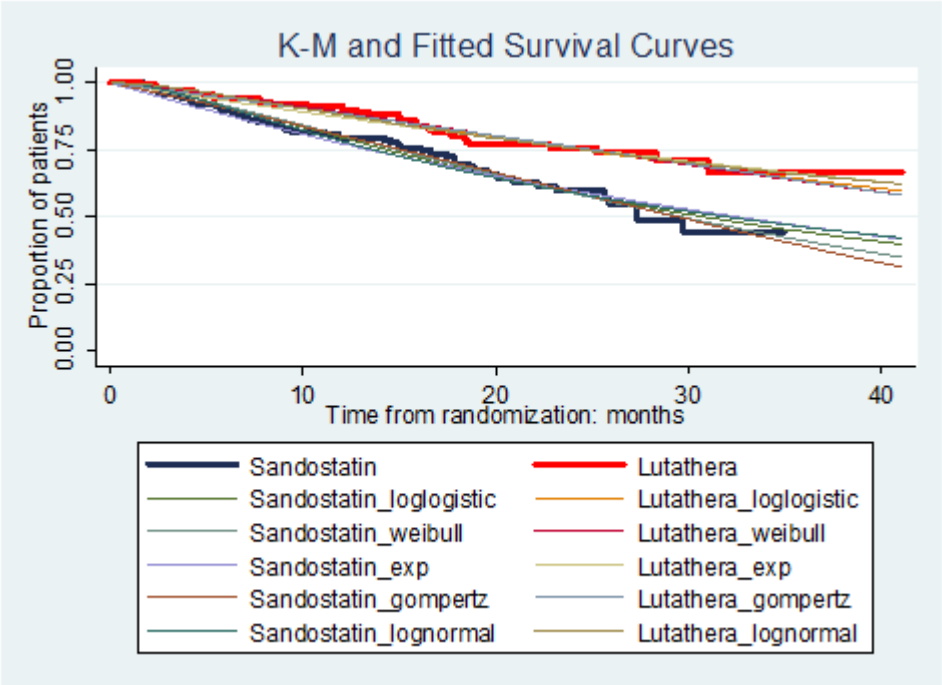

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Figure 19. Parametric curves (Weibull) - Lutathera vs BSC (Yao, 2016)

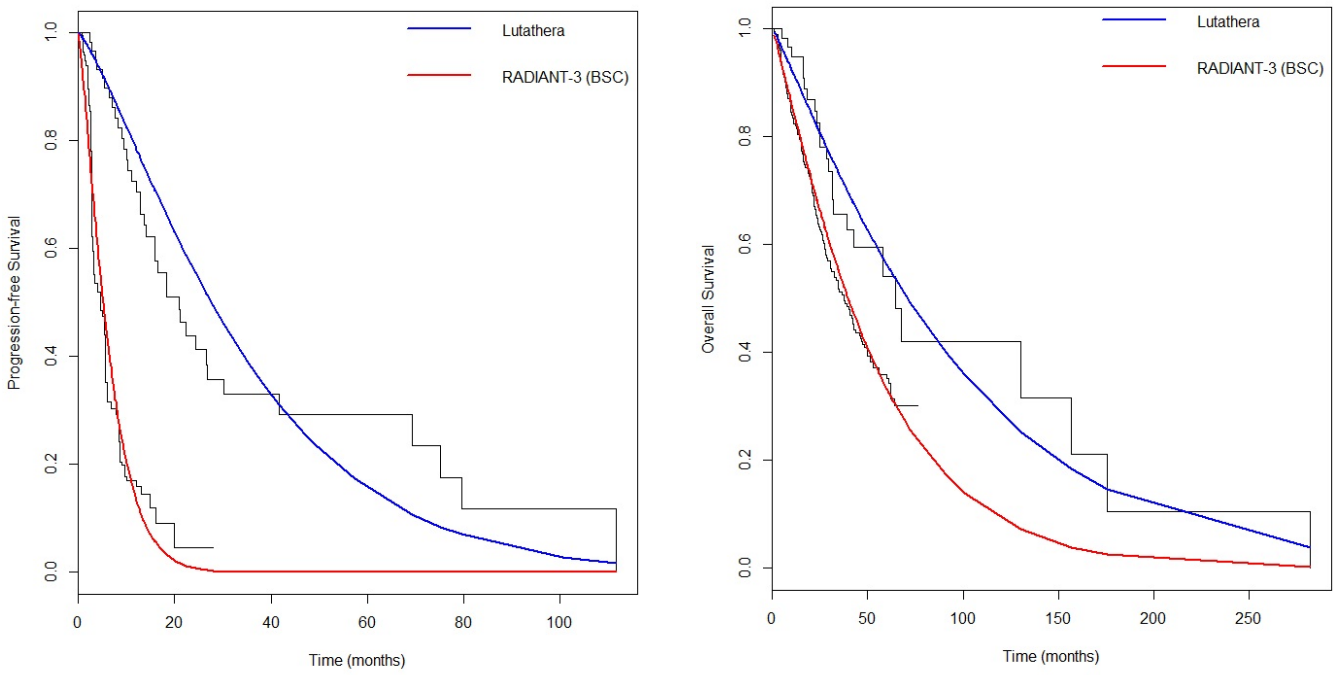

Figure 20. Parametric curves (Weibull) - Lutathera vs BSC (Faivre, 2016)

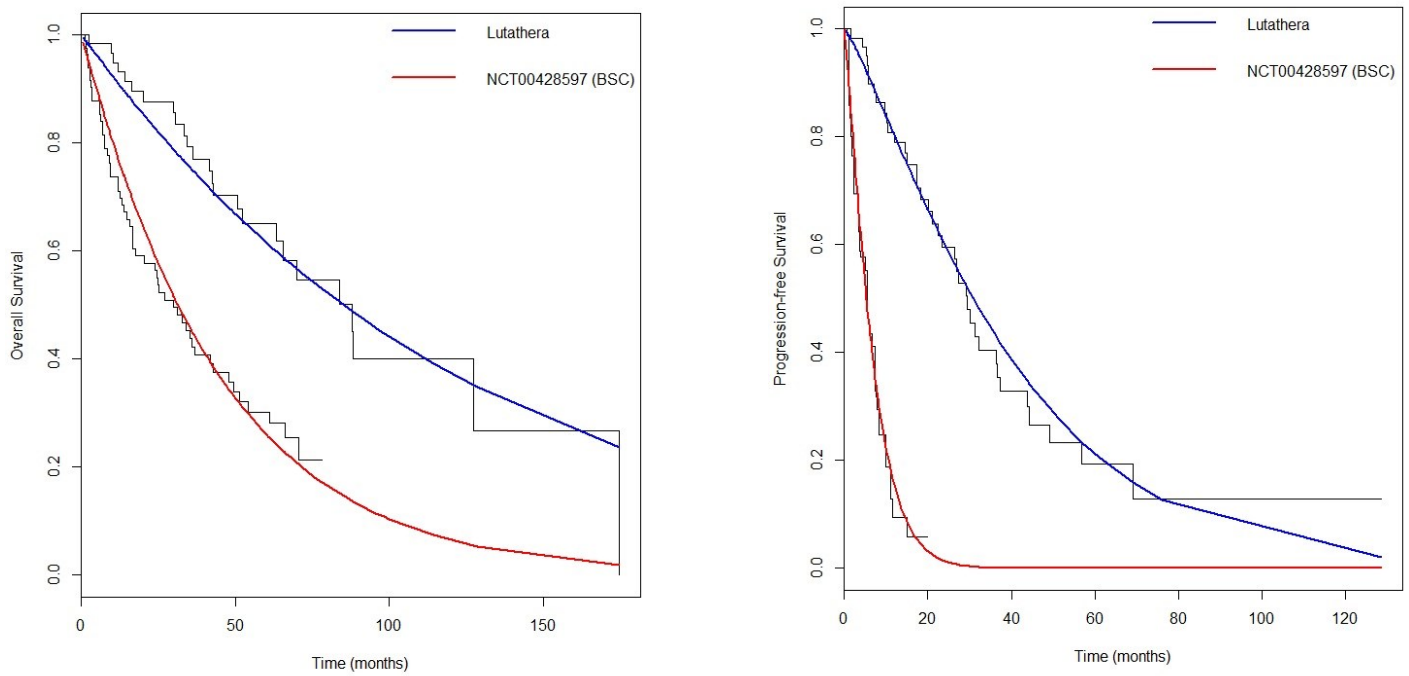

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Figure 21. Parametric curves (Weibull) – Lutathera vs Everolimus

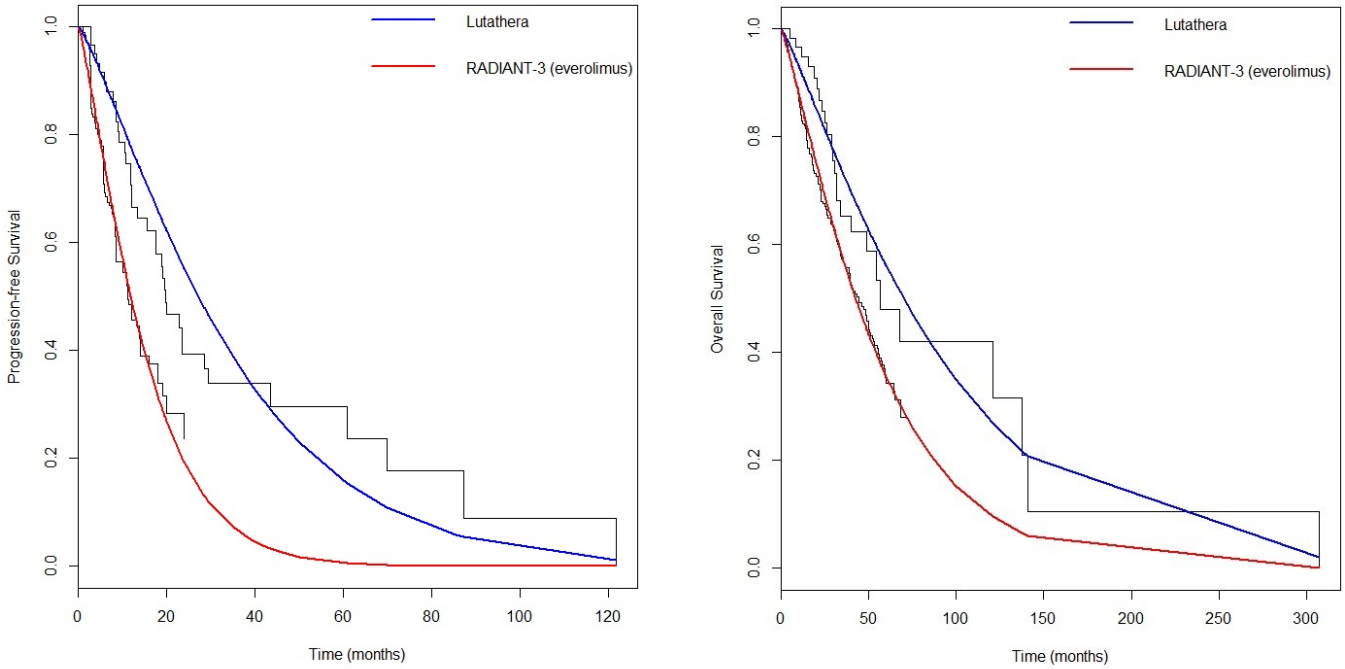
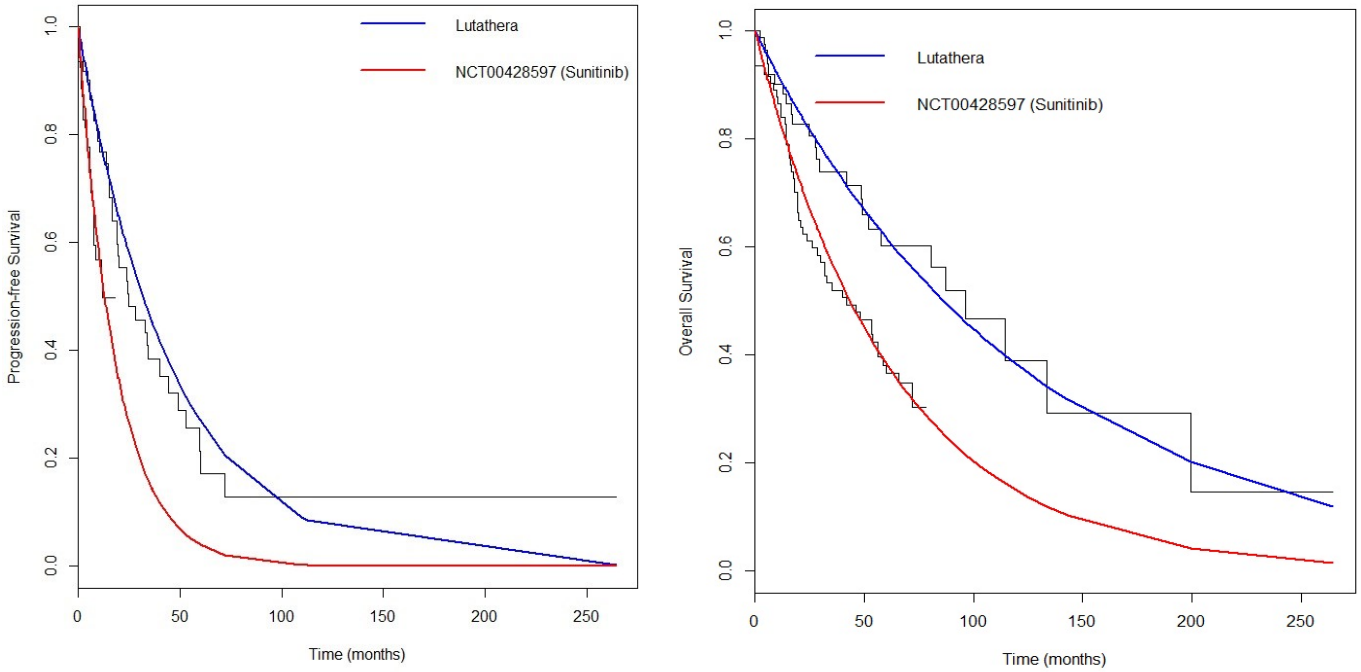


Figure 22. Parametric curves (Exponential) - Lutathera vs Sunitinib



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Clinical and biological plausibility

Visually, the fitted models presented above showed that the log-normal model in most cases is the best fitting model. This was corroborated by the output from the AIC and BIC tests.

We considered the appropriateness of the log-normal model for the NETTER-1 and the ERASMUS data taking the individual characteristics of the model into consideration.

Characteristics of the log-normal model:

- The failure rate increases to a maximum and then decreases to zero as time reaches infinity (Gupta et al., 1997).
- If deaths take place due to the competing risk of general aging, the log-normal distribution will give a poor fit when data are extrapolated (Gupta et al., 1997).
- Better for diseases with survival markedly skewed to the right (Gupta et al., 1997).

Considerations for NETTER-1 and ERASMUS patient level data:

- There is no evidence that survival for GEP-NET patients is skewed to the right as indicated by the log-normal model;
- Although a patient diagnosed with GEP-NET is likely to live for comparatively longer than other oncology patients, they are not cured of their condition and are likely to eventually die from the tumour. Failure rates do therefore not turn to zero as time approaches infinity as indicated by the log normal model;
- The mean patient age in the NETTER-1 trial was 63.7 years, indicating that death was likely to take place due to the competing risk of general aging.

Although the log-normal model after visual inspection and AIC/BIC tests was the best-fitting model, clinical and biological consideration indicated that it was not suitable for this data set. Owing to their functional form, log logistic models also result in long tails in the survival function (Kaltenthaler et al., 2011). Thus, like the log-normal model, the log logistic model was also not a clinically and biologically plausible choice. The next best fitting model for this data set was the Weibull. We used the Weibull model for the primary analysis. Parameter uncertainty has been captured in the model using the variance-covariance matrices for the different parametric models.

Implementing the fitted models in Excel

Based on the results from the goodness to fit statistic, PFS and OS were modelled with a Weibull function using ordinary least squares regression methods. In the case of the Weibull function, the unknown parameters, lambda (λ) and gamma (γ), were estimated by regressing the log of the negative log of survival versus the log of time (Rodríguez, 2010). These analyses were performed in STATA and R (for P-NETs analyses using MAIC) and the coefficients generated were used to implement the model in excel.

A partition survival model was implemented in excel with the coefficients presented above for PFS and OS using the Weibull survival function;

Weibull: $S(t) = \exp\{-(\lambda t)^{\gamma}\}$

Where:
S = survival; t = time (cycle); λ = location parameter; γ = shape parameter
The results from these regression analyses are presented below for GI-NET and P-NET patients.

The Weibull and exponential coefficients generated in STATA and used for modelling the PFS for GI-NET are presented in Table 24.

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GI-NET

The Weibull and exponential coefficients generated in STATA and used for modelling the PFS for GI-NET and P-NET are presented in Table 24. A partition survival model was implemented using Weibull: $S(t) = \exp\{-(\lambda t)^{\gamma}\}$, where: S = survival; t = time (cycle); λ = location parameter; γ = shape parameter. The results from these analyses are presented below for GI-NET patients.

Table 24. PFS and OS Weibull parameters GI-NET curve

Parameter (PFS)	Transformed coefficients
Location (lambda)	0.04
Shape (gamma)	1.36
Hazard ratio	0.16
Parameter (OS)	**Transformed coefficients**
Location (lambda)	0.01
Shape (gamma)	1.27
Hazard ratio	0.52

P-NET

The Weibull and exponential coefficients were generated in R (following MAIC) and used for modelling the PFS and OS for P-NET are presented in Table 25 to Table 28.

R uses a slightly different, but equivalent parameterisation to STATA. Weibull: $S(t) = \exp\{-(t/\beta)^{\alpha}\}$, where: S = survival; t = time (cycle); β = scale parameter; α = shape parameter. For Sunitinib, problems with convergence for some of the parametric curves was encountered and as such an exponential curve was chosen to reflect long terms outcomes. Exponential: $S(t) = \exp\{-(\alpha t)^{\alpha}\}$, where : S = survival; t =time (cycle); α = rate parameter. The results from these analyses are presented below for P-NET patients.

Table 25. PFS and OS Weibull parameters P-NET curve (vs BSC – Sunitinib MAIC)

Parameter (PFS)	Transformed coefficients
Shape (alpha)	1.22
Scale (beta)	7.18
Hazard ratio	0.17
Parameter (OS)	**Transformed coefficients**
Shape (alpha)	1.02
Scale (beta)	44.94
Hazard ratio	0.37

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Table 26. PFS and OS exponential parameters P-NET curve (vs Sunitinib – Sunitinib MAIC)

Parameter (PFS)	Transformed coefficients
Rate (alpha)	0.05
Hazard ratio	0.41
Parameter (OS)	**Transformed coefficients**
Rate (alpha)	0.02
Hazard ratio	0.36

Table 27. PFS and OS Weibull parameters P-NET curve (vs BSC – Everolimus MAIC)

Parameter (PFS)	Transformed coefficients
Shape (alpha)	1.27
Scale (beta)	6.94
Hazard ratio	0.19
Parameter (OS)	**Transformed coefficients**
Shape (alpha)	1.13
Scale (beta)	55.15
Hazard ratio	0.56

Table 28. PFS and OS Weibull parameters P-NET curve (vs Everolimus – Everolimus MAIC)

Parameter (PFS)	Transformed coefficients
Shape (alpha)	1.23
Scale (beta)	16.05
Hazard ratio	0.44
Parameter (OS)	**Transformed coefficients**
Shape (alpha)	1.17
Scale (beta)	58.30
Hazard ratio	0.61

4.3 Adverse events

Adverse events experienced by patients receiving Lutathera, octreotide LAR, everolimus (in GI-NET and P-NET patients), and sunitinib (P-NETs) were considered in the model. The data on utility and costs associated adverse events are the same as those included in the original submission. The proportions of patients experiencing adverse events has been amended to reflect the updated clinical study reports for Lutathera and are presented below for Lutathera and relevant comparators (Table 29 to Table 32).

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Table 29. Adverse events reported in the NETTER-1 trial for Lutathera and octreotide LAR (Advanced Accelerator Applications, 2017a)**.**

Adverse events	Proportion of patients with adverse event (%) (octreotide LAR)	Proportion of patients with adverse event (%) (Lutathera)
Nausea	0%	4%
Vomiting	0%	4%
Diarrhoea	0%	1%
Abdominal pain	0%	0%
Musculoskeletal pain	0%	0%
Thrombocytopenia	0%	3%
Lymphopenia	0%	8%
Neutropenia	0%	1%
Lymphocyte disease count	0%	4%

Table 30. Adverse events reported in the RADIANT-4 trial for everolimus GI-NET patients (Yao et al., 2016a)

Adverse events	Grade 3-4 AEs
Nausea	2%
Diarrhoea	7%
Stomatitis	9%
Fatigue	3%
Infections	9%
Asthenia	2%
Anaemia	4%
Pyrexia	2%
Hyperglycaemia	3%

Table 31. Adverse events reported in the RADIANT-3 trial for everolimus P-NET patients (Ito et al., 2012)

Adverse events	Grade 3-4 AE's
Nausea	2%
Diarrhoea	3%
Thrombocytopenia	4%
Stomatitis	7%
Fatigue	2%
Infections	2%
Asthenia	1%
Anaemia	6%
Hyperglycaemia	5%

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Table 32. Adverse events reported for sunitinib P-NET patients (Raymond et al., 2011)

Adverse events	Grade 3-4 AE
Nausea	1%
Diarrhoea	5%
Abdominal pain	5%
Thrombocytopenia	4%
Stomatitis	4%
Fatigue	5%
Asthenia	5%
Neutropenia	12%
Hypertension	10%

4.4 Relative dose intensity (RDI)

The economic model has been updated to include estimates of relative dose intensity for everolimus and sunitinib following new data becoming publicly available data during the NICE appraisal of these treatments.

The model allows for the drug cost of Lutathera and comparators to be calculated with and without the reported RDI (Table 33). In these analyses, RDI refers to the amount of drug administered over a specific time in relation to the amount originally ordered. Patients may have had a dose modified or skipped a dose altogether due to toxicities or adverse events, thereby altering the total amount of chemotherapy they received (Vachani, 2005). The modelled RDI was taken from the NETTER-1 study.

Table 33. Relative dose intensity

Regimen	Relative dose intensity	Source
Lutathera (177Lu-DOTA0-Tyr3)7.4GBq (200mCi)	86.4%	NETTER-1 study
Sunitinib	91.3%	A6181111 study
Everolimus	79.4%	RADIANT-4 study

5. Results

5.1 GI-NETS

Basecase analysis

Table 34 presents results of the basecase analysis of Lutathera compared to BSC (octreotide LAR 60 mg) in GI-NET patients. Lutathera is associated with an incremental cost of £37,080 and incremental QALYs of 1.27, resulting in an ICER of £29,196.

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Table 34. Summary of incremental costs per QALY (GI-NET: Lutathera versus octreotide LAR; deterministic analysis)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£86,370	4.53	3.46			
Octreotide LAR	£49,289	2.90	2.19	£37,080	1.27	£29,196

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

The results of the probabilistic analysis are presented in Table 35.

Table 35. Summary of incremental costs per QALY (GI-NET: Lutathera versus octreotide LAR; probabilistic analysis)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£88,118	4.82	3.68			
Octreotide LAR	£52,491	3.12	2.36	£35,627	1.33	£26,826

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Sensitivity analysis

The cost-effectiveness acceptability curve and plane from the probabilistic sensitivity analysis are shown in Figure 23 and Figure 24 respectively.

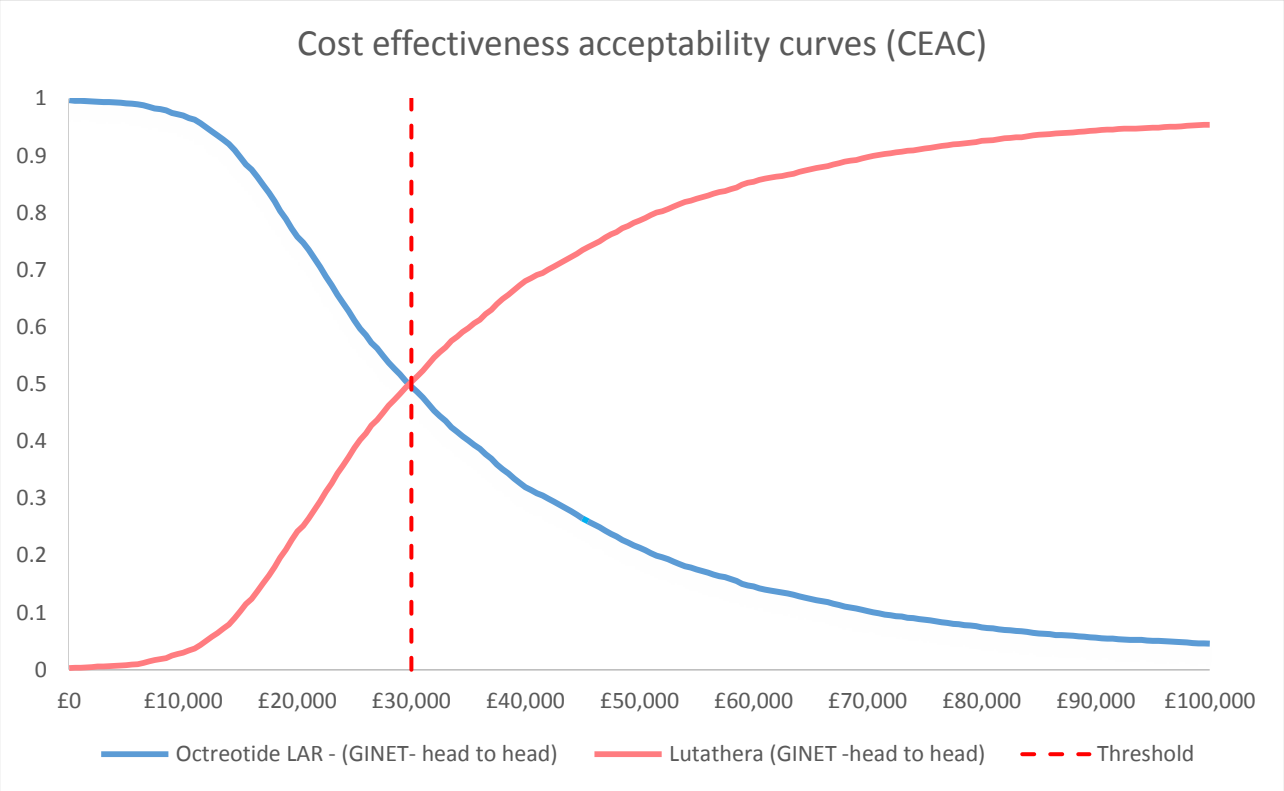

Figure 23. CEAC GI-NET basecase analysis

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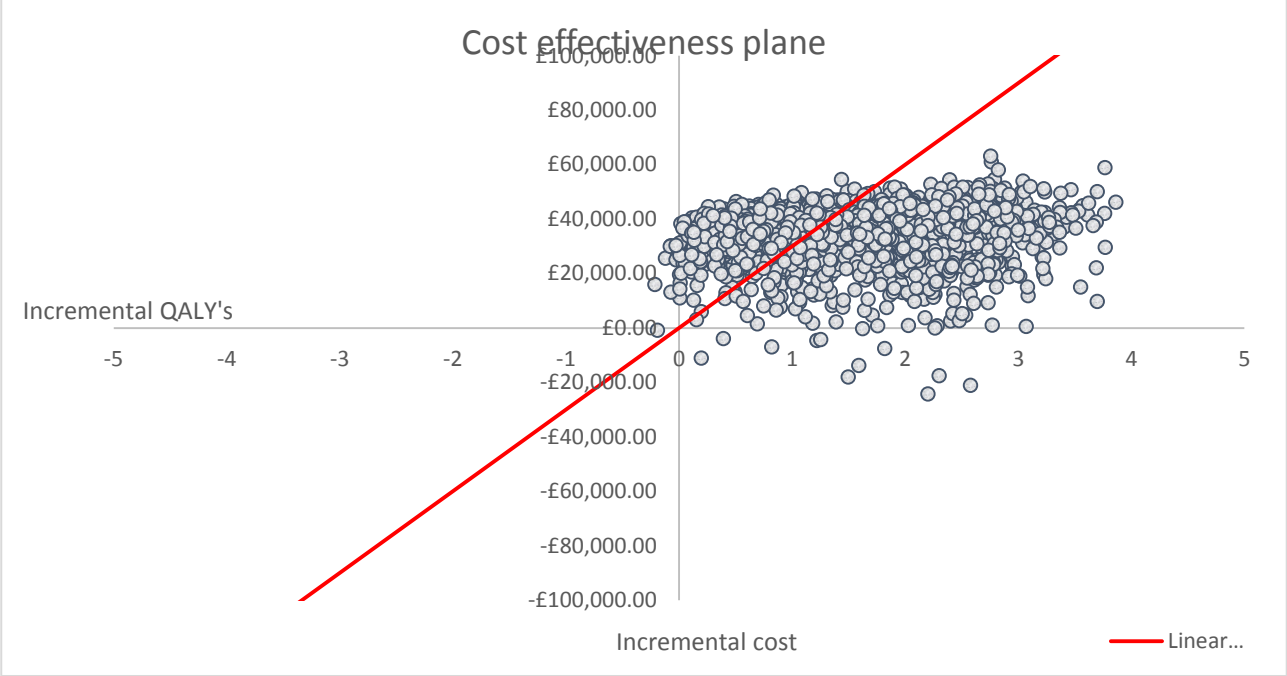

Figure 24. Cost-effectiveness plane: GI-NET basecase analysis

A tornado diagram of the sensitivity analysis results of the top 10 most influential parameters included in the model is presented in Figure 25.

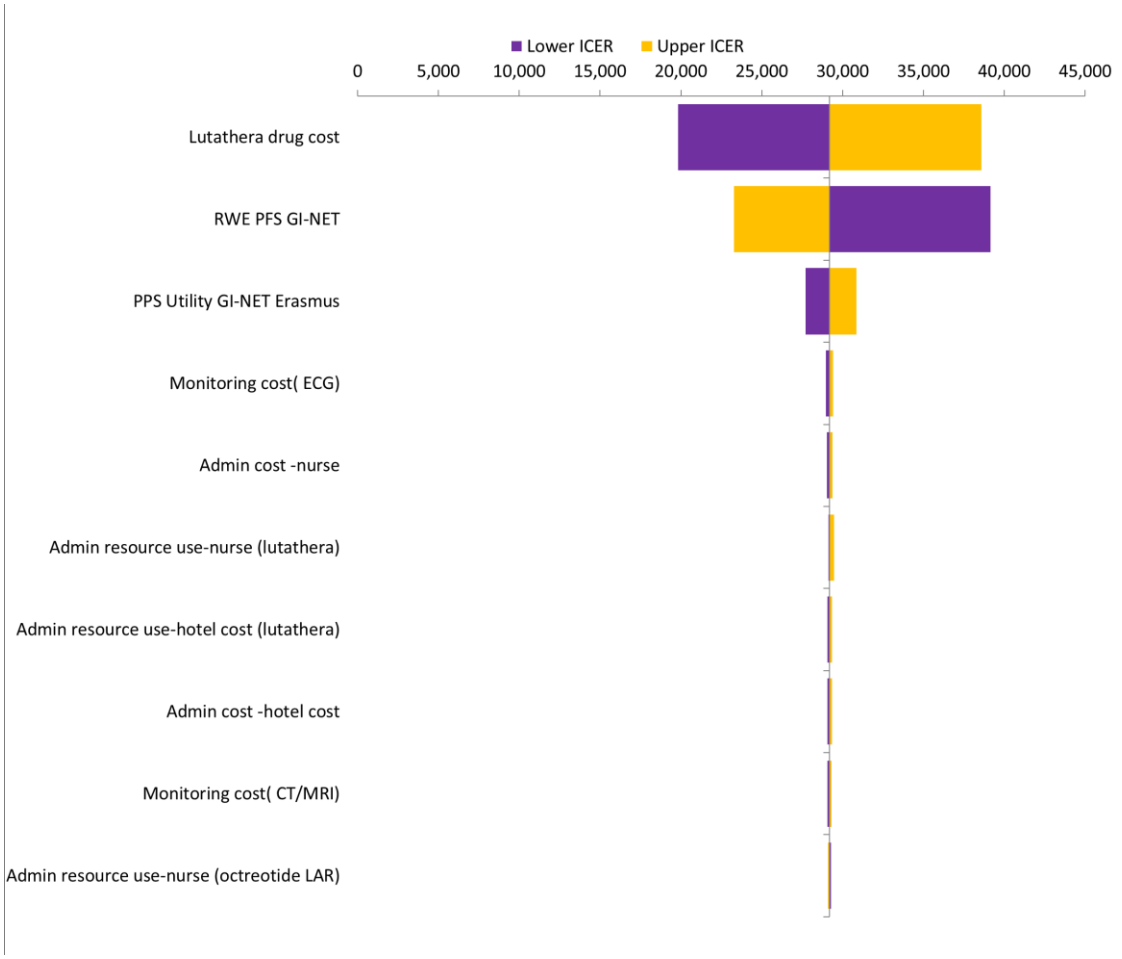

Figure 25. GI-NETs Basecase analysis tornado diagram

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Scenario analyses

A scenario analysis including relative dose intensity of 84.4% from the ERASMUS study is shown below. The ERASMUS study represents the largest source of data for Lutathera. The ICER in this scenario analysis is reduced to £28,110.

Table 36. Summary of incremental costs per QALY from scenario analysis including ERASMUS RDI (GI-NET: Lutathera versus octreotide LAR)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£84,990	4.53	3.46			
Octreotide LAR	£49,289	2.90	2.19	£35,701	1.27	£28,110

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

An additional scenario analysis was conducted using effectiveness data from NETTER-1 which adjusted for cross-over from the control arm of the trial to Lutathera. The proportion of patients that crossed over from the control arm to Lutathera was 22.8%. A rank preserving structural failure time (RPSFT) analyses was conducted to account for the cross-over using OS from the cut-off date 30 June 2016. The hazard ratio for OS with the RPSFT was 0.497 with 95% CI of 0.308 to 0.804 (Table 37). The cost-effectiveness results using this hazard ratio are presented in Table 38. The ICER is reduced to £28,284.

Table 37. Summary of RPSFT analyses accounting for cross-over from the control arm to Lutathera (FAS, 30 June 2016)

	Lutathera (N = 116) n (%)	Octreotide LAR (N = 113) n (%)
Number of deaths, n (%)	28 (23.9%)	43 (37.7%)
Number switched to Lutathera, n (%)	NA	26 (22.8%)
Analysis method: Kaplan Meier method Median* (months) (95% CI) Unstratified Hazard Ratio (95% CI) P-value** Stratified Hazard Ratio (95% CI) P-value**	 NR (NE, NE) 0.536 (0.333, 0.864) 0.0094 0.537 (0.332, 0.868) 0.0102	 27.4 (23.1, NE)
Analysis method: Rank preserving structural failure time (RPSFT) Median* (months) (95% CI) Unstratified Hazard Ratio (95% CI) P-value** Stratified Hazard Ratio (95% CI) P-value**	 NR (NE, NE) 0.497 (0.308, 0.804) 0.0036 0.488 (0.300, 0.795) 0.0033	 27.4 (20.9, NE)
* Estimated by Kaplan-Meier method, ** P value is from Log-rank test		

NA, not applicable; NE, not evaluable; NR, not reached

Table 38. Summary of incremental costs per QALY from scenario analysis including HR from RPSFT analysis (GI-NET: Lutathera versus octreotide LAR)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£88,461	4.68	3.58			
Octreotide LAR	£49,289	2.90	2.19	£39,172	1.38	£28,284

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

A scenario analysis comparing Lutathera to everolimus using the results of the NMA described in Section 2 was conducted and the results presented in Table 39

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Table 39. Summary of incremental costs per QALY from scenario analysis of Lutathera compared to everolimus using the NMA data (GI-NET: Lutathera versus everolimus)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£91,099	4.41	3.40			
Everolimus	£68,045	3.92	2.92	£23,054	0.47	£48,855

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

5.2 PNETS

A series of four pair-wise analyses are presented for the PNET population, which incorporate the MAIC analyses into the economic model. The first two comparison utilise data from the everolimus RCT (Yao, 2016) and compare Lutathera with BSC (Octreotide LAR 60mg) and everolimus. The second set of analyses utilise data from the sunitinib trial (Faivre et al., 2016a) to compare Lutathera with sunitinib and BSC (Octreotide LAR 60mg). The results are presented in Table 40.

Table 40. Cost-effectiveness results for PNETs (MAIC analyses)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera compared to everolimus (Yao, 2016)						
Lutathera	£109,805	6.10	4.81			
Everolimus	£70,974	4.11	3.23	£38,831	1.58	£24,526
Lutathera compared to BSC (octreotide LAR 60mg) (Yao, 2016)						
Lutathera	£111,416	6.21	4.90			
BSC	£59,759	3.94	3.12	£51,658	1.78	£29,091
Lutathera compared to sunitinib (Faivre, 2016)						
Lutathera	£114,763	7.16	5.65			
Sunitinib	£81,303	4.47	3.48	£33,460	2.17	£15,433
Lutathera compared to BSC (octreotide LAR 60mg) (Faivre, 2016)						
Lutathera	£119,837	7.13	5.63			
BSC	£52,756	3.39	2.69	£67,081	2.94	£22,854

Tornado diagrams presenting one-way sensitivity analyses are presented in Figure 26 to Figure 29. Results of the probabilistic analysis are presented in Table 41, and cost-effectiveness curves and planes are presented in Figure 30 to Figure 37.

Table 41. Cost effectiveness results for PNETs (probabilistic results)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera compared to everolimus (Yao, 2016)						
Lutathera	£109,771	6.12	4.83			
Everolimus	£71,111	4.11	3.23	£38,660	1.60	£24,236
Lutathera compared to BSC (octreotide LAR 60mg) (Yao, 2016)						
Lutathera	£111,653	6.23	4.92			
BSC	£59,920	3.95	3.13	£51,733	1.79	£28,940
Lutathera compared to sunitinib (Faivre, 2016)						
Lutathera	£114,460	7.16	5.65			
Sunitinib	£81,976	4.49	3.50	£32,483	2.15	£15,091
Lutathera compared to BSC (octreotide LAR 60mg) (Faivre, 2016)						
Lutathera	£118,815	7.07	5.59			
BSC	£52,872	3.40	2.70	£65,942	2.70	£22,809

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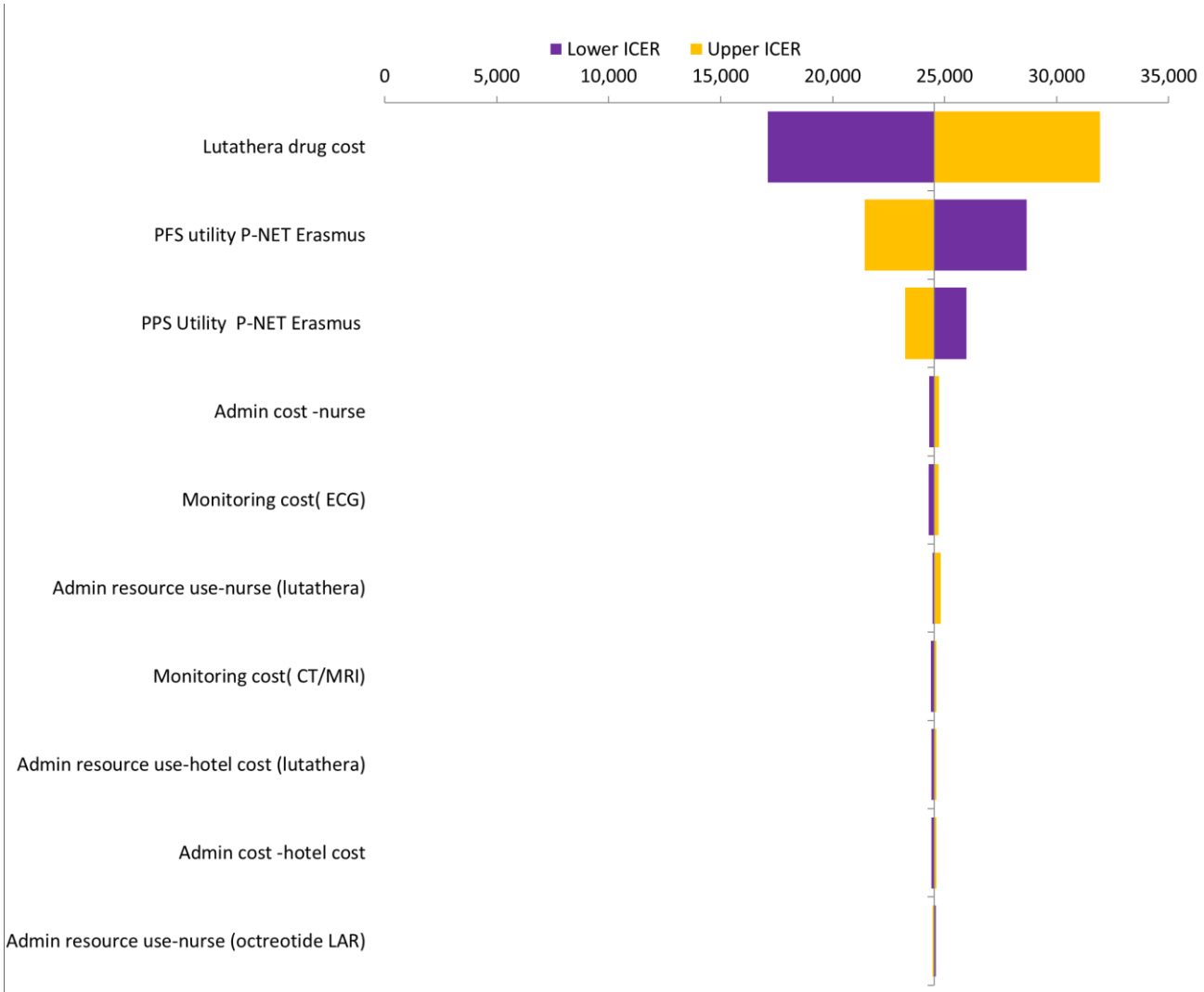

Figure 26. Tornado diagram for PNET (Lutathera compared to everolimus)

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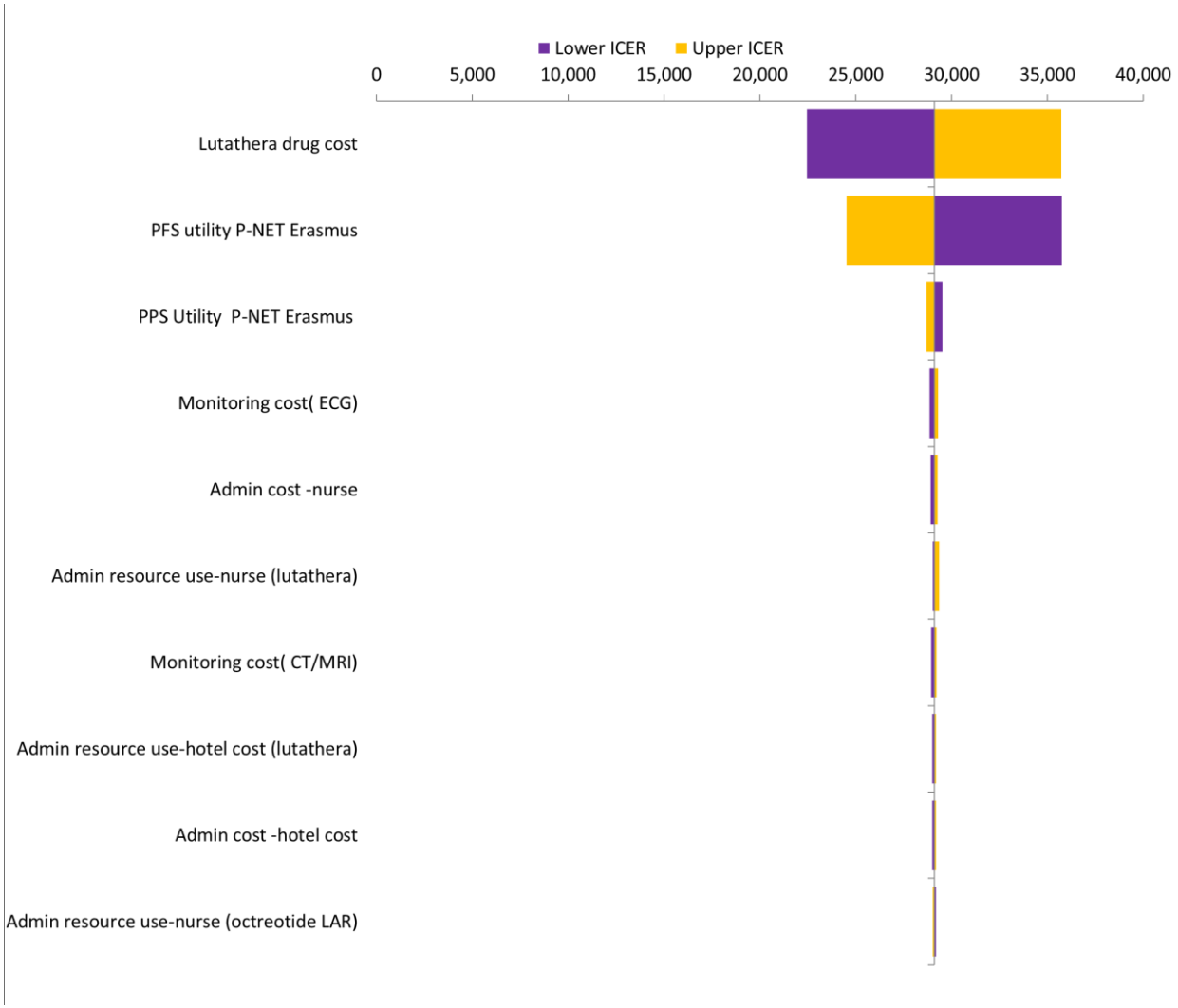

Figure 27. Tornado diagram PNETs (Lutathera compared to BSC, Yao 2016)

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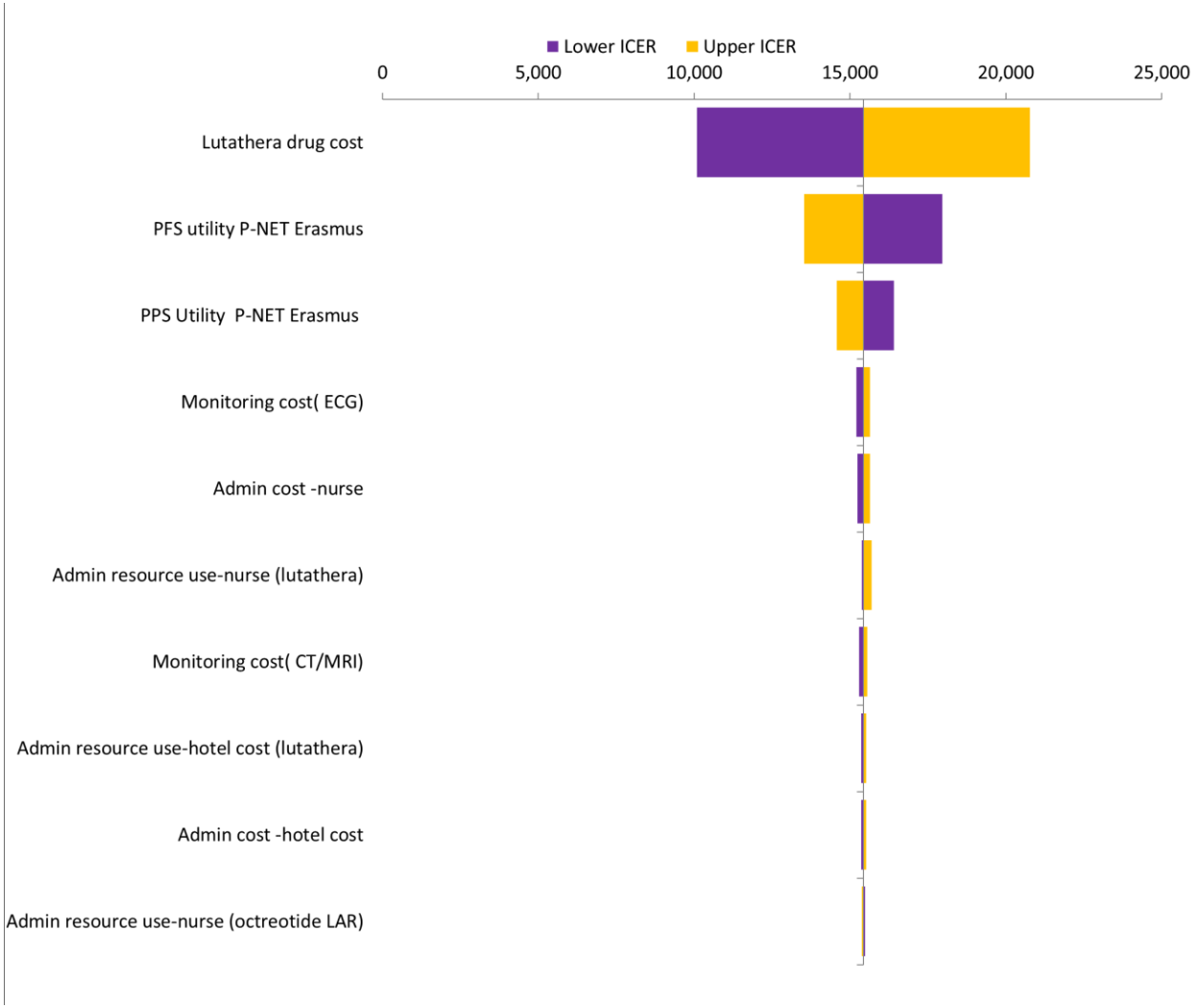

Figure 28. Tornado diagram PNETs (Lutathera compared to sunitinib)

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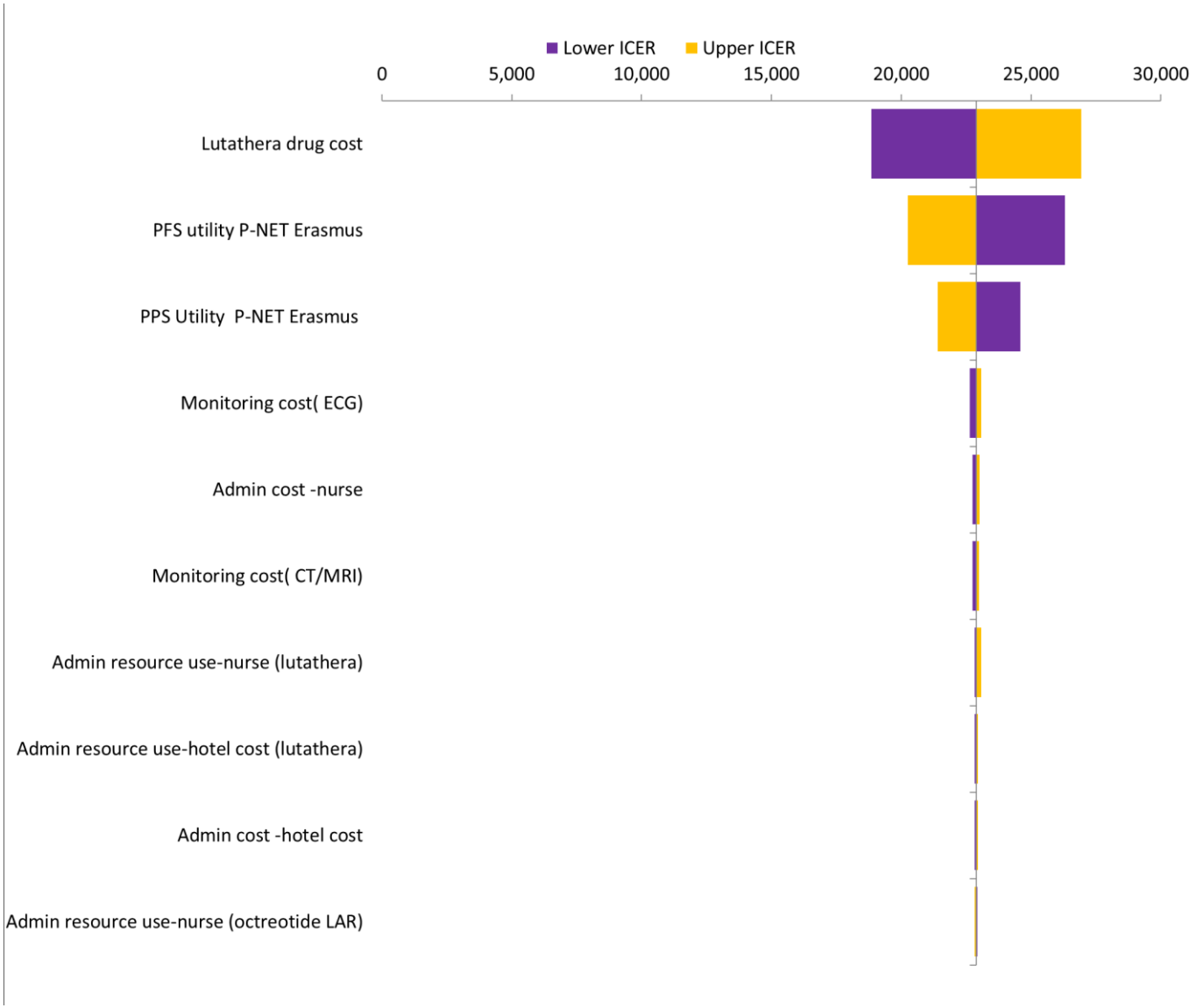

Figure 29. Tornado diagraom PNETs (Lutathera compared to BSC - Faivre 2016)

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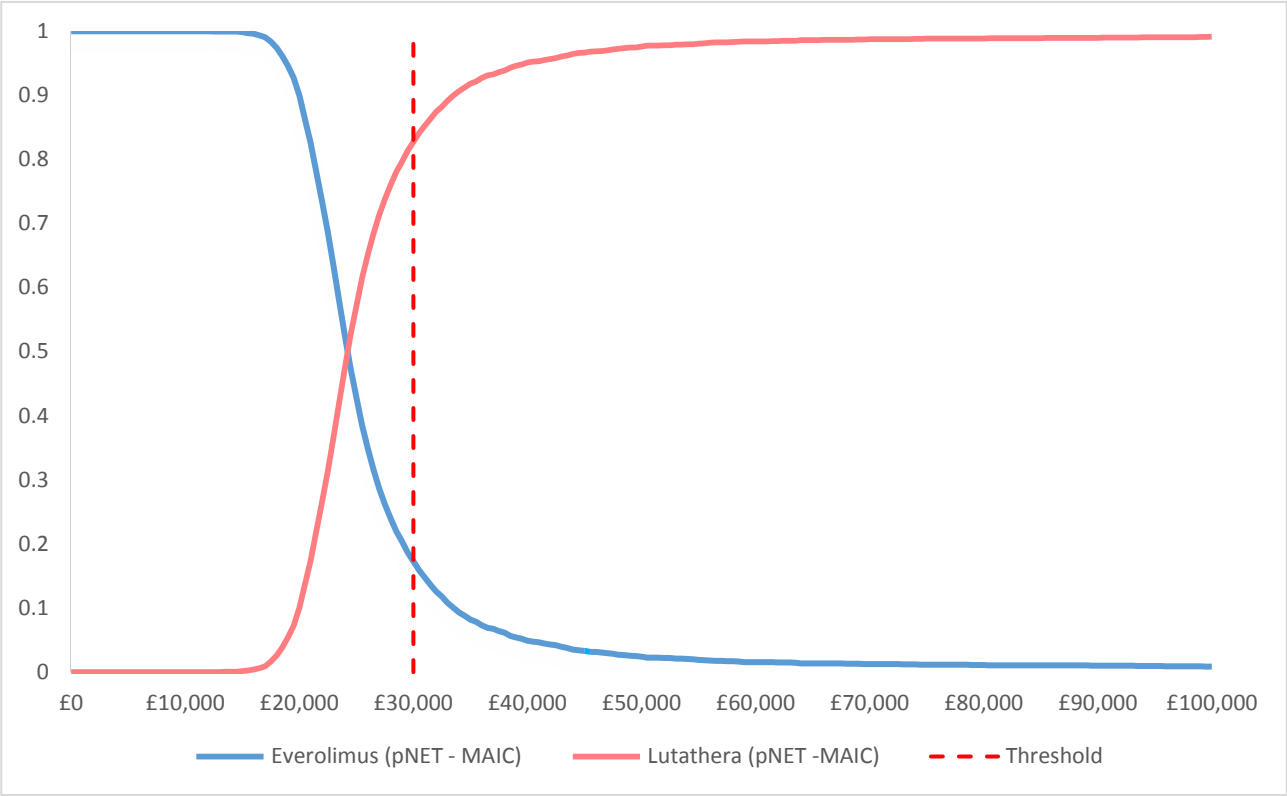

Figure 30. CEAC PNET analysis (Lutathera compared to everolimus)

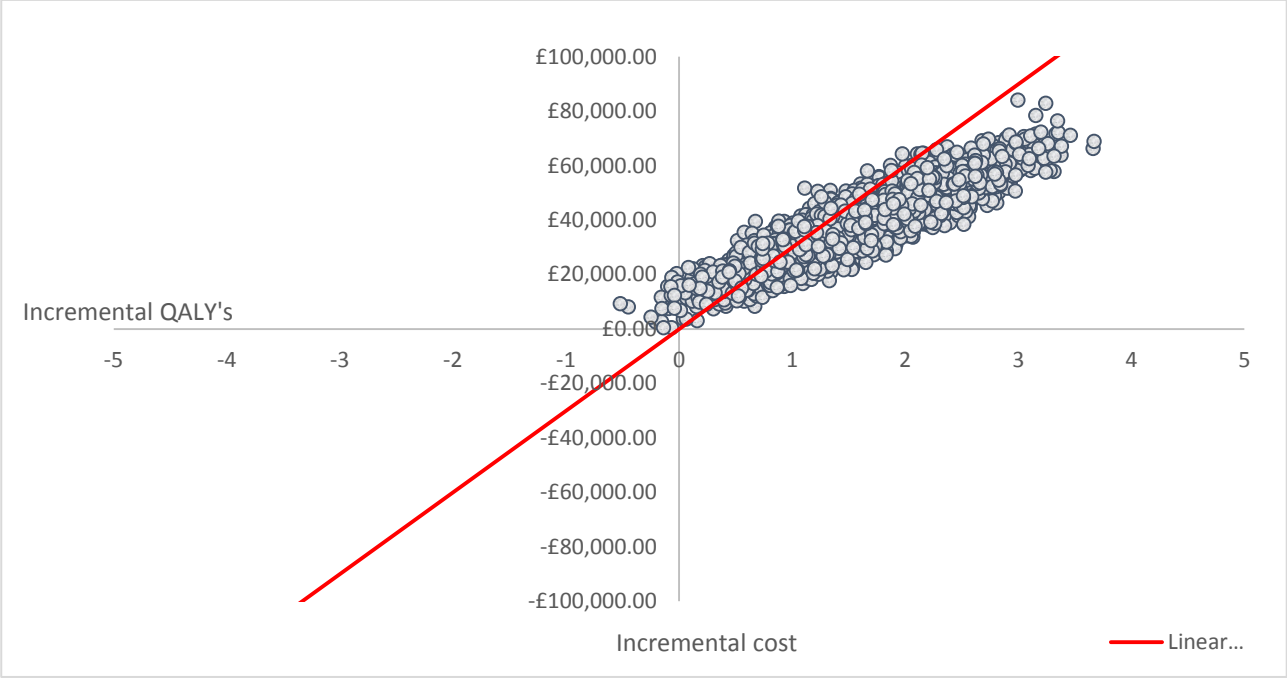

Figure 31. Cost-effectiveness plane (Lutathera compared to everolimus)

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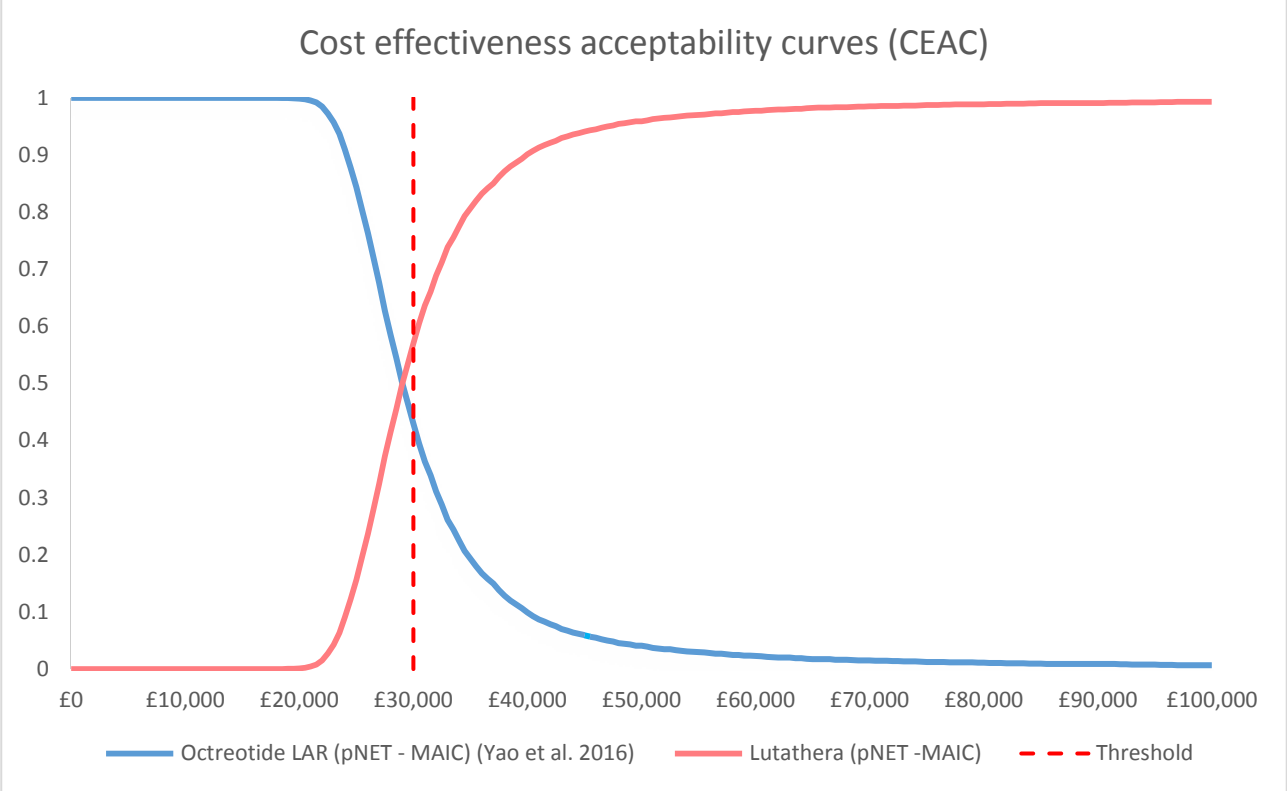

Figure 32. CEAC PNETs (Lutathera compared to BSC - Yao 2016)

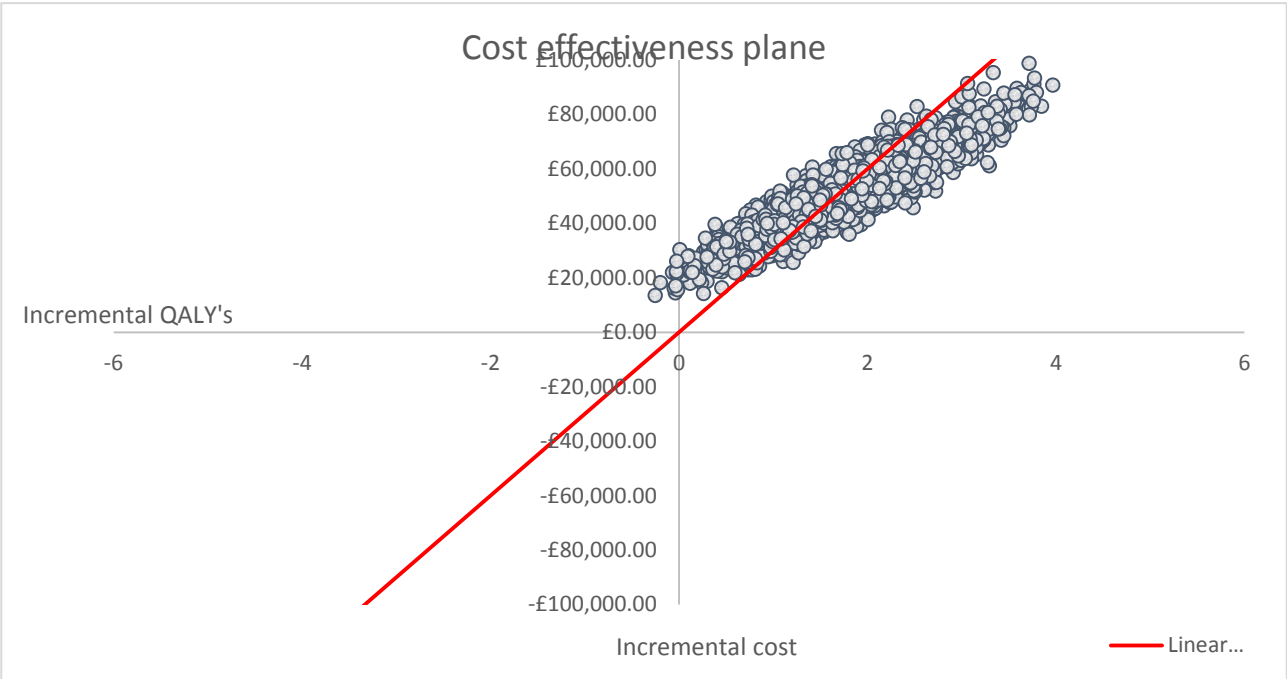

Figure 33. Cost-effectiveness plane PNETs (Lutathera compared to Yao 2016)

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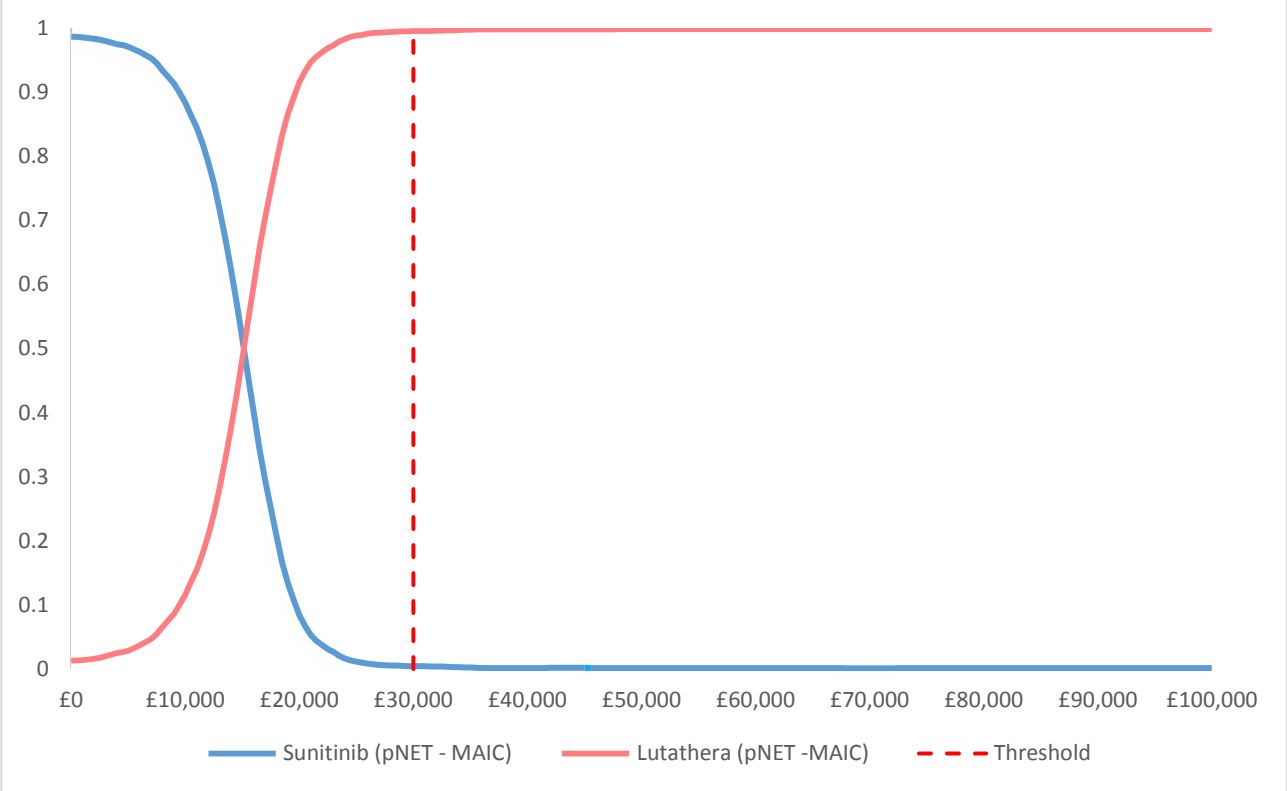

Figure 34. CEAC PNETs (Lutathera compared to sunitinib)

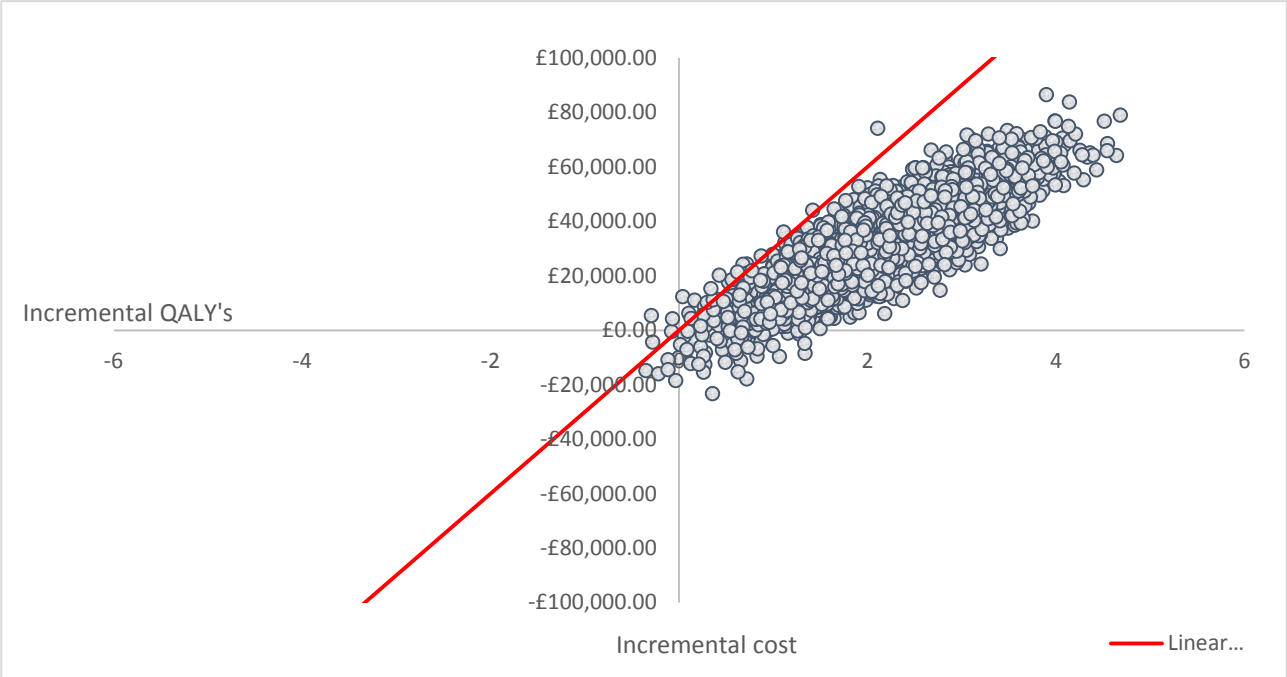

Figure 35. Cost-effectiveness plane (Lutathera compared to sunitinib)

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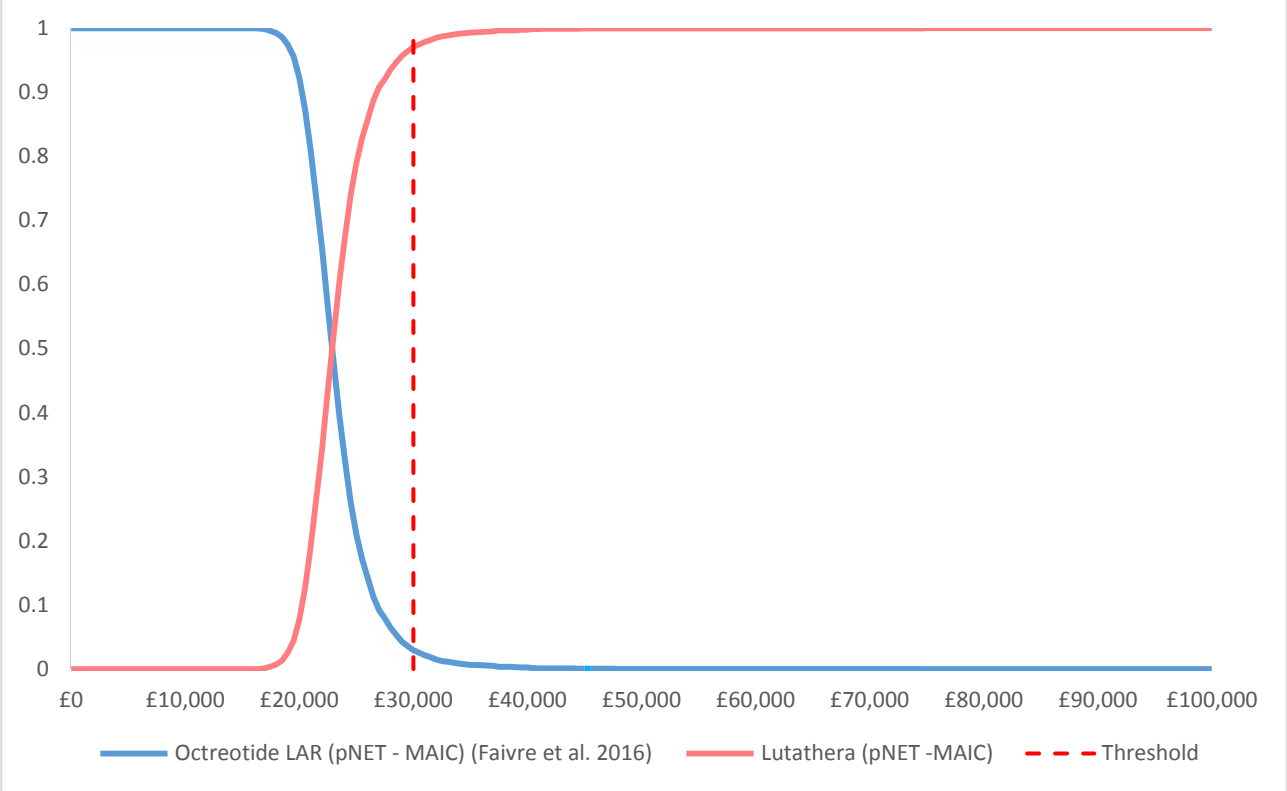

Figure 36. CEAC PNETs (Lutathera compared to BSC Faivre 2016)

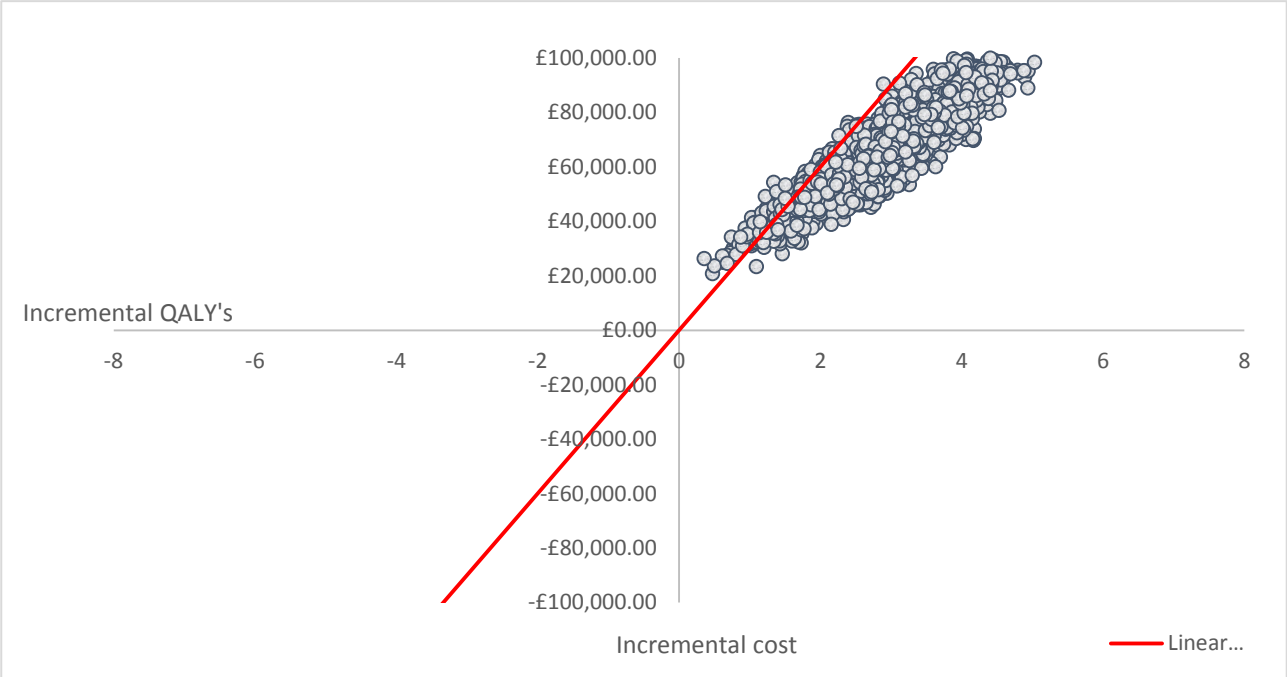

Figure 37. Cost-effectiveness plane PNETs (Lutathera compared to BSC Faivre 2016)

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6. Conclusions

The results of the updated economic analysis demonstrate that Lutathera is a cost-effective use of NHS resources. There are limited treatment options available for GEP-NET patients, and there are no routinely approved, effective treatments available for a significant group of patients, namely those with functioning GI tumours and those whose primary tumour site is the ileum.

Two pivotal clinical studies informed the EMA's decision to approve Lutathera as an efficacious treatment for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor positive GEP-NETs in adults: NETTER-1 and ERASMUS.

The NETTER-1 study is a randomised controlled trial comparing Lutathera (plus 30mg octreotide LAR) to standard care for patients with progressive disease (increased dose of 60mg octreotide LAR). The updated results from this trial forms the basis of the updated cost-effectiveness analysis and shows that Lutathera has an ICER of £29,196 compared to BSC (60mg octreotide LAR) for the GI-NET population. A revised MTC has also been provided and incorporated into the economic model; however, given the heterogeneity in the clinical trials we recommend that the results be treated with caution.

The ERASMUS study was a large investigator-led single-arm study of Lutathera, and is used to generate a comparison with BSC, sunitinib and everolimus in the P-NET population using a MAIC approach. The basecase ICERs ranged from £15,433 for the comparison with sunitinib to £29,091for the comparison with BSC (using data from the everolimus trial to match with the ERASMUS study).

In summary, Lutathera is a cost-effective option for the treatment of patients with GEP-NET. These results therefore support Lutathera being used as an option in treating unresectable or metastatic GEP-NETs with disease progression.

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Ms Kate Moore
Technology Appraisals Project Manager - Committee D
National Institute for Health and Care Excellence
Level 1A | City Tower | Piccadilly Plaza
Manchester M1 4BT | United Kingdom

26th February 2018

Dear Kate

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-dotatate [ID1224]

Please find enclosed additional analyses for the above appraisal, as agreed with Helen Knight on 1st February 2018 An amended economic model (MS Excel) is also provided. We will be happy to answer any queries you or the Assessment group may have regarding the analyses.

Best regards

[redacted]

[redacted]

UK & Ireland

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-dotatate [ID1224]

Advanced Accelerator Applications UK Limited

26 February 2018

Contents

List of tables and figures

1. Introduction

1.1 Background

NICE has requested AAA perform an analysis of the cost-effectiveness of Lutathera compared to everolimus in the gastro-intestinal (GI) neuroendocrine tumours (NETs) population using data from the ERASMUS clinical study and the RADIANT-4 trial using matching adjusted indirect comparison (MAIC) methods.

The results of the MAIC analysis and the new cost-effectiveness results are described below. We would like to highlight that it was not possible to conduct a MAIC for overall survival (OS) in the GI-NET population as OS data for the GI-subgroup from the RADIANT-4 trial are not available.

The model used to incorporate the MAIC analysis detailed below is that provided to NICE in December 2017, which incorporated the updated data from the NETTER-1 and ERASMUS studies, and allowed for inclusion of relative dose intensities for all comparators.

AAA have previously provided the following -effectiveness analyses:

- Mid-gut NETs: comparison with BSC (octreotide LAR) based on the head-to-head randomised NETTER-1 trial
- Mid-gut/GI NETs: comparison with BSC (octreotide LAR/placebo) and everolimus based on the results of a MTC
- Pancreatic NET (PNETs): comparison with BSC (octreotide LAR/placebo), sunitinib and everolimus based on the results of a MTC
- Pancreatic NET (PNETs): comparison with BSC (octreotide LAR/placebo), sunitinib and everolimus based on the results of MAIC analysis.

1.2 Methods and results of the MAIC analysis

The MAIC analysis for GI-NETs used a methodology similar to that outlined previously for the MAIC conducted for P-NETs. The findings of the analysis are outlined in brief below.

1.2.1 Data sources

For Lutathera, the only available choice to derive data to inform the ITC was the ERASMUS study. For everolimus and BSC, the GI NET subgroup of the RADIANT-4 study (Singh et al. 2016) provided data. Kaplan-Meier data for PFS is available in RADIANT-3 (Singh et al. 2016) however no data on OS are publicly available from this trial.

1.2.2 MAIC

A univariate analysis of the ERASMUS data was used to identify relevant prognostic variables for inclusion in the main analysis, these are summarised in Table 1.

Table 1: P-values showing the effect of each covariate on PFS and OS for ERASMUS.

Covariate	P-value	
	ERASMUS (PFS)	ERASMUS (OS)
Age mean, median (range) years	0.858	0.012
Sex	0.117	0.966
ECOG performance status	0.078	0.003
Previous chemotherapy	0.081	0.024

Table 2 to Table 5 outline the distribution of patient characteristics in the ERASMUS GI-NET cohort and in the GI-NET subgroup of RADIANT-4. The tables also show the distribution of characteristics in ERASMUS after carrying out the MAIC and summarise the weights produced by the MAIC.

Table 2. Balance table showing the number of patients that fall within each matching category for the everolimus arm of the RADIANT-4 GI NET trial subgroup, ERASMUS unweighted (pre-match) and ERASMUS re-weighted (post-match).

		ERASMUS (pre match)	ERASMUS (post match)	RADIANT-4 (GI-NET subgroup)
		Lutathera	Lutathera	Everolimus
N	**N** **Effective sample size:**	202	202 62	118
Sex	**Male** **Female**	54% 46%	41% 59%	41% 59%
ECOG performance status	**0** **1**	70% 30%	75% 25%	75% 25%
Previous chemotherapy	**Yes** **No**	4% 96%	19% 81%	19% 81%
Weights[1]	**Mean** **Range**		1.03 (0.25-13.81)	

Table 3. Balance table showing the number of patients that fall within each matching category for the BSC arm of the RADIANT-4 GI NET trial subgroup, ERASMUS unweighted (pre-match) and ERASMUS re-weighted (post-match).

		ERASMUS (pre match)	ERASMUS (post match)	RADIANT-4 (GI-NET subgroup)
		Lutathera	Lutathera	BSC
N	**N** **Effective sample size:**	202	202 71	57
Sex	**Male** **Female**	54% 46%	55% 45%	55% 45%
ECOG performance status	**0** **1**	70% 30%	84% 16%	84% 16%

Previous chemotherapy	**Yes** **No**	4% 96%	12% 88%	12% 88%
Weights	**Mean** **Range**		1.03 (0.19-9.70)	

Table 4. Overall survival: Balance table showing the number of patients that fall within each matching category for the everolimus arm of the RADIANT-4 GI NET trial subgroup, ERASMUS unweighted (pre-match) and ERASMUS re-weighted (post-match).

		ERASMUS (pre match)	**ERASMUS (post match)**	**RADIANT-4 (GI-NET subgroup)**
		Lutathera	Lutathera	Everolimus
N	**N** **Effective sample size:**	202	202 66	118
Age	**Mean (median)**	61 (61)	63	NA (63)
ECOG performance status	**0** **1**	70% 30%	75% 25%	75% 25%
Previous chemotherapy	**Yes** **No**	4% 96%	19% 81%	19% 81%
Weights	**Mean** **Range**		1.00 (0.04-11.19)	

Table 5. Overall survival: Balance table showing the number of patients that fall within each matching category for the BSC arm of the RADIANT-4 GI NET trial subgroup, ERASMUS unweighted (pre-match) and ERASMUS re-weighted (post-match).

		ERASMUS (pre match)	**ERASMUS (post match)**	**RADIANT-4 (GI-NET subgroup)**
		Lutathera	Lutathera	BSC
N	**N** **Effective sample size:**	202	202 70	57
Age	**Mean (median)**	61 (61)	60	NA (60)
ECOG performance status	**0** **1**	70% 30%	84% 16%	84% 16%

Previous chemotherapy	**Yes** **No**	4% 96%	12% 88%	12% 88%
Weights	**Mean** **Range**		1.00 (0.17-9.79)	

1.2.4 Outcome data post-match

Following the MAIC, outcome data were estimated for the reweighted population. Kaplan-meier survival curves are presented for each MAIC in Figure 1 to Figure 4, showing Lutathera survival before and after the reweighting and, where available, outcome data from the comparator trial that has been used in the reweighting.

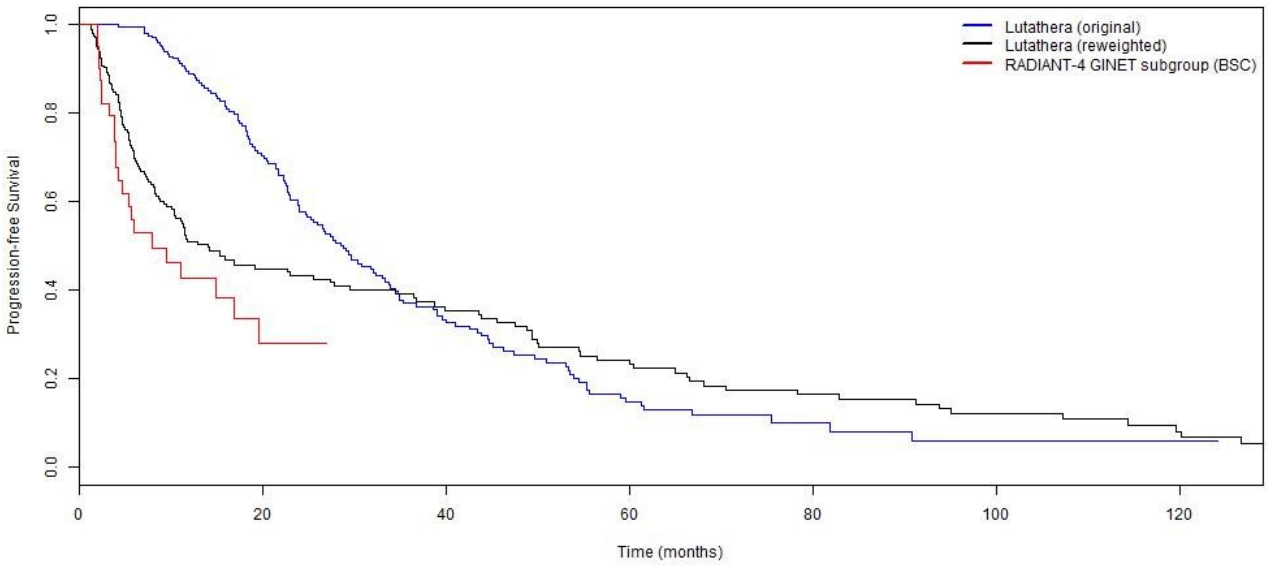

Figure 1. Kaplan-Meier survival curves for progression-free survival for everolimus (RADIANT-4 GI NET subgroup) and for lutathera before and after reweighting Erasmus data to match the characteristics of the everolimus arm of the RADIANT-4 GI NET subgroup.

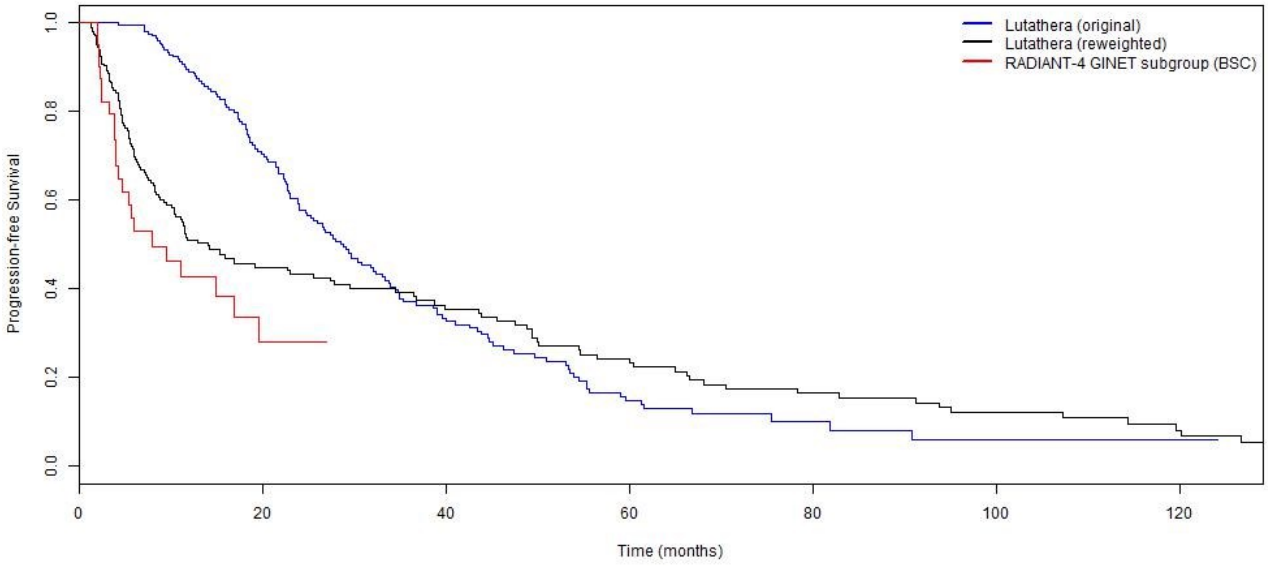

Figure 2. Kaplan-Meier survival curves for progression-free survival for BSC (RADIANT-4 GI NET subgroup) and for lutathera before and after reweighting Erasmus data to match the characteristics of the BSC arm of the RADIANT-4 GI NET subgroup.

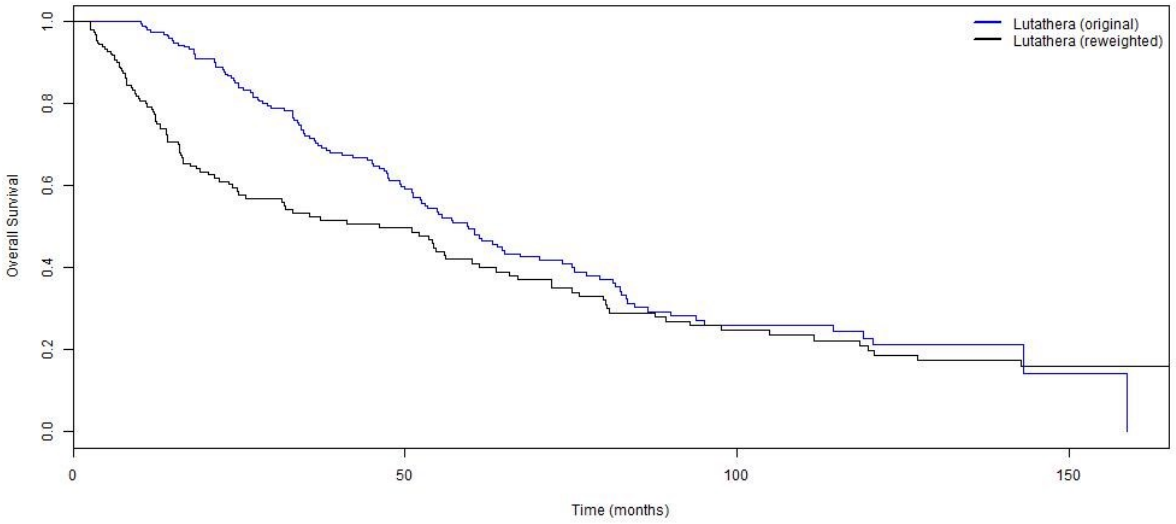

Figure 3. Kaplan-Meier survival curves for lutathera before and after reweighting Erasmus data to match the characteristics of the everolimus arm of the RADIANT-4 +GI NET subgroup. Overall survival data for the everolimus arm of the RADIANT-GI NET subgroup not shown as not available.

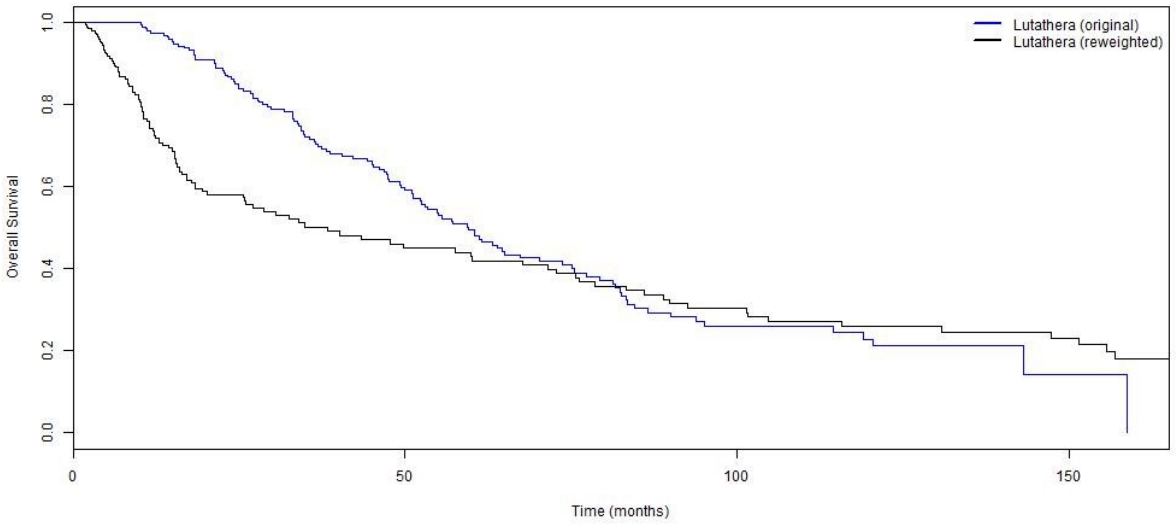

Figure 4. Kaplan-Meier survival curves for lutathera before and after reweighting Erasmus data to match the characteristics of the BSC arm of the RADIANT-4 +GI NET subgroup. Overall survival data for the BSC arm of the RADIANT-GI NET subgroup not shown as not available.

Given the availability of comparator outcome data for PFS, Cox proportional hazard models were fitted to the adjusted fitted to the adjusted Lutathera PFS data from ERASMUS, and respective reconstructed PLD for comparators, to comparators, to estimate hazard ratios (

Table 6).

Table 6: Hazard ratios estimated from Matching Adjusted Indirect Comparisons

Comparator	Hazard ratio PFS [95% CI]
Lutathera (reweighted ERASMUS) vs. Everolimus (RADIANT 4 GI NET subgroup)	0.72 [0.51, 1.04]
Lutathera (reweighted ERASMUS) vs. BSC (RADIANT 4 GI NET subgroup)	0.68 [0.43, 1.07]

In summary, the MAIC results suggest the relative effectiveness of Lutathera for GI-NETs may be lower than that indicated by a naïve analysis. However, the results suggest Lutathera provides superior progression free survival to its comparators.

1.3 Results of the economic analysis for GI-NETs (MAIC analysis)

The model was updated to incorporate the results of the MAIC analysis. As described above, a MAIC analysis was not possible for OS as data for the GI-NET subpopulation of the RADIANT-4 trial were not available. Therefore, following the proposed methods by Hoyle and colleagues a conservative assumption of equivalent post-progression survival was employed for Lutathera and all comparators (Hoyle et al., 2014).

Summaries of the results from the economic analyses including the MAIC are shown in Table 7 to

Table 10. Detailed results are shown in Table 11 for the comparison with everolimus and Table 12 for the comparison with BSC (Octreotide LAR).

Table 7: Summary of incremental costs per QALY (GI-NET: Lutathera versus everolimus; deterministic analysis)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£93,181	4.97	3.82	-	-	
Everolimus	£74,757	4.00	2.99	£18,424	0.83	£22,227

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Table 8: Summary of incremental costs per QALY (GI-NET: Lutathera versus everolimus; probabilistic analysis)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£93,221.27	4.98	3.83	-	-	-
Everolimus	£75,215.38	4.02	3.01	£18,005.88	0.82	£21,976

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Table 9: Summary of incremental costs per QALY (GI-NET: Lutathera versus BSC (Octreotide LAR); deterministic analysis)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£91,874.77	5.12	3.94	-	-	-
BSC (Octreotide LAR)	£73,387.87	4.00	3.05	£18,486.90	0.89	£20,741

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Table 10: Summary of incremental costs per QALY (GI-NET: Lutathera versus BSC (Octreotide LAR); probabilistic analysis)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutathera	£91,910.64	5.14	3.95	-	-	-
BSC (Octreotide LAR)	£74,742.92	4.05	3.09	£17,167.72	0.86	£19,983

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Table 11: Disaggregated costs and QALYs (GI-NET: Lutathera versus everolimus; deterministic analysis)

	Regimens	Lutathera (GI-NET MAIC)	Everolimus (GI-NET MAIC)
Costs	**Progression free survival (PFS)**		
	PFS Drug cost	£57,639.58	£41,066.13
	Admin cost	£1,878.89	£0.00
	Monitoring cost	£2,930.82	£1,876.85
	AE cost	£126.80	£1,655.87
	Post progression survival (PPS)		
	Drug cost	£27,210.78	£27,226.18
	Admin cost	£926.64	£463.58
	Monitoring cost	£2,467.37	£2,468.76
	AE cost	£0.00	£0.00
	Societal cost	£0.00	£0.00
	Palliative care cost	£0.00	£0.00
	Total cost	£93,180.89	£74,757.38
Life Years	PFS life years (LY)	2.70	1.73
	PPS life years (LY)	2.27	2.27
	Total Life years	4.97	4.00
QALY	PFS QALYs	2.14	1.31
	PPS QALYs	1.68	1.68
	Palliative care decrement	0.00	0.00
	Total QALYs	3.82	2.99
	Incremental cost		£18,423.50
	Incremental LY		0.97
	Incremental QALY		0.83
	ICER (£/Lys)		**£19,015.21**
	ICER (£/QALY)		**£22,226.90**

Figure 5: Cost-effectiveness acceptability curve: GI-NETs Lutathera compared to everolimus

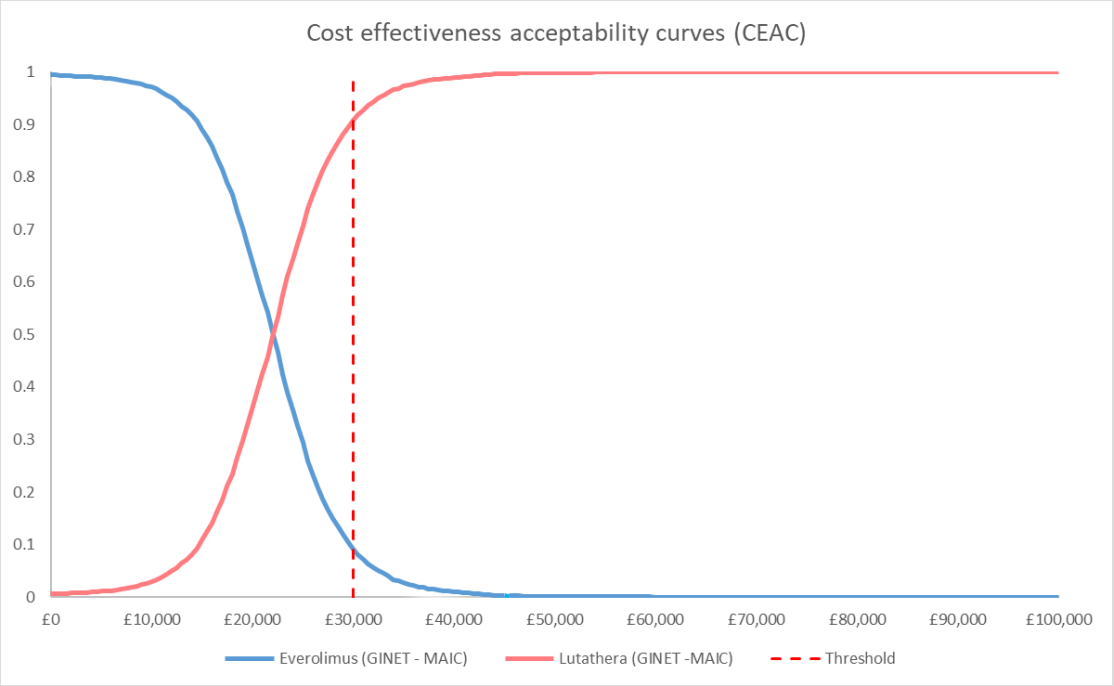

Figure 6: Cost-effectiveness plane: GI-NETs Lutathera compared to everolimus

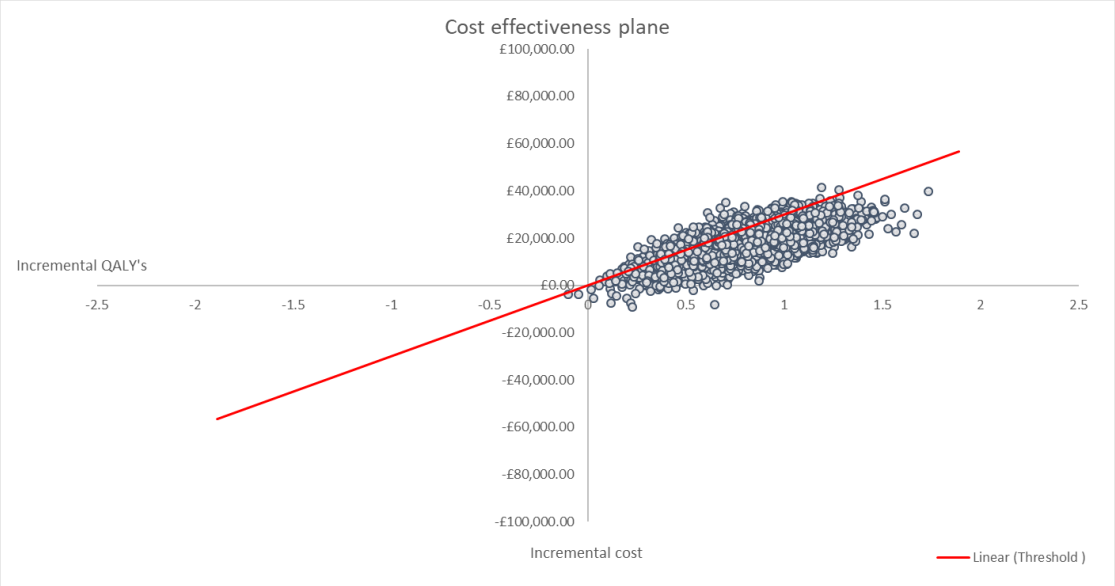

Table 12: Disaggregated costs and QALYs (GI-NET: Lutathera versus octreotide LAR; deterministic analysis)

	Regimens	Lutathera (GI-NET MAIC)	Octreotide LAR (GI-NET MAIC)
Costs	**Progression free survival (PFS)**		
	PFS Drug cost	£55,443.12	£40,331.93
	Admin cost	£1,889.39	£340.83
	Monitoring cost	£3,035.90	£1,815.07
	AE cost	£131.35	£0.00
	Post progression survival (PPS)		
	Drug cost	£27,895.59	£27,895.59
	Admin cost	£949.96	£474.98
	Monitoring cost	£2,529.46	£2,529.46
	AE cost	£0.00	£0.00
	Societal cost	£0.00	£0.00
	Palliative care cost	£0.00	£0.00
	Total cost	£91,874.77	£73,387.87
Life Years	PFS life years (LY)	2.79	1.67
	PPS life years (LY)	2.33	2.33
	Total Life years	5.12	4.00
QALY	PFS QALYs	2.22	1.33
	PPS QALYs	1.72	1.72
	Palliative care decrement	0.00	0.00
	Total QALYs	3.94	3.05
	Incremental cost		£18,486.90
	Incremental LY		1.12
	Incremental QALY		0.89
	ICER (£/Lys)		**£16,451.08**
	ICER (£/QALY)		**£20,741.33**

Figure 7: Cost-effectiveness acceptability curve: GI-NETs Lutathera compared to everolimus

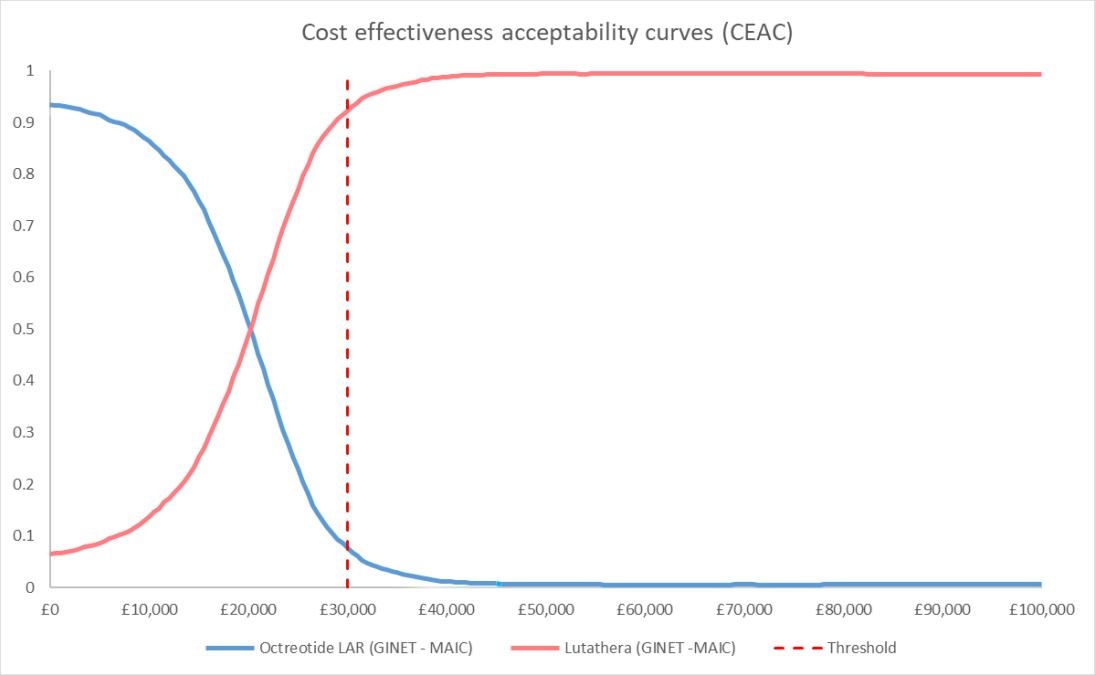

Figure 8: Cost-effectiveness acceptability curve: GI-NETs Lutathera compared to BSC (octreotide LAR)

1.4 Summary

The investigator-led, single arm ERASMUS study was used to generate a comparison of Lutathera with BSC and everolimus in the GI-NET population using the MAIC approach previously provided to NICE in December 2017. The results of the updated economic analysis demonstrate that Lutathera is a cost-effective within standard threshold ranges. The base case ICERs ranged from £22,227 for the comparison with everolimus to £20,741 for the comparison with BSC.

The publicly available RADIANT-4 trial data does not report OS for the subgroup of participants with GI-NETs only (instead RADIANT-4 reports OS for the combined group of GI + lung NETs), therefore it was not possible to perform a MAIC analysis for OS. Instead, a conservative approach was taken, using methods previously described by Hoyle et al. (2014), in which post-progression free survival was assumed to be equivalent for Lutathera and all comparators (2)

In summary, Lutathera is a cost-effective option for the treatment of patients with GEP-NETs. These results are supported by other analyses previously submitted to NICE, including the analysis based on the head-to-head trial NETTER-1.

1.5 References

1. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for Advanced Pancreatic Neuroendocrine Tumors. New England Journal of Medicine. 2011;364(6):514-23.
2. Hoyle M, Hamilton W, Rudin C. When It May Not Be Necessary To Model Overall Survival for Economic Evaluations of Anti-Cancer Drugs. Value in Health.17(7):A584.

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-DOTATATE [ID1224] -Erratum

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Date completed

22/03/2018, Erratum 20/04/2018

This document must be read as an addendum to the Assessment Report ID858

This addendum replaces the content presented in the report dated April 4th 2018 (Neuroendocrine Tumours AG Addendum Report, review of technology appraisal ID1224) related to resource dose intensity, progression-free survival (PFS) and overall survival (OS) outcomes and associated cost-effectiveness results of 177Lu-DOTATATE in the whole GI NET population. The changes result from excluding any individuals with 'Brochial' tumour class (n=21) in the ERASMUS dataset provided by AAA to the AG, which had been previously included in the results for the whole GI NETs population in the AG Addendum Report. Consequently there is a reduction in the effective sample size for the 177Lu-DOTATATE arm in the matched-adjusted indirect comparison to the whole GI NET RADIANT-4 population from n=75 to n=47.

The sections affected are the following:

- Section 3.3.2.1.2 "Overall GI" (pages 33 – 35)
- Table 22 "Parameter values used in the model for 177Lu-DOTATATE in GI-NETs" (page 50)
- Figure 15 "Progression Free Survival in AG model (Whole GI NETs)" and Figure 16 "Overall Survival in AG model (Whole GI NETs)" (page 52)
- Section 4.2.2 Dose intensity of 177Lu-DOTATATE (page 53)
- Section 4.3.1 Base case results for treatment strategies by tumour location (pages 55-56)
- Section 4.3.2 Base case results for treatment strategy comparisons by tumour location (page 58)
- Section 4.3.3 Probabilistic sensitivity analysis (pages 60,62,64)
- Section 4.3.4 No discounting of future costs and QALYs (page 65)
- Section 4.3.6 Univariate Scenario Analyses in Whole GI NETs (pages 73-79)
- Section 4.3.7 Comparison of AG results with AAA deterministic base case results (second paragraph, page 80)
- Section 4.3.7 Comparison of AG results with AAA deterministic base case results (pages 83-84)

The effect of the change is to reduce the base case ICER in GI NETs from £46,870 to £37,737 for 177Lu-DOTATATE vs. BSC and from £63,792 to £38,557 for 177Lu-DOTATATE vs. everolimus.

- **Section 3.3.2.1.2 “Overall GI” (pages 33 – 35)**

These outcomes were achieved at a mean cumulative dose intensity of 94.4% after weighting (27.95/29.6 GBq or 755.55/800 mCi) per planned infusions (94.9% before weighting).

3.3.2.1.2 Overall GI

We also conducted MAIC of the whole GI NETs sample in ERASMUS (n=264) to the overall GI subpopulation of RADIANT-4, using individual patient data provided by AAA. We requested data for ERASMUS from AAA on baseline patient characteristics for which we had published data from RADIANT-4. We obtained individual patient information for ERASMUS patients with GI NETs on the baseline variables listed in Table 3. After missing values 224 individual observations from the ERASMUS cohort had complete data and were matched to RADIANT-4 GI subpopulation. After matching, the effective sample size diminishes to 47 and three individual observations have weights larger than 8.

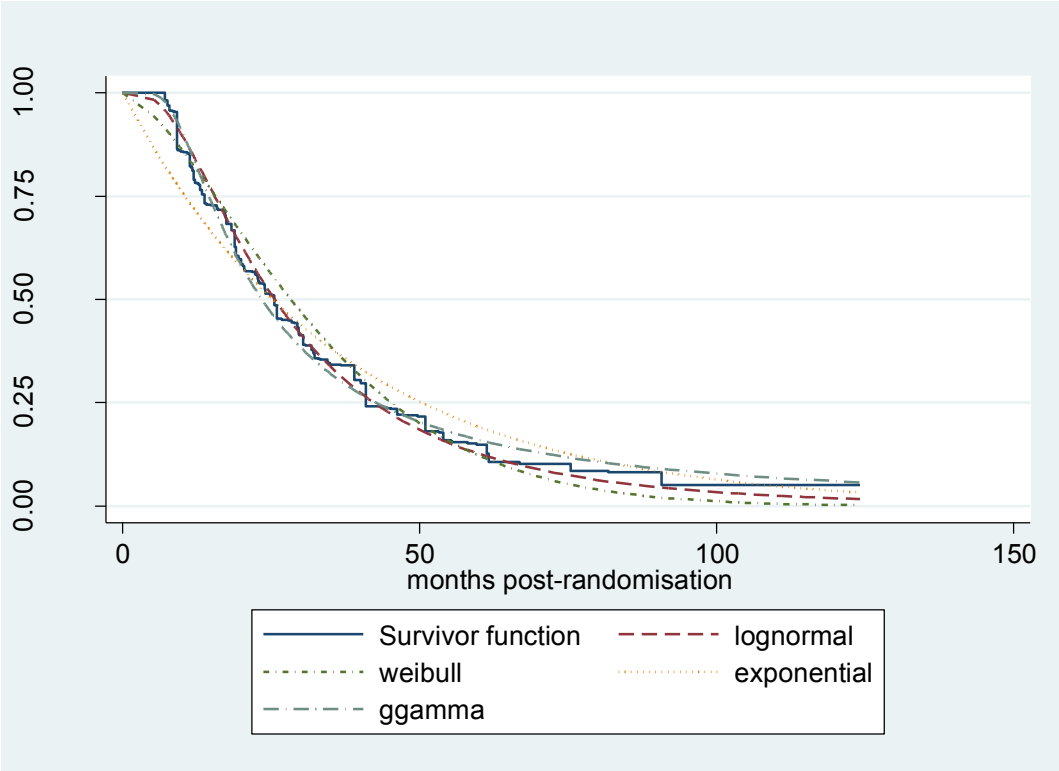
Table 1 Baseline characteristics pre and pots-matching ERASMUS whole GI-NETs cohort to RADIANT-4 GI subpopulation

Baseline variable	ERASMUS (before matching)	ERASMUS (after matching)	RADIANT-4 (reference population)*
N	224	224	175
ESS	N/A	46.9	N/A
Age (median)	60	62	62
Female	45.1	54.8	54.8
ECOG >1	70.0	21.7	21.7
Previous SSA	69.6	60.3	60.3
Previous surgery	55.3	74.3	74.3
Previous chemotherapy	7.1	16.5	16.5
Tumour class:			
Foregut (excl. bronchial)	4.9	6.2	4.2
Midgut	89.3	65.7	65.7
Hindgut	5.8	28.0	18.1
MAIC weights range	N/A	0.03-19.1	N/A

Note: N sample size; ESS: effective sample size after matching, N/A Not applicable. *Baseline characteristics reported in the ASCO poster by Singh et al. (Singh et al. 2016).

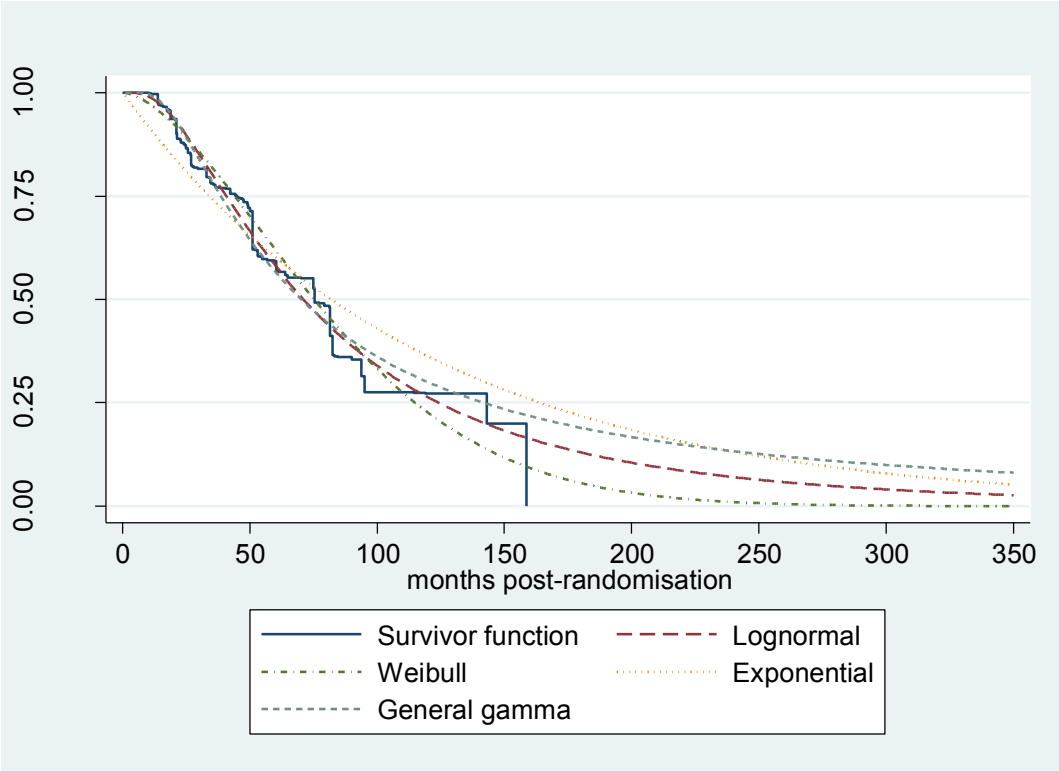
After applying weights to the ERASMUS GI sample, the generalised gamma and the lognormal distribution had the closest fit to the time to disease progression or death data (AIC: 441 and 449, BIC: 447 and 453, respectively). The Weibull form fitted the data better than the exponential and Gompertz functions (AIC: 483, 516, 509; BIC: 486, 518, 513).

Figure 1 MAIC-weighted K-M and parametric fits to PFS with 177Lu-DOTATATE: GI



After applying weights to the ERASMUS GI sample, the lognormal and generalised gamma distributions had the closest fit to the overall survival data (AIC: 335 and 335, BIC: 339 and 340, respectively). The Weibull form fitted the data better than the exponential and Gompertz functions (AIC: 347, 375, 363; BIC: 351, 376, 367). Of the best-fitting functions to the data, which became sparse beyond 100 months after randomisation (when one third of the sample was still alive), the generalised gamma function provided the most optimistic extrapolation, the Weibull function provided the most conservative one, with the exponential and lognormal functions providing projections in the middle of the predicted range. It is worth noting that the exponential underestimates survival in the early period up to 50 months, and then overestimate it from 70 to 140 months (Figure 8).

Figure 2 MAIC-weighted K-M and parametric fits to OS with 177Lu-DOTATATE: GI



These outcomes were achieved at a cumulative mean dose intensity of 96.8% after weighting (28.66/29.60 GBq or 774.73/800.0 mCi) of the four planned infusions (95.7% before weighting).

3.3.2.1.3 GI midgut

Since we had no information available on baseline characteristics of GI midgut patients from RADIANT-4 we matched the baseline characteristics of ERASMUS GI Midgut subgroup to those of GI NETs in RADIANT-4. Patients in the Midgut NETs group accounted for 117 (66.8%) out of the 175 GI NETs patients in RADIANT-4 (Singh et al. 2016). The results must therefore be interpreted with this caveat in mind.

Table 2 Baseline characteristics pre and pots-matching ERASMUS GI midgut-NETs cohort to RADIANT-4 GI subpopulation

Baseline variable	ERASMUS (before matching)	ERASMUS (after matching)	RADIANT-4 (reference population) *
N	108	108	175
ESS	N/A	33.1	N/A
Age (median)	61	62	62
Female	47.2	54.8	54.8
ECOG >1	70.4	21.7	21.7
Previous SSA	78.7	60.3	60.3
Previous surgery	57.4	74.3	74.3
Previous chemotherapy	10.2	16.5	16.5
MAIC weights range	N/A	0.03-7.12	N/A

Note: N sample size; ESS: effective sample size after matching, N/A Not applicable. * Since no information on baseline characteristics was available for the GI midgut subgroup of RADIANT-4 matching was performed to the baseline characteristics of whole GI RADIANT-4 patients (Singh et al. 2016).

- ***Table 22 "*Parameter values used in the model for 177Lu-DOTATATE in GI-NETs" (page 50)**

Table 3 Parameter values used in the model for 177Lu-DOTATATE in P-NETs

Intervention	Outcome	Model	Parameter	Estimate (Standard error)	Analysis	Method	Source
177Lu-DOTATATE	PFS	Weibull[1]	Scale	0.0003 (0.001)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			Shape	1.818 (0.204)			
177Lu-DOTATATE	PFS	Lognormal	Mean	4.879 (0.087)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.669 (0.076)			
177Lu-DOTATATE	OS	Exponential	Scale	0.009 (0.002)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
177Lu-DOTATATE	OS	Log-normal	Mean	4.163 (0.180)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.811 (0.127)			

Note: PFS progression free survival; OS overall survival. [1] Weibull cumulative survival function: exp(-Scale*time^shape).

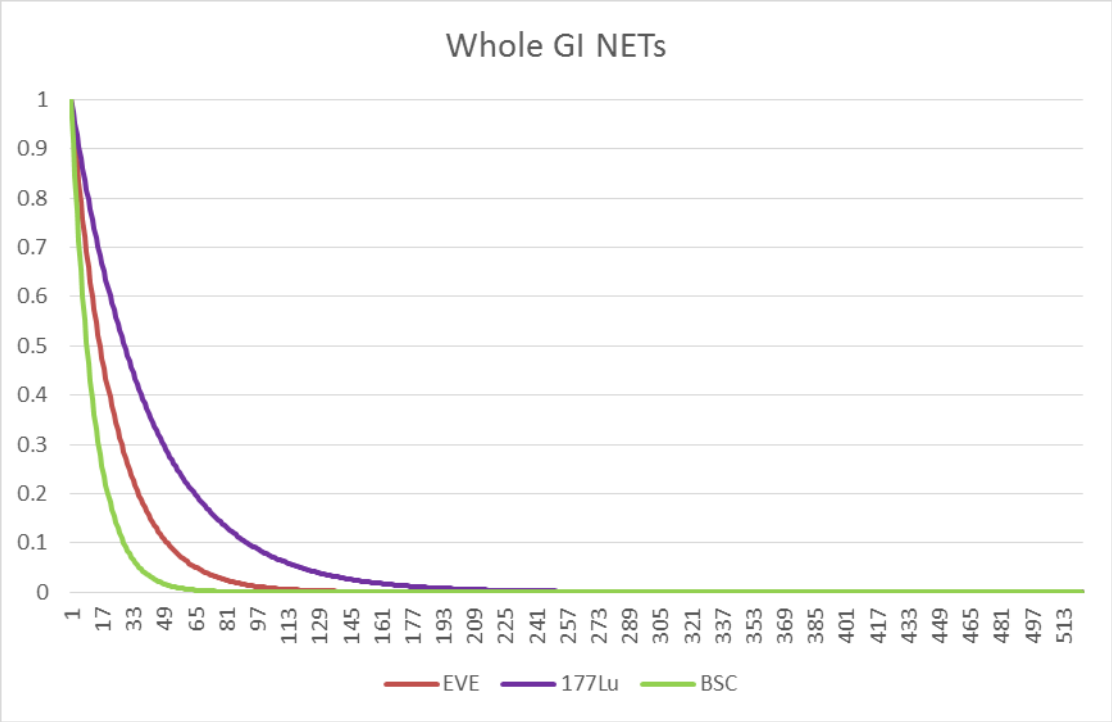
Table 4 Parameter values used in the model for 177Lu-DOTATATE in GI-NETs

Intervention	Outcome	Model	Parameter	Estimate (Standard error)	Analysis	Method	Source
177Lu-DOTATATE	PFS	Exponential	Scale	0.027 (0.004)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
177Lu-DOTATATE	PFS	Lognormal	Mean	3.243 (0.133)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.745 (0.067)			
177Lu-DOTATATE	OS	Exponential	Scale	0.008 (0.001)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
177Lu-DOTATATE	OS	Log-normal	Mean	4.264 (0.136)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.825 (0.090)			

Note: PFS progression free survival; OS overall survival.

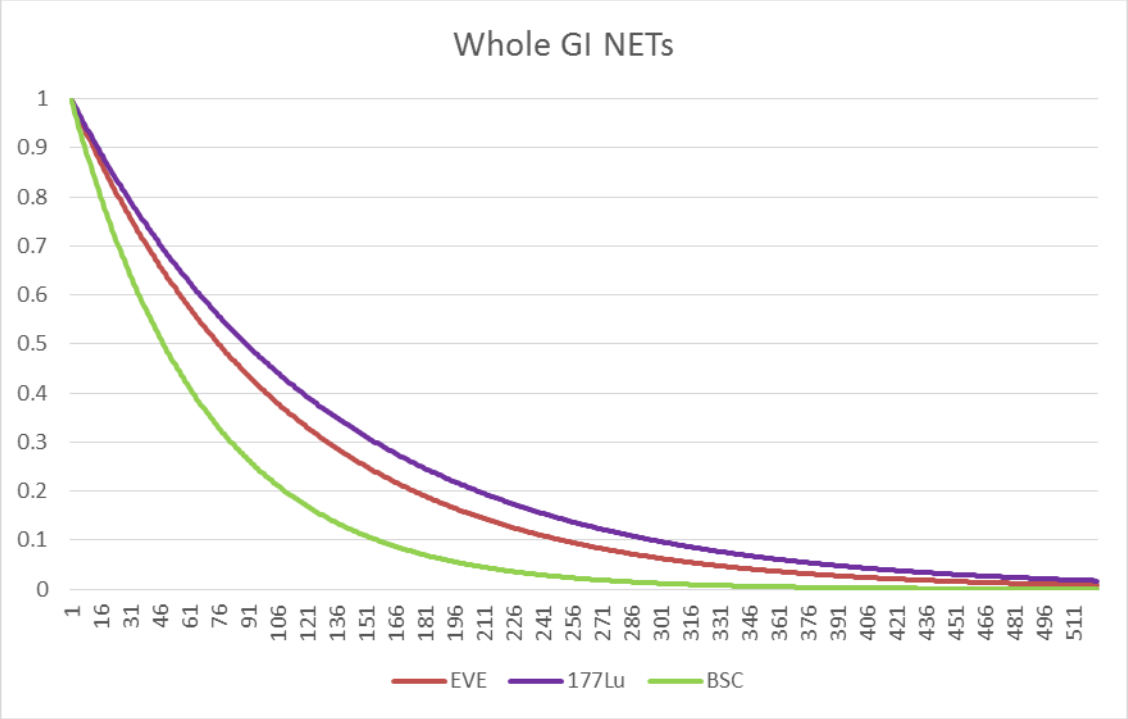
- **Figure 15 "Progression Free Survival in AG model (Whole GI NETs)" and Figure 16 "Overall Survival in AG model (Whole GI NETs)" (page 52)**

Figure 3 Progression Free Survival in AG model



* Note: These curves do not reflect the effect of background mortality which was applied in the base case analysis in the model.

Figure 4 Overall Survival in AG model



* Note: These curves do not reflect the effect of background mortality which was applied in the base case analysis in the model.

- **Section 4.2.2 Dose intensity of 177Lu-DOTATATE (page 53)**

4.2 AG revisions to the economic analysis

4.2.1 Cost of 177Lu-administration

In a change to the original base case, to reduce potential double counting of consumed resources for those patients who require overnight stay (admission), we used the national average cost of an elective inpatient excess bed day instead of the national average cost of a non-elective inpatient short stay.(27) The result is a reduction in the weighted unit cost of 177Lu-DOTATATE administration from £1,063.07 to £811.77.

4.2.2 Dose intensity of 177Lu-DOTATATE

For consistency with our source of effectiveness data, i.e. the ERASMUS dataset in MAIC based survival analyses, we have calculated and adopted the mean relative dose intensity of 177Lu-DOTATATE in the ERASMUS population. This has increased the previous base case estimate of 86.4%, which originated from NETTER-1, to 94.4% in P-NETs, 96.8% in Whole GI NETs, and 97.8% in midgut NETS, obtained from MAIC analyses described above.

The mean proportion of people who are alive and disease free (i.e. the area under the parametric PFS curve) under the 177Lu-DOTATATE arm over the first seven four-weekly model cycles, the period during which 177Lu-DOTATATE administration is scheduled, places a cap on the mean cumulative dose that is consumed in the model. For the base case analysis (which use an exponential PFS curve) that cap is 94.2%, 92.8%, and 92.1% in P-NETs, whole GI, and GI midgut, respectively. Therefore the effective relative dose intensity in the model are equal to the values just described times the cap imposed by the PFS distribution in the model (respectively, 89%, 90% and 90%). In sensitivity analysis where we assume 100% dose intensity the cap becomes the effective relative dose intensity, which thus becomes closer to the ERASMUS values we estimated from MAIC in section 3. Also note that the use of lognormal PFS curves changes the caps, which become 99.8%, 99.4%, and 99.0%, for P-NETs, GI NETs and GI midgut NETs, and again bring the effective relative dose intensity closer to the values we estimated from ERASMUS.

Therefore the base case assumptions of relative dose intensity tend to slightly underestimate costs from the point of view and 177Lu-DOTATATE, due to premature attrition of patients from treatment, and in this sense represent a slightly optimistic analysis.

1.1.1 Application of background mortality in the GI analyses

In the base case analysis of strategies for the treatment of patients with GI NETs we made adjustment in the survival analysis for background mortality (**Error! Reference source not**

found.). This was applied because of the short period of follow-up in the supporting indirect comparison of progression and mortality; in cases where a substantial extrapolation is fitted to a short period of observation the impact of death from other causes on relative health benefit can be significant. In this revised economic analysis by the AG we have for each strategy matched the point of adjustment to the point at which the last in-trial event is recorded.

- **Section 4.3.1 Base case results for treatment strategies by tumour location (pages 55-56)**

4.3 Results

The deterministic model was selected as the primary analysis.

In section 0 below the base case analysis estimates of costs and QALYs of each treatment arm as well as incremental results are presented. These are followed by the probabilistic results, section □. Presented below these are the results of relevant scenario analyses, each which an incorporated description, section **Error! Reference source not found.** and □.

Finally we have placed AG and Company results alongside one another for comparison in section □.

4.3.1 Base case results for treatment strategies by tumour location

177Lu-DOTATATE is estimated to produce the longest life expectancy across treatments for P-NETS, Whole GI and Midgut NETs patient populations. It was also the most effective and most costly option in all three tumour location groups, producing 4.2, 4.8 and 4.4 discounted QALYs, and £91,784, £93,341 and £89,790 discounted costs, respectively (Table 5). Drug acquisition is the cost driver accounting for 73% (£67 345) of its total (£91,784) in P-NETS, 68% (£63,617) of its total (£93,341) in whole GI NETs and 71% (£63,673) of its total (£89,790) in GI midgut.

Table 5 Base-case strategy results for Pancreatic NETs (deterministic discounted QALY and cost means, costs in £s)

	Pancreatic NETS				Whole GI NETs			Midgut NETs		
	BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus	177Lu-DOTATATE
Life years*										
Pre-progression	0.570	1.279	1.601	3.814	0.901	1.644	3.023	1.434	2.069	2.726
Post-progression	2.893	3.413	4.787	5.003	3.999	5.168	5.893	2.940	3.104	4.369
Total	**3.463**	**4.692**	**6.388**	**8.717**	**4.900**	**6.812**	**8.916**	**4.374**	**5.172**	**7.096**
QALYS										
Pre-progression	0.381	0.813	0.997	2.207	0.705	1.192	2.094	1.102	1.479	1.914
Post-progression	1.534	1.692	2.241	2.050	2.404	2.891	3.045	1.767	1.797	2.354
Total	**1.914**	**2.505**	**3.238**	**4.257**	**3.109**	**4.082**	**5.139**	**2.869**	**3.276**	**4.268**
Costs pre-progression										
Drug acquisition	2,003	25,547	22,216	63,689	405	29,813	63,617	634	30,353	63,673
Drug administration	510	1,104	1,308	2,840	3	168	2,861	4	170	2,864
Medical management	184	776	952	2,116	2,201	4,758	8,379	3,440	5,909	7,625
AEs	15	132	89	89	34	171	171	105	287	85
Total	2,712	27,559	24,566	68,733	2,642	34,910	75,029	4,184	36,719	74,247
Costs post-progression										
Drug acquisition	4,660	6,113	8,120	7,483	2,523	4,610	4,911	1,855	2,879	3,787
Drug administration	1,106	1,468	1,949	1,797	10	23	24	7	14	18
Medical management	3,394	3,759	4,993	4,601	7,862	9,520	10,076	5,780	5,907	7,771
End-of-life care	3,889	3,747	3,565	3,321	3,721	3,515	3,302	3,779	3,688	3,485
Total	13,049	15,087	18,627	17,202	14,115	17,697	18,313	11,422	12,488	15,063
Total Costs	**15,761**	**42,646**	**43,192**	**85,935**	**16,757**	**52,607**	**93,341**	**15,606**	**49,207**	**89,309**

Key: AEs = Adverse events (Serious); BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours; QALY = Quality-Adjusted Life Year. *Life years are presented as undiscounted.

- **Section 4.3.2 Base case results for treatment strategy comparisons by tumour location (page 58)**

In whole GI NETs, 177Lu-DOTATATE has an incremental ICER of £46,870 relative to BSC and of £63,792, relative to the second most effective alternative, everolimus (Table 6).

Table 6 Base-case incremental results for Whole GI NETs (deterministic discounted QALYs and cost means, costs in £s)

	177Lu-DOTATATE versus BSC	177Lu-DOATATE versus Everolimus
Life years gained*		
Pre-progression	2.122	1.380
Post-progression	1.894	0.725
Total	4.016	2.105
QALYS gained		
Pre-progression	1.388	0.902
Post-progression	0.641	0.154
Total	2.029	1.056
Costs pre-progression		
Drug acquisition	63,212	33,805
Drug administration	2,859	2,694
Medical management	6,178	3,621
AEs	137	0
Total	72,387	40,119
Costs post-progression		
Drug acquisition	2,387	271
Drug administration	14	1
Medical management	2,215	556
End-of-life care	-418	-213
Total	4,198	616
Total Costs	76,584	40,735
ICER – lifetime horizon	**37,737**	**38,557**
ICER – until progression	52,137	44,476

Key: AEs = Adverse events (Serious); BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio: NETs = Neuroendocrine Tumours; QALY = Quality-Adjusted Life Year. *Life years are presented as undiscounted.

- **Section 4.3.3 Probabilistic sensitivity analysis (pages 60,62,64)**

4.3.3 Probabilistic Sensitivity Analysis

Allowing for sampling uncertainty in model parameter values results in probabilistic mean ICER estimates of £29,434 versus BSC, £24,300 versus everolimus, and £40,428 versus sunitinib in P-NETS. These are respectively 2%%, 2%, and 4% lower than the deterministic estimates. In the Whole GI NETS population, the probabilistic ICER is £39,670 versus BSC and £40,903 versus everolimus which are respectively 5% and 6% above the deterministic estimate. For GI midgut NETS the PSA results are within 1.5% of the deterministic (Table 7). Results of the individual simulation are presented on the cost-effectiveness plane for the P_NETS comparison in **Error! Reference source not found.**, and the Whole GI comparisons in Figure 5.

Table 7 PSA of base case model by Strategy comparison and NETs location (probabilistic discounted QALY and cost means, costs in £s)

	Pancreatic NETS			**Whole GI NETs**		**Midgut NETs**	
	177Lu-DOTATATE versus:			177Lu-DOTATATE versus:		177Lu-DOTATATE versus:	
	BSC	Everolimus	Sunitinib	BSC	Everolimus	BSC	Everolimus
PSA ICER	29,434	24,300	40,428	39,670	40,903	53,416	40,589
Deterministic ICER	29,956	24,714	41,967	37,737	38,557	52,690	40,423

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours.

Figure 5 PSA simulations for Whole GI NETS on the cost-effectiveness plane

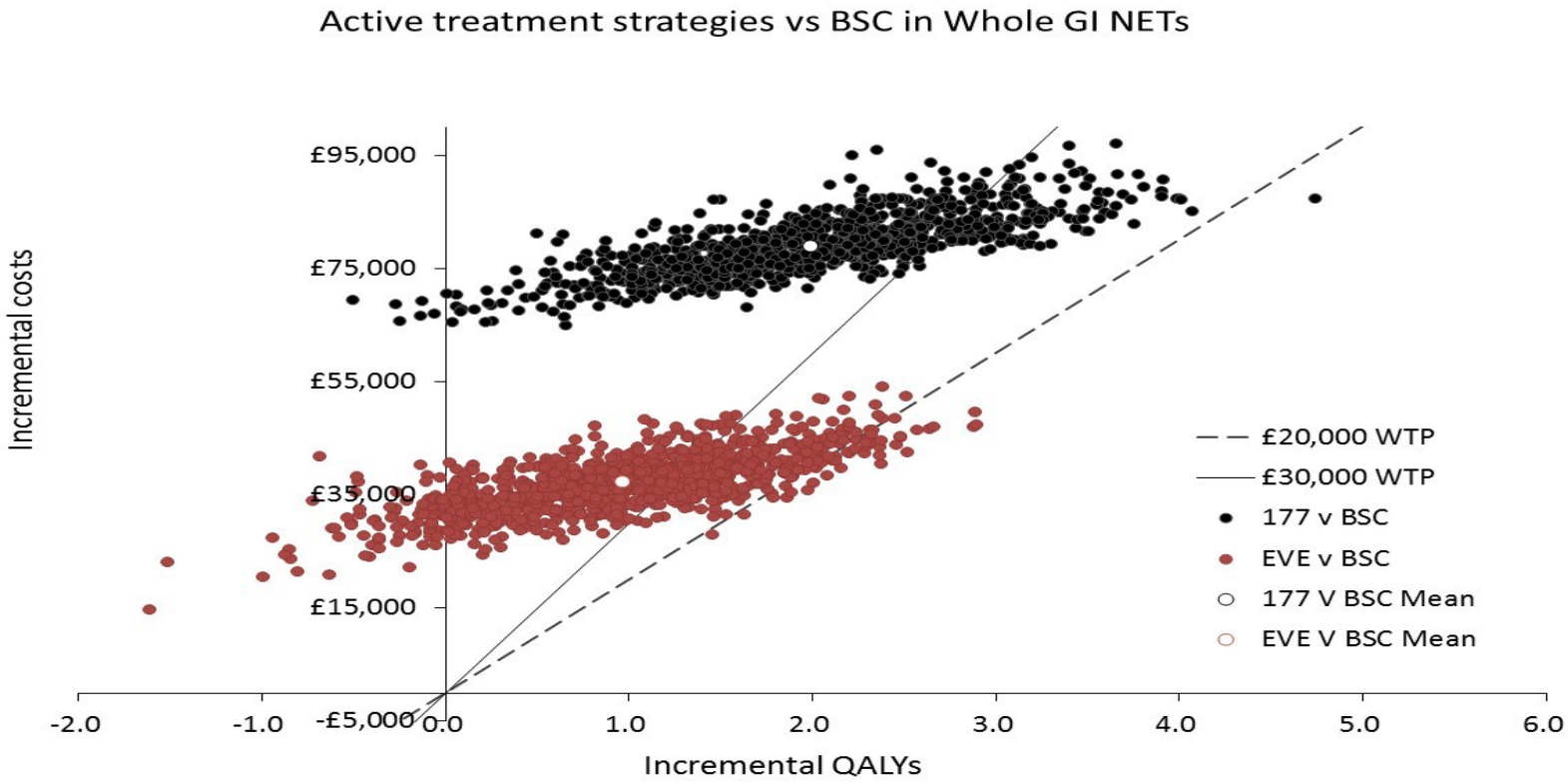
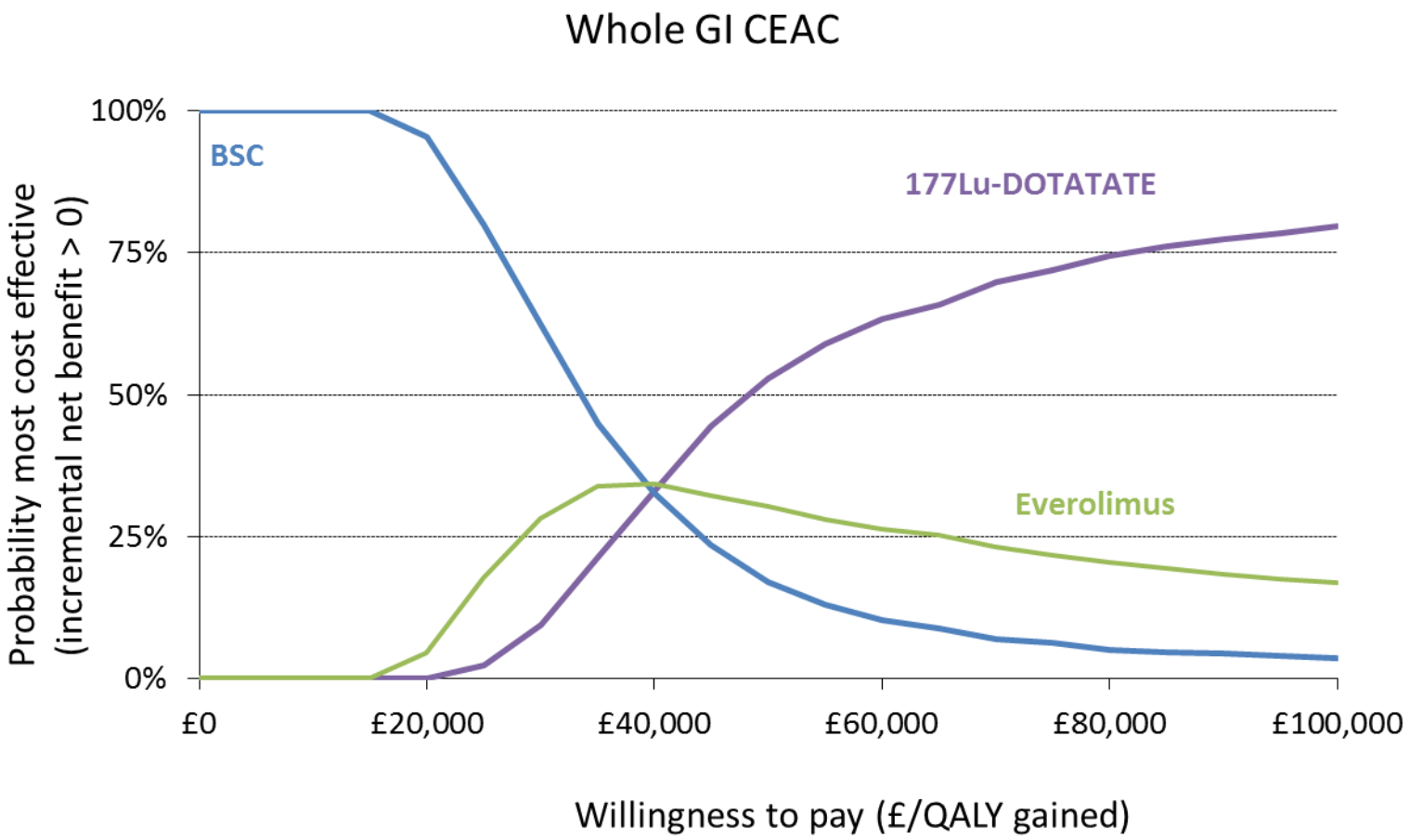


Figure 6 Cost Effectiveness Acceptability Curve (CEAC) for comparisons of 177Lu-DOTATATE in Whole GI NETS



- **Section 4.3.4 No discounting of future costs and QALYs (page 65)**

4.3.4 No discounting of future costs and QALYs

Table 8 Effect of no discounting, ICERs by Strategy comparison and NETs location (deterministic discounted QALY and cost means, costs in £s)

	Pancreatic NETS			Whole GI NETs		'Midgut' NETs	
	177Lu-DOTATATE versus:			177Lu-DOTATATE versus:		177Lu-DOTATATE versus:	
	BSC	Everolimus	Sunitinib	BSC	Everolimus	BSC	Everolimus
No discount ICER	22,996	18,546	29,242	28,301	27,599	39,896	29,710
Deterministic ICER	29,956	24,714	41,967	46,638	38,207	52,690	40,423

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours.

- **Section 4.3.6 Univariate Scenario Analyses in Whole GI NETs (pages 73-79)**

4.3.6 Univariate Scenario Analyses in Whole GI NETs

The scenario analyses presented below (Table 9 to Table 21) explore plausible alternatives to base case assumptions or input estimates (sources).

Note that we have not presented scenario analyses of the Midgut NETs model since the results of the base case analysis of this sub-population show inferior cost-effectiveness of 177Lu-DOTATAE versus BSC compared to 177Lu-DOTATATE when used across the Whole GI population. Also, the quality of evidence supporting the analysis of midgut NETS is limited due to lack of midgut NET-specific data from RADIANT-4, the reference trial, on i) baseline data, for matching, and ii) overall survival outcomes.

Table 9 Full dose intensity in pre-progression in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Dose intensity of Everolimus, Sunitinib and 177Lu-DOTATATE at 100%

The base case uses includes estimates of dose intensities for everolimus, sunitinib and 177Lu-DOATATE from clinical trials, these are all below 100%. In this scenario we remove this assumption and estimate cost-effectiveness at full dose intensity. Because of attrition in the model, the effective cumulative dose intensity is 92.8%.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	2,642	**42,106**	**77,205**		
	Post	14,115	17,697	18,313		
				Scenario Lifetime ICER	**38,810**	**33,805**
				c.f. Base case ICER	*53,705*	*38,911*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 10 177Lu-DOTATATE dose intensity in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Dose intensity of 177Lu-DOTATATE dose

The base case uses a dose intensity of 96.8% (effective cumulative dose intensity of 89.9%), an estimate derived from usage in ERASMUS, the reference trial of the MAIC. Another plausible estimate for the dose intensity of 177Lu-DOTATATE is that observed in NETTER-1 (86.4).

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	2,642	34,910	**72,489**		
	Post	14,115	17,697	18,313		
				Scenario Lifetime ICER	**36,486**	**36,152**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 11 Duration of everolimus treatment in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Mean duration of treatment with everolimus increased

The base case mean duration of everolimus treatment is 13.3 months, however in this scenario we test a longer duration based on the estimate from the midgut population; this is 16.3 months.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	2,642	**40,938**	75,029		
	Post	14,115	17,697	18,313		
				Scenario Lifetime ICER	37,737	**32,851**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 12 Increased resources for disease monitoring

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Alternative approach to disease monitoring utilisation rate

Disease monitoring in the base case is included for the whole period of disease until death. In this scenario we increase the amount of resources to those reported from RADIANT-4 by Novartis in their submission to NICE (see Assessment Report ID 858).

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	**2,948**	**36,293**	**77,465**		
	Post	**16,037**	**20,014**	**20,765**		
				Scenario Lifetime ICER	**39,048**	**39,681**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 13 First-cycle post-progression costs in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Including the cost of therapies bundled into the first cycle of treatment post-progression

In the base case analysis, the use of Chemoembolization, Radiotherapy and Chemotherapy (the cost of which were applied only to the first cycle post-progression) was not included despite observed utilisation post-progression in the RADIANT-3 trial. Here we have re-introduced these costs.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	2,642	34,910	75,029		
	Post	**15,883**	**21,601**	**21,236**		
				Scenario Lifetime ICER	**38,307**	**37,629**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 14 Alternative sources of utility estimates

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Alternative sources of utility estimates

In GI NETs the base case pre-progression utility estimates were based on a Novartis treatment arm analysis of RAD-4 for everolimus and BSC (0.767 and 0.807 respectively); and the ERASMUS study for 177Lu-DOTATATE (0.77). Post-progression the estimates for patients on all treatments were based on a Novartis pooled estimate of arms in RAD-4 (0.725). In this scenario a mix of alternative plausible sources are used: pre-progression a pooled RAD-4 analysis for everolimus and BSC (0.779), and the Guy's and St Thomas' registry for 177Lu-DOTATATE (0.79); post-progression the treatment arm analysis of RAD-4 for everolimus and BSC (0.714 and 0.747 respectively), and the ERASMUS study for 177Lu-DOTATATE (0.74).

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	**0.681**	**1.210**	**2.127**		
	Post	**2.477**	**2.847**	**2.999**		
Costs	Pre	2,642	34,910	75,029		
	Post	14,115	17,697	18,313		
				Scenario Lifetime ICER	**38,925**	**38,132**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 15 No background mortality in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Removing adjustment for background mortality in PFS and OS event rate

The treatment strategies of the GI analyses include in the base case an adjustment for the effect of all-cause age specific mortality in the background event rates. In this analysis this adjustment is removed, leaving a naïve rate.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	**0.902**	**1.652**	**3.030**		
	Post	**4.285**	**6.594**	**6.657**		
QALYs	Pre	**0.706**	**1.197**	**2.097**		
	Post	**2.535**	**3.491**	**3.260**		
Costs	Pre	**2,644**	**34,940**	**75,040**		
	Post	**14,661**	**20,558**	**19,354**		
				Scenario Lifetime ICER	**36,427**	**58,177**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 16 Parametric curve choice for PFS in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Using Lognormal instead of Weibull

Statistical exploration and clinical validity drove the choice in the base case of the Weibull parametric curve for the fitting and extrapolation of progression events across the life-time horizon. Here we test PFS estimates of the 177Lu-DOTATATE strategy by fitting the accelerated failure time distribution the lognormal. The other strategies are unchanged.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	**2.810**		
	Post	3.999	5.168	**6.153**		
QALYs	Pre	0.705	1.192	**1.986**		
	Post	2.404	2.891	**3.168**		
Costs	Pre	2,642	34,910	**79,980**		
	Post	14,115	17,697	**18,921**		
				Scenario Lifetime ICER	**40,177**	**43,200**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 17 Parametric curve choice for OS in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Using Lognormal instead of Exponential

Statistical exploration and clinical validity drove the choice in the base case of the Exponential parametric curve for the fitting and extrapolation of death events across the life-time horizon. Here we test OS estimates of the 177Lu-DOTATATE strategy by fitting the accelerated failure time distribution the lognormal. The other strategies are unchanged.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	**4.722**		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	**2.593**		
Costs	Pre	2,642	34,910	75,029		
	Post	14,115	17,697	**16,134**		
				Scenario Lifetime ICER	**47,182**	**63,828**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 18 Alternative definition of BSC 1

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

BSC: No supportive therapies in stable disease except SSRAs, used with increased dose and prevalence (High dose Octreotide, 60mg, in 40% pts)

The base case simulation of the BSC strategy uses estimates taken from the observed rates of resource utilisation in the RAD-4 RCT, which was 1% of patients, using Octreotide 30mg. Expert clinical advice suggests this is a low estimate versus real-world usage in this population, so this sensitivity analysis presents a plausible alternative to the base case.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	**9,851**	34,910	75,029		
	Post	14,115	17,697	18,313		
				Scenario Lifetime ICER	**34,185**	38,557
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 19 Alternative definition of BSC 2

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

BSC: No supportive therapies in stable disease except SSRAs, used with increased dose and prevalence (High dose Octreotide, 60mg, in 100% pts)

The base case simulation of the BSC strategy uses estimates taken from the observed rates of resource utilisation in the RAD-4 RCT, which was 1% of patients, using Octreotide 30mg. Expert clinical advice suggests this is a low estimate versus real-world usage in this population, so this sensitivity analysis presents an alternative to the base case designed to demonstrate the extent of impact of high SSRA usage in BSC in stable disease. This scenario is one where SSRAs are essentially used as per the design of the comparator arm of NETTER-1, but note that SSRAs are not used here adjunct to 177Lu-DOTATATE, as was the design of NETTER-1.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	**21,203**	34,910	75,029		
	Post	14,115	17,697	18,313		
				Scenario Lifetime ICER	**28,591**	38,557
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 20 'Real world' SSRA approach

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Generally higher use of SSRAs versus base case

This scenario tests a general increase in SSRA usage versus the base case; when used with and without concurrent active treatment, and both pre and post progression. Estimates prevalence and dose of Octreotide is based on expert clinical opinion: Octreotide 30mg in 90% of pts pre-progression, reducing to 85% post-progression. This level is maintained whether or not pts are treated with other active treatments (i.e. 177Lu-DOTATATE or Everolimus).

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	**11,059**	**49,736**	**77,684**		
	Post	**44,468**	**53,948**	**56,681**		
				Scenario Lifetime ICER	**38,848**	**29,041**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 21 177Lu-DOATATE administration as Day Case

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Increase in the proportion of patients administered 177Lu-DOTATATE as Day case

This scenario assumes a greater number of patients will be able to leave hospital care following 177Lu-DOTATATE treatment and observation versus the base case. In the base case the estimate for the proportion of day case administrations was 10%, based on the average of estimates from two clinical experts in Nuclear medicine with experience of 177Lu-DOTATATE preparation and administration. Here we increase this proportion to 65% of patients, which may represent a plausible near future scenario.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	3.023		
	Post	3.999	5.168	5.893		
QALYs	Pre	0.705	1.192	2.094		
	Post	2.404	2.891	3.045		
Costs	Pre	2,642	34,910	**74,833**		
	Post	14,115	17,697	18,313		
				Scenario Lifetime ICER	**37,641**	**38,371**
				c.f. Base case ICER	*37,737*	*38,557*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

- **Section 4.3.7 Comparison of AG results with AAA deterministic base case results (second paragraph, page 80)**

4.3.7 Comparison of AG results with AAA deterministic base case results

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Table 22 present AG and company results for P-NETS and GI NETS, respectively, side-by-side. Company results are those produced and displayed by the company model (version submitted February 2018). Strategy selection are based on those that produce the base case ICERs described in the company's report (version submitted February 2018).

Unfortunately the company's results in P-NETS have an error in the calculations for the sunitinib strategy. We have presented the result that we obtained from the company's model as opposed to those presented in the company's submission to NICE, since the latter results cannot be substantiated with the model submitted to NICE. As a result we cannot comment here on the comparison of sunitinib strategies between models.

Pancreatic NETS

For P-NETS, as the figures in the last three columns of **Error! Reference source not found.** show, AAA produced three different set of estimates of costs, QALYs and ICERs for 177Lu-DOTATATE, one set for each comparator (BSC, everolimus and sunitinib). The reason for having as many estimates of costs and health outcomes of its sponsored targeted therapy, is that AAA performed MAIC of the ERASMUS P-NETS sample to each of the two arms of RADIANT-3 separately, everolimus plus BSC and BSC only (AAA ID1224 submission to NICE December 8, 2018, Table 15), and to the sunitinib arm of A6181111. This complicates the interpretation of results since the numbers refer to at least two and possibly three different patient populations. Instead the AG matched the sunitinib arm by Bucher indirect comparison method and the ERASMUS arm by MAIC to the same population of RADIANT-3 as a whole (rather than each of the everolimus plus BSC and the BSC arms separately as the company did). It is worth noting how different AAA's cost and QALY estimates for 177Lu-DOTATATE are even between arms of the same RADIANT-3 trial population: the life years before progression for 177Lu-DOTATATE after MAIC re-weighting to match the BSC arm of RADIANT-3 is 3.063; versus 2.714 after MAIC re-weighting to match the everolimus arm of the same trial.

- **Section 4.3.7 Comparison of AG results with AAA deterministic base case results (pages 83-84)**

It is not possible to compare between models the ICERs for 177Lu-DOATATE versus sunitinib for the reasons mentioned above.

Whole GI NETS

As was the case with the ICER results in the P-NETs analysis, the AG's GI-NETS analysis when compared to the company's produced higher ICERs: for both 177Lu-DOTATATE versus BSC, and 177Lu-DOTATATE versus everolimus. Although here we see that the differences are larger and the AG estimates fall above the conventional threshold for cost-effectiveness: £37,737 per QALY gained in the AG analysis versus £20,741 (45% lower), and £38,557 versus £22,227 (42% lower), for comparisons versus BSC and everolimus respectively.

The reasons for these large differences may be explained in the comparison with BSC by the company's definition of BSC (I.e. high dose octreotide for all, leading to large costs); and in the comparison with everolimus, by the company's low estimate of its effectiveness. The AAA model estimates a whole QALY less per person over a lifetime following treatment with everolimus, compared to the AG model. The large discrepancy in survival estimates for everolimus and 177Lu-DOTATATE produced by the company and AG is explained by the fact that the company's results were derived from using OS data from the GI/Lung RADIANT-4 patient group, whereas the AG had access to the data for the GI-only patient group in RADIANT-4, as provided by Novartis as part of responses to the Assessment Report for ID858. This meant that AAA severely underestimated the proportional amount of life extension past disease progression in the BSC and in the everolimus plus BSC arms of RADIANT-4 in GI patients. For example, according to AG estimates patients live on average 1.95 times the mean number of years lived without progression under 177Lu-DOTATATE treatment vs. 4.14 times under everolimus. In contrast, the company's estimates based on GI and lung patients, are respectively 1.83 versus 2.3.

When other differences in assumptions/input estimates are changed in the AG model to match those in the company model (to ubiquitous high dose octreotide use in BSC pre-progression and lower 177Lu-DOTATATE administration cost and dose intensity), the ICERs versus BSC and everolimus fall to £27,188 and £35,861 respectively. When the adjustment for background mortality (specific to the GI-NETS analysis) is removed, these ICER change to £26,305 and £53,916.

Sensitivity analyses of AG results, including changing the survival curves for all treatments, support the observation that AAA's results are severely limited by their lack of data in the GI only population.

Table 22 Comparison of incremental summary results in Whole GI NETs

(Discounted means, costs in £s) AAA model version February 2018, with updated GI-NETs MAIC analysis

		BSC		**Everolimus**		**177Lu-DOTATATE**	
		AG	Company	AG	Company	AG	Company
Life years*	Pre	0.901	1.671	1.644	1.728	3.023	2.794
	Post	3.999	2.328	5.168	2.272	5.893	2.328
	Total	**4.900**	**3.999**	**6.812**	**4.000**	**8.916**	**5.123**
QALYS	Pre	0.705	1.325	1.192	1.310	2.094	2.216
	Post	2.404	1.724	2.891	1.683	3.045	1.724
	Total	**3.109**	**3.049**	**4.082**	**2.992**	**5.139**	**3.940**
Costs	Pre	2,642	42,488	34,910	44,599	75,029	60,500
	Post	14,115	30,900	17,697	30,159	18,313	31,375
	Total	**16,757**	**73,388**	**52,607**	**74,757**	**93,341**	**91,875**
ICER, 177Lu vs.		**37,737**	**20,741**	**38,557**	**22,227**	**-**	**-**

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. Company estimates are from the AAA model selections as driven by the results reported in the submission: **BSC** = Octreotide LAR (GINET - MAIC); **Everolimus** = Everolimus (GINET – MAIC); **177Lu** = Lutathera (GINET – MAIC). The 177Lu strategy was not selected with Octreotide 30mg (in line with reported base case result), and the BSC care strategy was selected as high dose 60mg octreotide (in line with reported base case result). *Life years are presented as undiscounted.

Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-DOTATATE [ID1224]

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This document must be read as an addendum to the Assessment Report ID858

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1 Summary of Results and Discussion

AAA submitted new evidence on effectiveness and cost –effectiveness for 177Lu-DOTATATE in patients with pancreatic neuroendocrine tumours (P-NETs), gastro-intestinal tumours (GI)-NETs and GI-midgut NETs. The P-NETs analysis was based on an indirect comparison of outcomes in the single arm trial of 177Lu-DOTATATE in ERASMUS and the trial arms of sunitinib plus BSC and BSC only in the A6181111 trial, and the trial arms of everolimus plus best supportive care (BSC) and BSC only in RADIANT-3 trial. This comparison was based on very low numbers of patients from ERASMUS, which is likely to lead to unreliable estimates. The Assessment Group (AG) therefore undertook their own indirect comparison using the company's data from ERASMUS, but including non-Dutch patients, which the company's analysis excluded. This less stringent entry criteria arguably led to additional risk of bias from high loss to follow-up of non-Dutch patients, which may have been more than compensated by a gain in precision due to a larger sample size, relative to the company's effectiveness estimates.

The company's evaluation on GI NETs was based on an indirect comparison of progression-free survival (PFS) outcomes of GI-NETs patients from the ERASMUS cohort, treated with 177Lu-DOTATATE, with those of the GI subgroup of the RADIANT-4 trial population, treated with everolimus plus BSC and BSC only. The company had no data available from the RADIANT-4 GI NET subgroup to perform indirect comparison of overall survival (OS) outcomes in the RADIANT-4 and ERASMUS populations. As a consequence, in their cost-effectiveness analysis the company assumed that the time from disease progression to death was the same across treatments. In contrast the AG had available data on OS outcomes in the overall GI patient group of RADIANT-4, previously provided by Novartis for Appraisal ID858, and performed cost-effectiveness analysis using that data.

In P-NETs patients the company's base case analysis found that 177Lu-DOTATATE had an ICER of £22,883 relative to BSC only, whereas in the respective analysis by AG the ICER was £29,956. The difference between these numbers is due mainly to the costs of SSRAs in BSC which AAA assumes are consumed by all patients at the higher dose of 60mg as opposed to AG's values of 40% of patients consuming SSRAs at the 30-20 mg doses observed in RADIANT-3. It must be noted however, that AG's figure slightly under-estimates the ICER since the parametric distribution used to extrapolate progression free-survival (i.e. exponential function) underestimates the proportion of patients alive and progression free in the early part of the modelled when patients receive 177LU-DOTATATE. Further, the base case result increases when the progression free survival is modelled using alternative parametric survival functions (accelerated failure time instead of proportional hazards models). AG's fully incremental analysis including the competitor treatments of sunitinib and

everolimus showed that the willingness to pay per QALY would have to be above £40,000 for 177Lu-DOTATATE to become the cost-effective treatment option.

In GI-NETs patients the company's base case analysis found that 177Lu-DOTATATE had an ICER of £20,741 relative to BSC only, whereas in the respective analysis by AG the ICER was £46,870. In addition to the methodological differences described above for P-NETs, the different data underlying the two estimates is the most important explanation for their very different results. AAA did not have access to data on overall survival outcomes for GI patients in RADIANT-4 and therefore had to assume that the expected time after disease progression was the same across treatment arms. In contrast the AG based on their analysis on actual data in the relevant population of RADIANT-4, that is from GI only trial patient group. Our sensitivity analyses for methods of extrapolation, resource use and costs and utility parameters produced ICERs consistently above £30,000. Fully incremental analysis including the competitor treatment of everolimus conducted by AG found that the willingness to pay per QALY would have to be above £75,000 for 177Lu-DOTATATE to be the most likely cost-effective treatment option.

Additional results on P-NETs and GI-NETs were obtained using the agreed PAS discount to the price of everolimus. These results are presented in a separate confidential appendix.

AG also conducted an economic evaluation based on results from MAIC analysis of outcomes in the GI midgut NETs patient group of ERASMUS versus those of the GI midgut patient subgroup in RADIANT-4. ICER estimates were in the same order of magnitude as those obtained by AG for the whole GI patient population just described, but the economic evaluation in the midgut NETs subgroup was subject to the limitation there were no available data on baseline characteristics and OS outcomes specific to the GI midgut subgroup from RADIANT-4 to perform the MAIC. We thus had to match to the baseline characteristics and use OS data from of the whole GI group of RADIANT-4. Therefore, our results should be considered with caution.

The company also submitted an economic evaluation of 177Lu-DOTATATE plus octreotide 30 mg relative to octreotide 60 mg in GI-midgut NETs using head-to-head effectiveness data from NETTER-1 trial. The analysis adjusted for the 22% rate of treatment cross-over from octreotide 60mg trial arm to the 177Lu-DOTATATE arm. Based on the fact that octreotide 60 mg was out of scope for the ID858 NICE Appraisal that led to this additional appraisal, the AG considered that the company's economics assessment based on the results of this trial is of limited relevance to this appraisal. In any case, the company adopted implausibly high costing assumptions about the amount of use of the high dose of octreotide 60 mg which meant the additional costs of 177Lu-DOTATATE were underestimated. Nevertheless, the company reported that 177Lu-DOTATATE increased life by 2.78 years and had an ICER of

£28,284. This result suggests that the true ICER of Lu-DOTATATE is above £30,000 in the NETTER-1 population.

In summary, our review of the evidence and our own analyses of the effectiveness data provided by the company and cost-effectiveness modelling suggest that 177Lu-DOTATATE has an ICER relative to BSC between £30,000 - £40,000 in P-NETs and above £40,000 in GI NETs and GI midgut NETs.

A word of caution is warranted, however, regarding the quality of the effectiveness evidence behind the evidence used to arrive at these estimates, which is based on indirect comparisons of outcomes of 177Lu-DOTATATE from a single arm cohort (ERASMUS). These 'unanchored' MAIC analyses do not permit some basic validity testing, for example by comparing that the matched control arms have similar outcomes and Kaplan –Meier curves. In terms of the ERASMUS data in particular this trial did not have an adequate recorded baseline measures of grade and stage, which are the most important prognostic factors and treatment effect modifiers in this clinical area, as advised by our clinical experts. Thus it is likely that estimates of relative treatment effects on PFS and OS outcomes for treatments in P-NETs, GI-NETs and especially GI-midgut NETs may be affected by confounding.

2 Background, Challenges and New Information

2.1 Attainment of market authorisation

AAA received EMA marketing authorisation for 177Lu-DOTATATE on 26 September 2017 for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) in adults. Following requests for further analyses the company supplied two updates of their second submission, in January and then in February 2018.

177Lu-DOTATATE is now licensed across all GEP-NETs irrespective of the location origin or functional status of the primary tumour. In their original report the company anticipated the granting of market authorisation in January 2017, thus the original assessment was carried out prior to market authorisation.

2.2 Progress of the technology appraisal

Recommendations were published in June 2017 for Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (TA449). Because NICE cannot release any recommendations until it has a positive opinion is given from the European Medicines Agency's Committee for Medicinal Products for Human Use, the review of 177Lu-DOTATATE now proceeds separately with this addendum to the main report.

In January 2018 the Assessment Group (AG) received from NICE revised analyses conducted by AAA for the review of 177Lu-DOTATATE. This followed the publication of the NICE Appraisal consultation document (ACD issued 3 August 2017). The company comment that they have taken on suggestions from both NICE and the AG in their new submission.

2.3 Main supporting trial data

The main trials of 177Lu-DOTATATE used in support of their GEP-NETs license, and their original submission to NICE remain as the source of effectiveness evidence in this revised submission (the controlled NETTER-1 and the single-arm ERASMUS). The main difference is that the data from NETTER-1 trial now uses a new data cut-off (primary analysis cut-off date unknown; revised cut-off 30 June 2016). Between these two included trials of 177Lu-DOTATATE a broad range of primary tumour sites are studied; including the 229 P-NETs patients of NETTER-1, and 360 (FAS) GEP-NETs patients in the Dutch population of the ERASMUS trial.

2.4 Challenges with scope of decision problem

To recap, octreotide was originally defined as outside of the scope of the decision problem, which led to the exclusion of NETTER-1 from the main body of the AG report. Instead the review of 177Lu-DOTATATE was included as an addendum to the AG report because the only source of data available on this treatment was that from NETTER-1. Indeed NETTER-1 is included in this review of AAA's new submission contrary to scope, for the reason that it is the only randomised controlled trial of 177Lu-DOTATATE in the GEP-NETs population, and in response to the interests on this targeted therapy by the medical community and NICE.

2.5 Heterogeneity in study design

The AG included only those studies of trials which administered the reviewed interventions within their license or anticipated licence. This led to the exclusion of RADIANT-2, which included patients with functioning GI-NETs. In their new submission, AAA have followed this requirement.

The separation of a general population of patients with GEP-NETs into primary site-specific populations has been rationalised independently by both the company and the AG. Separate analyses of P-NETs and GI-NETs populations was seen by AAA as appropriate since they state that P-NETs and GI-NETs have different clinical profiles and management. The AG approach was to conduct separate analyses for P-NETs, GI-NETs, and GI(midgut)-NETs and Lung-NETs. The AG's rationale was to analyse evidence according to trial populations involved in the three identified RCTs relevant to this technology assessment review. P-NETs covered the trial populations of the RADIANT-3 and A6181111 trials; GI(midgut)-NETs was the tumour location of patients in NETTER-1 and of a subgroup of patients from the RADIANT-4 study; for the Lung location the only data available was a subgroup from the RADIANT-4 trial and the AG analysed this population upon request from the NICE appraisal committee; the overall 'Whole' GI NETs location was also of interest to the NICE appraisal committee and only available from a subgroup of patients in RADIANT-4 (which also included patients with lung NETs).

An additional factor is the impact of high dose SSRA (e.g. 60mg) versus low dose (e.g. 30mg). Also, this variation in the definition of BSC matters for the effectiveness and cost-effectiveness evaluations in this technology appraisal of both177Lu-DOTATATE and the alternative interventions everolimus and sunitinib which also form part of this review

2.6 Use of SSRAs

2.6.1 Best Supportive Care

In the first submission by AAA (2016) the comparators to 177Lu-DOTATATE in the pancreatic NETs evaluation were everolimus (10mg per day) and sunitinib (37.5mg per day);

the comparator in the GI-NETs evaluation was everolimus (10mg per day) only. Although included in their submitted model by AAA, a strategy of Best Supportive Care (BSC) was not reported as a comparator strategy for either population and so was not included in our critique. In this second submission the company do report a BSC strategy, for both pancreatic and GI populations, and compare this strategy to 177Lu-DOTATATE. The company's assumptions around what constitutes best supportive care is a key aspect of their evaluation. In this second submission the company define it as treatment with high dose octreotide (60mg), reflecting the design of the NETTER-1 comparator arm. This definition of BSC is an area of important contrast between the company and AG approaches.

2.6.2 Post-progression

The use of SSRAs in the post-progression health state is another area of contrast between company and AG approaches. Whilst the AG have estimated a utilisation rate for octreotide - as well as other supportive therapies - from RADIANT-3 (pancreatic NETS) and RADIANT-4 (GI-NETS), the company has made the simplifying assumption that all patients who progress with NETS are treated with low-dose octreotide. As a result, the cost of resources for patients in this health state are significantly higher in the company model.

2.7 Issues not addressed in the company's re-submission

In respect to the pancreatic NETs population the revisions made by the company include an economic evaluation based on a matched adjusted indirect comparison (MAIC) of PFS and OS outcomes of patients in ERASMUS with those in RADIANT-3 and A6181111. The AG considered that these analyses were based on a very small sample and failed to adjust for important baseline prognostic factors. We therefore conducted analyses that extended that sample by including non-Dutch P-NETs patients in ERASMUS which the company excluded from its analyses - and included additional baseline covariates in the MAIC adjustment.

In respect to the GI-NETs population the revisions made by the company did not initially include the requested MAIC of ERASMUS and RADIANT-4. Further, the indirect comparison of OS outcomes drew on outcomes for a mixed GI and lung NETs population from RADIANT-4. The company provided the requested analysis on 27 February 2018. In these analyses, the company still lacked OS data from RADIANT-4 specific to the GI-NETs population, and thus conducted cost-effectiveness analyses based on a MAIC of PFS outcomes from ERASMUS with RADIANT-4 in GI-NETs patients and assumed that survival after disease progression was the same in 177Lu-DOTATATE, everolimus plus BSC and BSC only. We sought to address this limitation as explained below.

2.8 Summary of new analyses from the AG

In response to the NICE request to explore the use of the single arm data on a cohort of 177Lu-DOATATE-treated patients held by AAA, the ERASMUS cohort study, in order to expand the evidence base beyond the NETTER-1 population, we include two new analyses in this addendum of the AG report.

The first analysis uses a matched adjusted indirect comparison (MAIC) of ERASMUS pancreatic NETs patients to the pancreatic NETs patient population of RADIANT-3, which compared everolimus with BSC. These analyses are thought to be less open to confounding than similar analyses conducted by AAA, as explained below.

Our second analysis evaluates 177Lu-DOTATATE in ERASMUS by MAIC to the population of RADIANT-4, which compared Everolimus and BSC in GI-NETs. This indirect comparison uses published information on progression-free survival and information provided by Novartis in response to our Assessment Report on overall survival for the GI-only sub-population from RADIANT-4. We have also checked the company's newly performed RPSFT adjustment for cross-over in NETTER-1, and revisit contented areas of economic modelling. In respect to the GI-NETs NMA, our analyses in the main report are still current, and AAA has now revised their original analysis in line with our own as explained below. We also update our GI-NETs NMA to include the new RPFST-adjusted results for treatment crossover provided by the company.

In pursuing the above, we provide new independent ICERs for 177Lu-DOTATATE versus BSC, everolimus and sunitinib in pancreatic NETs, and relative to everolimus and BSC in GI-NETs, both for a Whole GI NETs population as well as a 'Midgut' only NETs population.

3 Clinical Effectiveness Evidence

3.1 Identification of non-RCT data by the AG

Here we review the evidence previously identified by the AG and new evidence provided by AAA Ltd.

From our previous report, we identified all non-RCT published evidence for 177Lu-DOTATATE up to our search date of May 2016. We identified 32 non-RCTs that reported outcome data for individuals with NETs who had received treatment with 177Lu-DOTATATE. These data were reported in section 4.4 of the report.

We have reviewed the studies identified, and highlight the following eight studies.(1-14) These are all studies that report over 30 participants for an individual tumour location. It was deemed 30 participants would be the minimum needed to be used in a MAIC analysis. Table 1 gives the study and baseline participant characteristics of these 8 studies.(1-14) Three studies published by the same author / group of authors had multiple publications with different sample sizes, in each case, the publication with the largest sample size has been presented.(2, 4, 5, 7, 8, 10, 11, 13) Three studies report data on individuals just with P-NETs,(1, 3, 12) two report data on individuals with just GI NETs,(9-11) and the remaining three studies report outcome data for a mix NET locations.(2, 4-8, 13, 14) Table 2 gives the headline outcome data from these 8 studies.

Table 1 Baseline characteristics from non-randomised studies for 177Lu-DOTATATE

Author and Year	Country	N	Location of NETS	177Lu-DOTATATE dose	Other drugs	Age (yrs)	Males n/N	Tumour Functioning n/N	Tumour Differentiation n/N	Previous Treatments n/N
Claringbold & Turner 2015a(1)	Australia	30	P-NETs	7.9GBq	1,500mg/m2 capecitabine and 200mg/m2 temozolomide, amino acids: 11.6 g/l lysine and 23 g/l arginine at 240 ml/h. Tropisetron and lorazepam.	Range: 38-78 yrs Median60 yrs	18/30 (60)	Non-functioning 21/30 Functioning 9/30	30/30 (100) Well differentiated	Surgery 8/30 SSA 4/30 Chemotherapy 3/30 Targeted agents 3/30 Radiopeptide 2/30
Ezziddin et al. 2011a(4) linked to Ezziddin et al. 2011b(5)and 2014a(2)	Germany[a]	81	37 P-NETs 44 GE-NET (5 foregut,19 midgut, 2 hindgut and 18 undetermined primary)	Mean activity 7.9 GBq per cycle	NR	Range: 33-83 yrs Mean 61 yrs	46/81 (57)	Non-functioning 63/81 Functioning1 8/81	79 /81 Well-differentiated 2 / 81 Poorly-differentiated	Previous treatments: 63/81 Octreotide 29/81 IFN 5/81 Chemotherapy 23/81 Ablative treatment 13/81 Surgery 40/81
Ezziddin et al. 2014b(3)	Germany[a]	68	P-NETs	Mean activity per cycle 8.0 GBq (216 mCi)	Nephroprotective 2.5% Lysine and 2.5% arginine in 1L 0.9% NaCl; infusion 250 ml/h	Range: 37-82 yrs Mean 62 yrs	35/68 (52)	Non-functioning 50/68 Functioning 18/68	68/68 (100) Well-differentiated	Surgery 30/68 Biotherapy 20/68 Chemotherapy 17/68 Locoregional treatment 7/68
Kong et al. 2014(6)	Australia	68	5 lung, 33 P-NETs, 35 non-pancreatic NET (small bowel, large bowel, gastrinoma, glucagonoma, thymus, unknown)	Median cumulative 31 GBq (21-45.3FBq)	Granisetron and dexamethasone with amino acid infusion (25g lysine and 25g arginine in 1 L normal saline). 5-FU chemotherapy (200mg/m^2/24h).	Range: 17-76 yrs Median 56 yrs	39/68 (57)	NR	NR	NR
Kwekkeboom et al. 2008(7) linked to Kwekkeboom et al. 2005(8), van Vliet et al. 2013(13)and 2015(14)	Netherlands	310	188 carcinoid 72 non-functioning P-NETs 31 unknown 12 gastrinoma 5 insulinoma 2 VIPoma	750 to 800 mCi (27.8-29.6 GBq). Cycle dosages were 100mCi (3.7 GBq), 150 mCi (3.6GBq) and 200mCi (7.4GBq)	Granisetron 3mg or ondasentron 8mg, amino acids (lysine 2.5%, arginine 2.5% in 1 l 0.9% NaCl:250ml/h)	Range: 21–85 yrs Mean 59 yrs	164/310 (53)	NR	NR	Surgery 153/310 Radiotherapy 16/310 Chemotherapy 52/310 SSA168/310
Paganelli et al. 2014(9)	Italy	43	43 GI NETS (2 stomach, 1 appendix, 34 small intestine (midgut), 5 colon 1 rectum)	Cumulative 18.5 or 27.8GBq, 3.7 or 5.5 GBq. 25 (58%) treated with a 'standard' Lu-PRRT full dosage of 25.7 (range 22.2-27.8), while 18.4 reduced dosage for patients at	Amino acids (lysine 70 Meq in 500ml of saline:250cc in 30 min immediately before therapy, 250cc during therapy, lysine 70 Meq in 500 ml of saline in the first 3 hours after therapy and lysine 60 Meq in 500 ml of saline	Range: 44-82 yrs Median 65 yrs	28/43 (65)	NR	49/49 (100) Well-differentiated	Surgery 35/43 SSA 34/43 Chemotherapy 4/43 Y-PRRT 4/43 Other treatments 13/43

				risk. Some treated with reduced dosage of 3.7GBq/cycle	over 1 hour twice the following day)					
Sabet et al. 2015(10) linked to Sabet et al. 2013a(11)	Germany	61	Advanced small intestinal NETs	Mean activity per cycle 7.9 GBq (214 mCi) (4 cycles) Mean cumulative activity per patient was 27.2+-5.9 GBq.	Amino acid (2.5% lysine and 2.5% arginine in 110.9% NACI, infusion of 250 ml/h)	Range: 34–83 yrs Mean 62 yrs	34/61 (56)	Non-functioning 17/61 Functioning4 4/61	61/61 (100) Well-differentiated	Biotherapy 53/61 Surgery 41/61 Chemotherapy 9/61 Locoregional treatment 10/61
Sansovini et al. 2013(12)	Italy	52	Advanced P-NETs	n=26 received FD of 25.5 GBq (range 20.7-27.8); n= 26 received RD of 17.8 GBq (11.1-19.9).	Amino acids (lysine 70 Meq in saline)	Range: 26–82yrs Mean 61 yrs	30/52 (58)	NR	NR	Surgery 22/52 Chemotherapy 14/52 SSA 34/52 Y-PRRT 14/52 Other treatments 8/52

Notes: Baseline data extracted for all patients; a, likely study location based on author institute locations

Key: CI, confidence interval; FD, full dose; RD, reduced dose; ECOG-PS, Eastern Cooperative Oncology Group-performance status; P-NETS, pancreatic neuroendocrine tumours; GBq, gigabecquerel; Gy, gray unit of radiation; GEP/NEN gastroenteropancreatic neuroendocrine neoplasms; WHO PS, WHO Performance status; Meq milliequivalents; SSA, somatostatin analogues; CUP, cancer of unknown primary ; GEP-NETS, gastroenteropancreatic neuroendocrine tumours

Table 2 Outcomes from non-randomised studies for 177Lu-DOTATATE

Author and Year	Follow-up	Progression Free Survival (PFS) n/N (%)	Overall Survival (OS) n/N (%)	Response Rate (RR) n/N (%)	Adverse Events n/N (%)	Health Related Quality of Life
Claringbold & Turner 2015a(1)	Median 33 months Range 13-58 months	Median PFS 48 months	Not reached after 33 months follow-up	ORR 80% (95%CI 66, 93) CR: 4/30; PR 20/30; SD 6/30	Adverse events Thrombocytopenia (grade 3 severity) 3/30 Myelodysplastic syndrome 1/30	NR
Ezziddin et al. 2011a(4) linked to Ezziddin et al. 2011b(5)and 2014a(2)	Median 47 months (95% CI 44.5, 49.5)	Outcome not reported by tumour location	P-NETs: median 57 months (95% CI 48, 66) Other GEP NETs: median 43 months (31, 55)	P-NETs: PR 54.5%; MR 18.2%; SD 18.2; PD 9.1% Other GEP NET: PR 22%; MR 17.1%; SD 48.8%; PD 12.2%	Outcome not reported by tumour location	NR
Ezziddin et al. 2014b(3)	Median 58 months Range 4–112 months	Median PFS: 34 months (95% CI 26, 42)	Median 53 months (95%CI 46, 60)	PR 41/68; MR 8/68, SD 9/68 and PD 10/68	Reversible haematotoxicity (grade 3 or more) 4/68. No significant nephrotoxicity (grade 3 or more).	NR
Kong et al. 2014(6)	Median 60 months Range 5-86 months	NR	Outcomes not reported by tumour location	Partial and minor responses: P-NETs: 55% Non-pancreatic NETs: 81% (OR 0.28, [95% CI 008, 0.94])	NR	NR
Kwekkeboom et al. 2008(7) linked to Kwekkeboom et al. 2005(8), van Vliet et al. 2013(13)and 2015(14)	NR	Outcome not given by tumour location	Outcome not given by tumour location	Carcinoid: CR 1/188; PR 41/188; MR 31/188; SD 78/188; PD 37/188 P-NETs: CR 4/72; PR 26/72; MR 13/72; SD 19/72; PD 10/72 Unknown: PR 10/31; MR 3/31; SD 7/31; PD 11/31 Gastrinoma: PR 5/12; MR 4/12; SD 2/12; PD 1/12 Insulinoma: PR 3/5; SD 1/5; PD 1/5 VIPoma: PR 1/2; PD 1/2	Outcome not given by tumour location	Outcome not given by tumour location
Paganelli et al. 2014(9)	Median 38 months Range 11-59 months	Median PFS was 36 months (95% CI 24, NR)	Mean overall survival not yet reached	Median duration objective response 25 months (95% CI 7, 50) CR: 3/43; SD 33/43; PD 7/43 Disease control rate: 84% (95% CI 73, 95)	No cases of major toxicity; most common side-effects were nausea (max grade 2), asthenia and mild alopecia	NR
Sabet et al. 2015(10) linked to Sabet et al. 2013a(11)	Median 62 months (95% CI 57-67)	Median PFS 33 months (95% CI 25-41)	Median OS 61 months (95% CI NA)	PR 8/61; MR 19/61; SD 29/61; PD 5/61 OR was associated with longer survival (median OS not reached vs 49 months)	Reversible haematotoxicity (>= grade 3) 5/61.	NR

	Range 4-102 months				Relevant haematotoxicity (grade 3/4) 5/61 No other relevant toxicities (including nephrotoxicity) or treatment-related deaths were observed.	
Sansovini et al. 2013(12)	Median 25 months Range 9 -39 months	Median PFS whole group 29 months (95% CI 19-39) Median PFS not reached in FD group and was 20 months in the RD group.	Median OS not reached	Whole group: CR: 4/52; PR 11/52; SD 27/52; PD 10/52 Disease control rate 81% (95%CI 68-89)	No major acute or delayed haematological toxicity. The most common minor side effects were nausea (max grade 2), asthenia and mild alopecia. 1 patient developed grade 3 renal toxicity.	NR

Notes: Outcome data extracted for pancreatic and gastroenteropancreatic neuroendocrine tumours where possible. If unavailable, data was extracted for all study patients and recorded in notes section. a, Paper focuses on dose response: i.e. dose absorption and tumour size; b Non-randomised comparative study to 90Y-DOTATATE

Key: PFS, progression-free survival; CI, confidence interval; CR, complete response; PD, progressive disease ; PR, partial response; RR, remission response; SD, stable disease; FD, full dose; RD, reduced dose; OR, objective response; ORR, overall response rate; OS, overall survival; TTP, time-to-progression; ECOG-PS, Eastern Cooperative Oncology Group-performance status; P-NETs, pancreatic neuroendocrine tumours; GBq, gigabecquerel; GEP/NEN gastroenteropancreatic neuroendocrine neoplasms; WHO PS WHO Performance status; Meq milliequivalents; SSA somatostatin analogues; CUP, cancer of unknown primary ; GEP-NETS, gastroenteropancreatic neuroendocrine tumours; RE-HEDP, Rhenium-186-1-hydroxyethylidene-1,1-diphosphonate

3.2 New from the Company

3.2.1 New evidence P-NETs: 177Lu-DOTATATE (ERASMUS)

AAA Ltd. in section 2 of their updated submission present outcome data from ERASMUS for P-NETs.(15) The ERASMUS trial is a single arm, non-RCT trial. The company do not report how they identified this study and why this study has been used, and none of the other seven studies (1-6, 9-12) identified by the AG in section **Error! Reference source not ound.**3.1 have been considered. It has therefore been assumed that ERASMUS has been used as it is the largest of all the non-RCT trials using 177Lu-DOTATATE. AAA Ltd. updated submission does not provide a published reference for the ERASMUS trial. From our searches we know ERASMUS has four articles published, each subsequent publication presenting data following a longer period of data collection. Since the sample size of the data reported in the updated submission does not match any of the published articles, the data presented by AAA Ltd. for ERASUMS is unpublished.

We would also like to highlight the bias of this evidence, given that none of the other companies have had any of their non-RCT evidence (published or unpublished) considered.

3.2.1.1 ERASMUS

Since the data presented by AAA Ltd. from ERASMUS is unpublished, the following information has been taken from AAA's original submission in 2016 and their more recent one from 2017.(15, 16)

ERASMUS was a phase I-II, single arm, prospective trial retrospectively analysed that evaluated the efficacy of 177Lu-DOTATATE in patients with SSTR-positive tumours. A total of 1,214 patients received treatment with of 177Lu-DOTATATE between January 2000 and December 2012. Overall, about 67% of the enrolled patients were from The Netherlands (Dutch patients), and the other 33% from abroad. There was a high percentage of the abroad patients lost to follow up which resulted in a substantial amount of missing data. As a result, the Dutch population (n=810) has been considered the main population of relevance supporting the license application to European Medicines Agency for the indication of 177Lu-DOTATATE in unresectable or metastatic, somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) including foregut, midgut and hindgut in adults.

Treatment

Treatment was four intravenous (i.v.) administrations of 200 mCi (7.4 GBq) at 6 – 13 week intervals, aiming for a cumulative amount of up to 800 mCi (29.6 GBq) 177Lu-DOTATATE.

Concomitant amino acids were given with each administration for kidney protection. Safety monitoring was performed at baseline, 4 weeks after the first treatment, and 2 weeks before and 4 weeks after each subsequent treatment.

Follow-up occurred at 6 weeks, 3 to 4, 6 to 8, 9 to 12 and 12 to 16 months after the last treatment and thereafter every 6 months, up to the moment of disease progression or death or lost to follow-up.

Inclusion / Exclusion Criteria

The inclusion and exclusion criteria for the ERASMUS trial are taken from Table 28 and 29 of the original AAA Ltd submission and are presented below in Table 3.(16)

Table 3 Inclusion and Exclusion criteria for the ERASMUS study

Inclusion	Exclusion
For patients with GEP-NET: Presence of histology proven GEP-NET, including bronchial carcinoids. Presence of somatostatin receptors on the known lesions demonstrated by somatostatin receptor imaging within 6 months of the first dose of radiolabelled 177Lu-DOTA0-Tyr3-Octreotate. The uptake on the somatostain receptor imaging should be at least as high as normal liver uptake on planar imaging Life expectancy >12 weeks.	Subjects with another significant medical, psychiatric, or surgical condition, currently uncontrolled by treatment, which may interfere with completion of the study Any patient receiving therapy with short-acting somatostatin analogues in whom these analogues cannot be interrupted for 12h before and 12h after the administration of the radiolabelled somatostatin analogues, or any subject receiving therapy with long-acting somatostatin analogues in whom these analogues cannot be interrupted for at least 6 weeks before the administration of the radiolabelled somatostatin analogues, unless the uptake on the OctreoScan® during continued somatostatin analogue medication is at least as high as normal liver uptake on planar imaging Uncontrolled congestive heart failure
Serum creatinine <150 µmol/L and a calculated (Cockroft's formula), or preferably a measured creatinine clearance, based on two 24-hour urine collections, of >40 ml/min	Patients with known brain metastases, unless these metastases have been treated and stabilized for at least six months prior to study start. Patients with a history of brain metastases must have a head CT scan with contrast to document stable disease prior to study start
Hb concentration ≥5.5 mmol/L; WBC ≥2×109/L; platelets ≥75×109/L. Total bilirubin ≤3 × ULN	Surgery, radiotherapy, chemotherapy, or other investigational therapy, within 3 months prior to the start of therapy Pregnancy
Serum albumin >30 g/L. PS ≥50	Possible surgery with curative intent

Population characteristics

A summary of the population characteristics for the Dutch population (n=810), taken from the AAA Ltd's original submission in 2016 is presented in
Table 4.(16) AAA Ltd. do not report any baseline characteristics for the data they present in the updated submission of 2017 for ERASMUS.(15)

Table 4 ERASMUS population characteristics

Characteristic	Mean ± SD (Median, Range)
Age (years) n=810	59.7 ± 11.7 (60.0, 18 to 90)
Height (cm) n=715	173 ± 10 (172, 103 to 203)
Weight (kg) n=745	74.3 ± 15.2 (73.0, 41.0 to 150)
BMI (kg.m2) n=690	24.8 ± 5.1 (24.2, 15 to 97)

Outcome results

Outcome results for the Dutch population (n=810), taken from the AAA Ltd's original submission in 2016 are presented in Table 5 and Table 6.(16)

Table 5 PFS and OS observed in the Phase I/II study in Dutch patients with GEP and bronchial NET – (FAS, N=360)

	N	PFS (months)			OS (months)		
		Median	95% CI		Median	95% CI	
*GEP-NET**	360	29.8	25.4	33.0	64.4	57.0	75.3
Bronchial	19	18.3	10.3	25.4	50.5	31.2	ND
Pancreatic	133	30.5	24.9	36.2	70.8	63.2	ND
Foregut	12	NR			NR		
Midgut	183	29.6	24.8	34.4	55.4	49.8	70.1
Hindgut	13	29.3	22.3	39.0	NR		
Progressive Midgut	98	28.4	22.8	33.9	49.0	36.4	60.2
Progressive GEP-NET	184	29.8	25.3	33.4	60.2	53.5	73.6
Progressive P-NET	62	35.6	25.0	43.8	80.7	57.0	

Key: PFS = Progression free survival; OS = Overall survival; NR = Not reached; ND = Not determined.
Notes: * Includes Foregut, Midgut and Hindgut; **Foregut NETs other than bronchial and pancreatic.

Table 6 ERASMUS outcome results

	N	**CR**		**PR**		**SD**		**ORR**			**DoR (months)**	
Tumour type		n	%	n	%	n	%	n	%	95% CI	Median	95% CI
*GEP-NET**	360	11	3%	146	41%	178	49%	157	44%	38, 49%	15.9	12.1, 17.7
Bronchial	19	0	0%	7	37%	10	53%	7	37%	15, 59%	23.8	1.7, 29.9
Pancreatic	133	7	5%	68	51%	49	37%	75	56%	48, 65%	16.2	11.8, 22.9
*Foregut***	12	1	8%	5	42%	5	42%	6	50%	22, 78%	18.8	0.0, 37.9
Midgut	183	3	2%	60	33%	108	59%	63	34%	28, 41%	13.1	10.1, 17.1
Hindgut	13	0	0%	6	46%	6	46%	6	46%	19, 73%	17.8	1.5, 29.8

Key: CR = Complete response; PR = Partial response; SD = Stable disease; ORR = Objective response (CR+PR); DoR = Duration of response.
Notes: * Includes Foregut, Midgut and Hindgut; **Foregut NETs other than bronchial and pancreatic.

Outcome data presented in the updated submission is presented in Figure 1 and Figure 2 and Table 7.(15). (On February 27 2018 the company provided an update including additional outcome data in the form of Kaplan-Meier progression free survival and overall survival curves for the ERASMUS GI NET location; although this evidence is not described here due to limited time to process the evidence before the March 22 deadline for submitting this report, it has informed the analyses that follow and is discussed below).

Figure 1. PFS curves for progressive P-NET patients

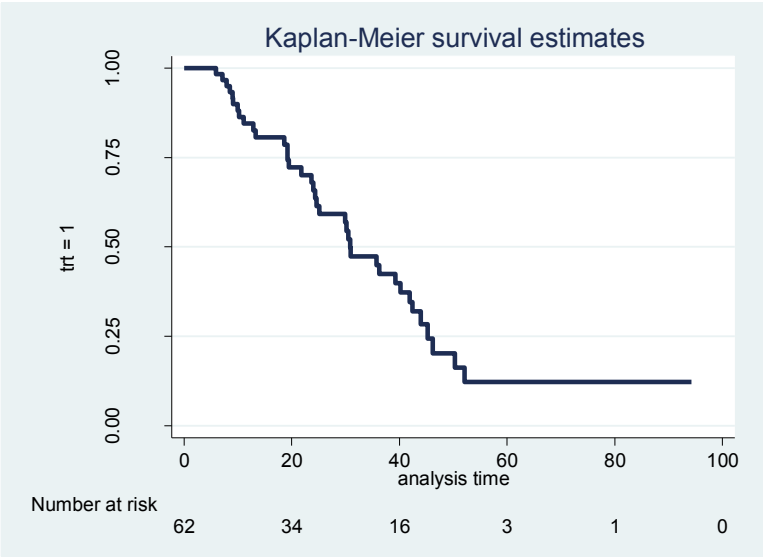


Figure 2. OS KM curves for progressive P-NET patients

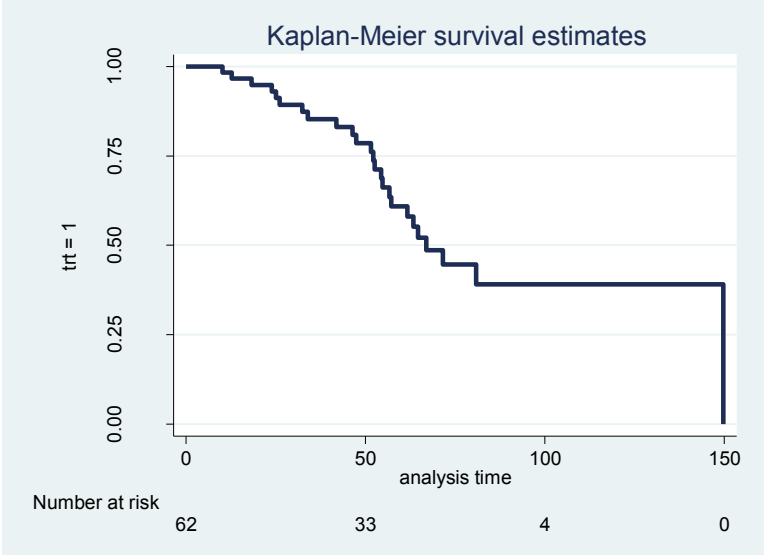


Table 7 Progression-free survival (PFS), time-to-progression (TTP) and overall survival (OS) for Dutch population according to functional status of P-NET (n=113) in ERASMUS FAS

Tumour type	PFS			TTP			OS		
	% events	Median (months)	95% CI	% events	Median (months)	95% CI	% events	Median (months)	95% CI
Functioning P-NET (n=20)	55.00	32.7	23.7 – NA	45	32.7	23.7	35.0	57.2	41.9-NA
Non-functioning P-NET (n=113)	63.72	30.3	24.3-36.3	59.29	31.0	25.1-37.2	44.25	66.4	57.9-80.9
*Combined P-NETS (?)**		30.88	24.31-41.89					66.92	56.74-NR

Notes: *additional data was presented in the updated report, however it is unclear which sample this data relates to, it is assumed to be the combined P-NETs.

3.2.2 New evidence GI-NETs: 177Lu-DOTATATE (NETTER-1)

The company in section 2 of their updated submission present outcome data from NETTER-1 for GI NETs.

There are the following issues with the NETTER-1 data:

1. The allocation of treatments to each arm. 177Lu-DOTATATE was given in combination with best supportive care (30 mg octreotide LAR). This was compared to octreotide LAR (60 mg). In our previous report, the AG searched for RCT evidence comparing different dosing strategies of Octreotide LAR, but were unable to find any evidence as to whether the effectiveness changes given the different doses. Since the dose of octreotide LAR is different in both arms, the outcome results will be confounded by this uncertainty.
2. NETTER-1 only reports data for mid-gut NETs and does not provide evidence for the whole GI.
3. The data reported is an update of the data that was published in 2017. Therefore, for the most part this is unpublished data supplied by the company.

3.2.2.1 NETTER-1

Taken directly from our previous report:

Study Design

NETTER-1 compares treatment with 177Lu-DOTATATE plus best supportive care (30 mg octreotide LAR) to treatment with high dose octreotide LAR (60mg). All participants had metastatic midgut NETs and were previously receiving octreotide LAR (20 or 30mg) prior to randomisation to NETTER-1.

Participants were recruited from 41 centres and were stratified by highest radiotracer uptake observed on planar somatostatin receptor scintigraphy and by the length of time on constant dose of octreotide (≤6 and >6 months).

177Lu-DOTATATE was administered with a dose of 7.4 GBq (200 mCi), over 8 ±1 week intervals. For kidney protection, amino acid infusions (Vamin 18 in Europe centres and Aminosyn II 10% in the USA centres) and for symptom control, 30mg of octreotide LAR were given concomitantly with 177Lu-DOTATATE. For the comparator arm, 60mg of octreotide LAR was given every 4 weeks. Additional octreotide subcutaneous rescue injections were allowed in either arm if clinical symptoms associated with the carcinoid tumour were experienced. Average dose intensity overall was 25.6 GBq and per cycle 7.2 GBq.

A sample size of 230 was calculated as being required for statistical significance for PFS and OS. A total of 229 patients were recruited to the NETTER-1 trial.

Participant Characteristics

Baseline characteristics of participants recruited to NETTER-1 are presented in Table 8. This data were taken from the AGs previous report.

Table 8 Baseline characteristics from NETTER-1

		177Lu-DOTATATE + octreotide LAR 30mg (n=116)	Octreotide LAR (n=113)
Male n/N (%)		63/116 (54.3)	53/113 (46.9)
Age, yrs (median)		63.5	65
Age, yrs, (mean ± SD)		63.3 ±9.4	64.1 ±9.7
ENETS grade 1 (≤2% +ve tumour cells)		76/166 (65.5)	81/113 (71.7)
ENETS grade 2 (3-20% +ve tumour cells)		40/166 (34.5)	32/113 (28.3)
Tumour functioning		Not available	Not available
Tumour Differentiation	*Well differentiated, n/N (%)*	76/116 (65.5)	81/113 (71.7)
	Moderately differentiated, n/N (%)	40/116(35.5)	32/113 (28.3)
WHO PS		Not available	Not available
Previous treatments, n/N (%)			
Resection		90/116 (77.6)	93/113 (82.3)
Ablation		6/116 (5.2)	11/113 (9.7)
Chemo-embolisation		14/116 (12.1)	11/113 (9.7)
Chemotherapy		47/116 (27.2)	51/113 (30.0)
Radiotherapy		7/116 (4.0)	8/113 (4.7)
Somatostatin Analogues		116/116 (100)	113/113 (100)
Other		48/116 (27.7)	40/113 (23.5)

Note: Tumour differentiation completed by company following data request from AG, ENETs grade provided in company submission, numbers are the same.
Source: AAA company submission and data on file from AAA

Outcome results

The following results are unpublished and are taken from the updated submission by AAA Ltd.(15)

Figure 3. PFS KM curves for octreotide LAR versus 177Lu-DOTATATE

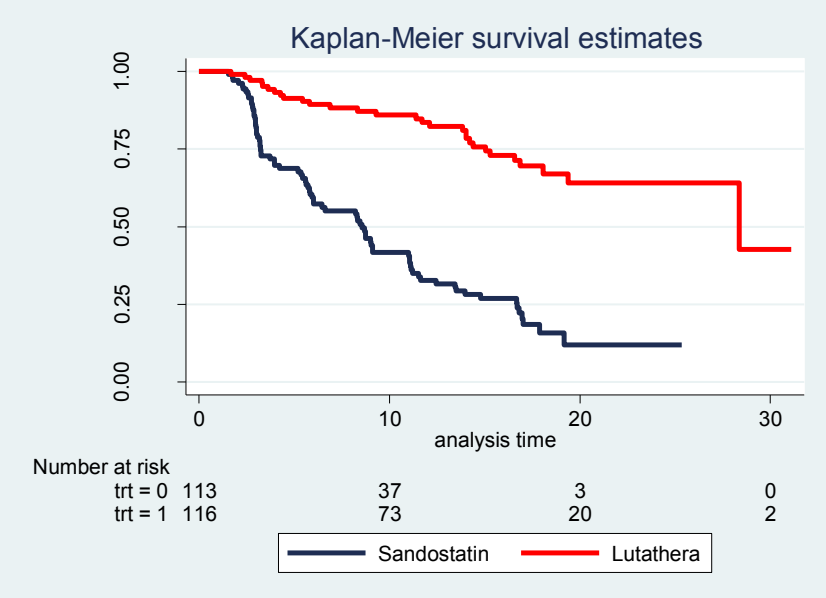
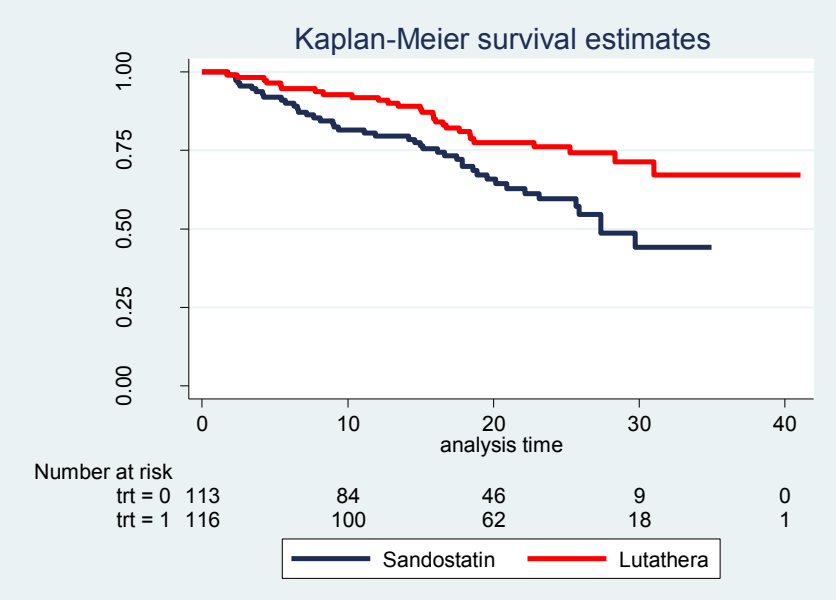


Figure 4. OS KM curves for octreotide LAR versus 177Lu-DOTATATE



Summary survival results are taken from the updated submission from AAA Ltd. and are presented in Table 9.(15)

Table 9 PFS and OS median survival estimates (GI-NET)

Comparator		Median PFS (weeks)	95% Confidence interval	Hazard ratio (95% CI)
Octreotide	PFS	8.54	5.81 – 11.0	0.21 (0.14 - 0.33)
177Lu-DOTATATE		28.35	28.35 – N/R	
Octreotide	OS	27.37	23.13 – N/R	0.54 (0.33 – 0.86)
177Lu-DOTATATE		N/R	N/R	

Key: PFS, progression free survival; OS, overall survival; N/R, not reached

3.2.2.1.1 Scenario Analysis

Taken from the updated submission from AAA Ltd. a scenario analysis was run using NETTER-1 where they adjusted for cross-over from the control arm of the trial to 177Lu-DOTATATE. In total, 22.8% of the patients receiving Octreotide LAR (control arm) crossed over to the treatment arm of 177Lu-DOTATATE. A rank preserving structural failure time (RPSFT) analyses was conducted to account for the cross-over using OS from the cut-off date 30 June 2016 (Table 10).

Table 10 Summary of RPSFT analyses accounting for cross-over from the control arm to 177Lu-DOTATATE (FAS, 30 June 2016)

Statistic	177Lu-DOTATATE (N = 116) n (%)	Octreotide LAR (N = 113) n (%)
Number of deaths, n (%)	28 (23.9%)	43 (37.7%)
Number switched to 177Lu-DOTATATE, n (%)	NA	26 (22.8%)
Analysis method: Kaplan Meier method		
Median* (months) (95% CI)	NR (NE, NE)	27.4 (23.1, NE)
Unstratified Hazard Ratio (95% CI)	0.536 (0.333, 0.864)	
P-value**	0.0094	
Stratified Hazard Ratio (95% CI)	0.537 (0.332, 0.868)	
P-value**	0.0102	
Analysis method: Rank preserving structural failure time (RPSFT)		
Median* (months) (95% CI)	NR (NE, NE)	27.4 (20.9, NE)
Unstratified Hazard Ratio (95% CI)	0.497 (0.308, 0.804)	
P-value**	0.0036	
Stratified Hazard Ratio (95% CI)	0.488 (0.300, 0.795)	
P-value**	0.0033	

Notes: * Estimated by Kaplan-Meier method, ** P value is from Log-rank test
Key: NA, not applicable; NE, not evaluable; NR, not reached

3.2.3 New evidence: Sunitinib (A6181111)

AAA Ltd in their MAIC of P-NETS, use updated data for sunitinib (A6181111) from the paper Faivre et al. 2017.(17) This paper was published between the date of the searches run for the previous AG report and the updated submission from AAA Ltd. The identification of this paper has not been provided to us by the company. We, the AG have not updated our systematic review. Therefore the results presented by AAA Ltd. do not constitute results from a systematic review. There may be additional relevant studies or updates to previously

identified studies that have since been published that have not been highlighted to us. This incorporates signification study identification bias to all these new results.

However, the data presented in the Faivre paper(17) were reported in the previous report by the AG. This is because the updated data was provided by Pfizer in their submission to NICE. Therefore, there is no new data to report for the evidence relating to Sunitinib.

3.3 Critique of the Company's New Effectiveness Evidence

3.3.1 New indirect comparison on P-NETs (New MAIC using ERASMUS)

AAA Ltd have updated their P-NETs indirect comparison by performing a matched adjusted indirect treatment comparison (MAIC). The MAIC was performed using data from ERASMUS (for 177Lu-DOTATATE), RADIANT-3 (Everolimus) and A6181111 (Sunitinib). The outcomes assessed were PFS and OS. As mentioned previously ERASMUS is a non-RCT whilst RADIANT-3 and A6181111 are both RCTs.

AAA Ltd. note the following limitations to their MAIC:

- The inclusion criteria between the three trials differed. Most particularly, participants from ERASMUS needed to have had the presence of somatostatin receptors within the last 6 months.
- All patients recruited to RADIANT-3 and A6181111 have advanced, unresectable or metastatic P-NETs with disease progression within the last 12 months. These criteria are not mentioned for ERASMUS.

The company matched their Erasmus P-NETs population to each of Sunitinib arm of A6181111, Everolimus arm of RADIANT-3 and BSC arm of RADIANT-3 separately. The problem with this approach is that these pairwise analyses of 177Lu-DOTATATE against the three other treatments are not strictly comparable, because the matching is to two different populations A6181111 for sunitinib, and RADIANT-3 for everolimus and BSC.

There are also problems in the way the company implemented their MAIC analysis. The company matched the ERASMUS P-NETs sub-population to the P-NETs RADIANT-3 population on the basis of four out of the 10 covariate measures of baseline characteristics: Age, ECOG performance status, proportion previously treated with chemotherapy, proportion previously treated with radiotherapy were selected from the list of variables presented in (Table 11), reproduced from AAA's new submission.

To select covariates for its MAIC analysis, AAA ran univariate regression analyses of each candidate baseline covariate and PFS and OS outcomes in the ERASMUS P-NETs cohort. Those variables with statistically significant effects (the critical p value was not stated) on

any of these two survival outcomes were used for matching to the mean values of the corresponding baseline variables of individual treatment arms in RADIANT-3 and A6181111 trial.

This approach to the choice of matching variables has the following limitation. These variables appear to have been chosen on the basis of whether their individual association with outcomes had a p<0.20. The problem is that the sample size (n=62) may have been too low to detect key treatment effect modifiers. It would have been more appropriate to base the inclusion of baseline variables for matching on the estimated magnitude of effect, regardless of conventional critical (p) values for statistical significance. In consultation with our clinical expert, the chosen set of four matching variables do not include appropriate measures for grade and stage of disease. In the expert's opinion tumour functionality is a more important prognostic factor, a priori, than previous chemotherapy and radiotherapy.

Table 11 MAIC covariate p-values

Covariate	ERASMUS (PFS)	ERASMUS (OS)	Included in PFS	Included in OS
	P-value	P-value		
Age mean, median (range) years	<0.001	<0.01	X	X
Sex	0.83	0.54		
ECOG performance status	<0.05	<0.01	X	X
Organ involved	0.53	0.27		
Time from initial diagnosis	0.30	0.33		
Time from disease progression to randomisation	0.73	0.76		
Tumour functionality	0.99	0.57		
Previous chemotherapy	0.19	<0.001	X	X
Previous radiotherapy	0.25	<0.001	X	X
Previous surgery	0.54	0.70		

Although the company achieved covariate balance after matching on the four selected variables, it did not report the extent to which other candidate baseline covariates excluded from matching compared between ERASMUS and the arms of A6181111 and RADIANT-3. Furthermore, the small sample size available for analysis was reflected by the fact that after matching the cohort of ERASMUS P-NETs to the respective baseline covariate values for each alternative treatment arm (sunitinib and BSC in A6181111 and everolimus and BSC in RADIANT-3) the resulting effective sample sizes were very small (i.e. n= 31, 36, 17, 18, respectively). This is very limited available information on which to base comparative effectiveness estimates, especially for the case of the MAIC of 177Lu-DOTATATE with everolimus and BSC in the RADIANT-3 population.

In justifying their method, the company state that “The aim was to limit the number of covariates to avoid extreme weighting values.”. Extreme values raise the issue of validity in MAIC since they suggest limited overlap in patient’s characteristics across the weighted (ERASMUS) and reference (RADIANT-3 and A6181111) populations to which the former is matched, making the balancing of baseline characteristics reliant on heavy weighting of data from a few ERASMUS individuals. In this regard, the quality of matching to the RADIANT-3 population was of much lower quality, as the weight ranges were 0.3-11.2 (BSC) and 0.4-12.2 (everolimus), than that of matching to the A6181111 population, with ranges of 0.1-6.9 (BSC) and 0.0-5.3 (sunitinib).

Overall, the whole approach of conducting pairwise comparisons against individual treatment arms across two trial populations means that AAA does not analyse a closed network. That is, the results submitted by AAA are difficult to interpret since the reference population varies across the comparative analyses of 177Lu-DOTATATE with sunitinib and everolimus. The company could not perform a closed network using MAIC analysis since they lacked the individual patient data from RADIANT-3 and/or A6181111 to obtain effectiveness estimates for the same reference population. However, they could have built a network using Bucher type indirect comparison analysis, in the same way the AG did in its Assessment Report. The AG did have access to IPD from A6181111 study and could perform MAIC of PFS (but lacked the data to do cross-over adjusted OS) for one and the same population across studies (due to time limitations AG has not done this MAIC of PFS outcomes with sunitinib matched to RADIANT-3; AG’s economic evaluation below is based instead on the Bucher comparison in the Assessment Report for ID858). Furthermore, given the problems of low effective sample sizes discussed below, the AG extended the analysis to cover all available P-NETs patients as opposed to restrict it to Dutch only patient population as AAA did.

3.3.2 Indirect comparison on P-NETS

3.3.2.1 By AG

3.3.2.1.1 P-NETs

Previously, in the AG report (section 4.2.5.2), we used the Bucher method to indirectly compare Everolimus to Sunitinib. Since no RCT evidence for 177Lu-DOTATATE was available for the population of P-NETs, 177Lu-DOTATATE was not included in this analysis.

Table 12 reports the results original presented in the AG report.

Table 12 Indirect Treatment Comparison using Bucher for Sunitinib vs Everolimus for PFS and OS for individuals with P-NETs

Intervention	Comparator	Data source	HR (95%CI)
HRs (95%CI) for disease progression or death in pancreatic NETs based on local radiology review			
Everolimus	Placebo	RADIANT-3(18)	0.35 (0.27, 0.45)
Sunitinib	Placebo	A6181111(19)	0.42 (0.26, 0.66)
Everolimus	Sunitinib	Calculated by AG	0.83 (0.49, 1.42)
HRs (95%CI) for disease progression or death in pancreatic NETs based on central radiology review			
Everolimus	Placebo	RADIANT-3(18)	0.34 (0.26, 0.44)
Sunitinib	Placebo	From Pfizer submission (A6181111)	0.32 (0.18, 0.55)
Everolimus	Sunitinib	Calculated by AG	1.06 (0.57, 1.97)
HRs (95%CI) for overall survival in pancreatic NETs			
Everolimus	Placebo	RADIANT-3(18)	1.05 (0.71, 1.55)
Sunitinib	Placebo	A6181111(19)	0.41 (0.19, 0.89)
Everolimus	Sunitinib	Calculated by AG	2.56 (1.08, 6.08)
HRs (95%CI) for death in pancreatic NETs based on final follow-up data			
Everolimus	Placebo	RADIANT-3(20)	0.94 (0.73, 1.20)
Sunitinib	Placebo	From Pfizer submission (A6181111)	0.73 (0.50, 1.06)
Everolimus	Sunitinib	Calculated by AG	1.26 (0.82, 2.02)

The AG have updated their analysis by conducted their own MAIC analysis of 177Lu-DOTATATE. Contrary to what AAA has done, the AG has used all the available data on P-NETs patients n=169. We considered the following baseline covariates for matching: age, gender, ECOG performance status, time from initial diagnosis, prior SSA treatment, and prior radiotherapy treatment. After excluding cases that had baseline ECOG class>2 (n=1), and those with missing data on any of this matching baseline variables (time from initial diagnosis, n=12), N=156 remained for analysis, as opposed to the 62 observations used by AAA's MAIC P-NETs analysis described above.

We matched ERASMUS 177Lu-DOTATATE to the mean baseline values for the whole sample of RADIANT-3 (21), as opposed to AAA Ltd's approach of matching to each individual arm of the latter trial. This avoids two problems of AAA Ltd's method; first we produce only one set of MAIC results for 177Lu-DOTATATE, as opposed to AAA's four different MAIC results, as many as alternative treatment-by-trial combinations (i.e. everolimus, BSC in RADIANT-3, and sunitinib and BSC in A6181111). Second, we match to a single reference population, that of RADIANT-3 so that we may produce results for the complete network in that population, as opposed to the collection of incomplete pairwise economic analyses by AAA in different reference populations (i.e. the population of RADIANT-3 and A6181111). In the Assessment Report we have already produced results for a network for the P-NETs population of RADIANT-3 using Bucher type indirect comparisons with A6181111. Therefore we complete this network by unanchored MAIC of 177Lu-DOTATATE in ERASMUS to the population of RADIANT-3.

The summary values of baseline characteristics that are comparable across ERASMUS and RADIANT-3 are presented below, including effective sample sizes and range of values of resulting matching weights.

Table 13 Baseline characteristics pre and pots-matching ERASMUS P-NETs cohort to RADIANT-3 population

Baseline variable	ERASMUS (before matching)	ERASMUS (after matching)	RADIANT-3 (reference population)	A6181111 (without matching)
N	156	156	210	171
ESS	N/A	45.0	N/A	N/A
Age (median)	55	58	58	56
Female	52.6	44.6	44.6	52.0
ECOG ≥1	62.2	33.7	33.7	44.4
Time since initial diagnosis>24 months	33.3	31.2	59.8	[3]
Previous SSA	36.5	49.5	49.5	36.3
Previous radiotherapy	1.9	21.5	21.5	12.3
Previous chemotherapy	12.8	19.6	50.0	69.0%
Functioning tumours	17.9	24.0	24.0[1]	26.9[2]
MAIC weights range	N/A	0.11-15.8	N/A	N/A

Note: N sample size; ESS: effective sample size after matching, N/A Not applicable. [1] The proportion with functional tumours was not available; only information was that 24% of patients had Gastrinoma, Glucagonoma, Vipoma, Insulinoma, or Somatostatinoma,(Yao et al. 2011) and that 0.5% (2 cases) were unknown (Source: Novartis CSR RADIANT-3).[2] It was reported that 50.3% (86/171) were non-functioning tumours, 26.9% (46/171) were functioning tumours, and 22.8% (39/171) were 'not specified'. [3] It is reported that 50% of sunitinib arm and BSC only arm patients had more than 2.4 years and 3.2 years since diagnosis, respectively (Raymond et al. 2011).

Figure 5 MAIC-weighted K-M and parametric fits to PFS with 177Lu-DOTATATE: P-NETs

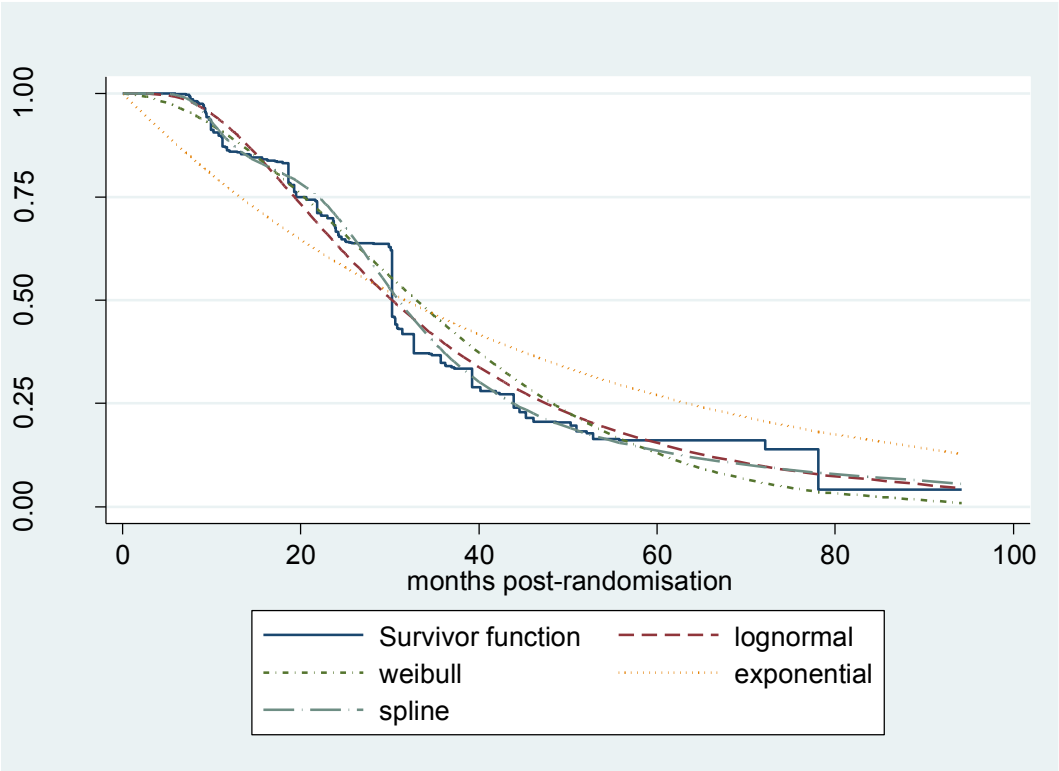
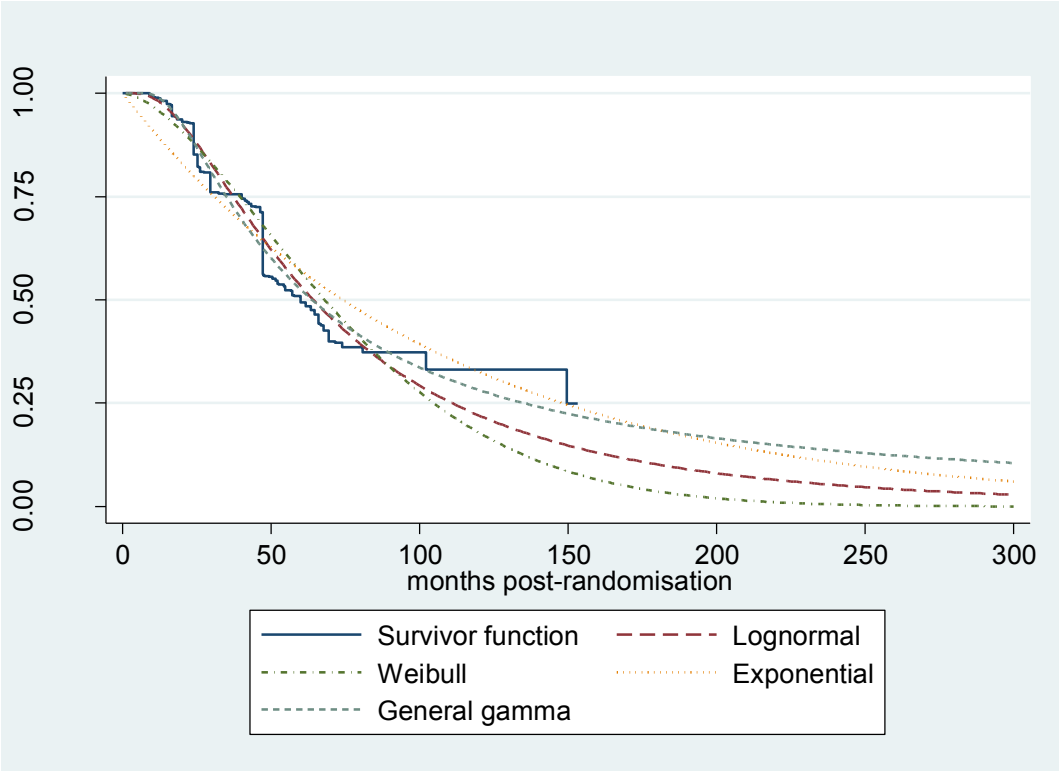


Figure 6 MAIC-weighted K-M and parametric fits to OS with 177Lu-DOTATATE: P-NETs



These outcomes were achieved at a mean cumulative dose intensity of 94.4% after weighting (27.95/29.6 GBq or 755.55/800 mCi) per planned infusions (94.9% before weighting).

3.3.2.1.2 Overall GI

We also conducted MAIC of the whole GI NETs sample in ERASMUS (n=264) to the overall GI subpopulation of RADIANT-4, using individual patient data provided by AAA. We requested data for ERASMUS from AAA on baseline patient characteristics for which we had published data from RADIANT-4. We obtained individual patient information for ERASMUS patients with GI NETs on the baseline variables listed in Table 3. After missing values 245 individual observations from the ERASMUS cohort had complete data and were matched to RADIANT-4 GI subpopulation.

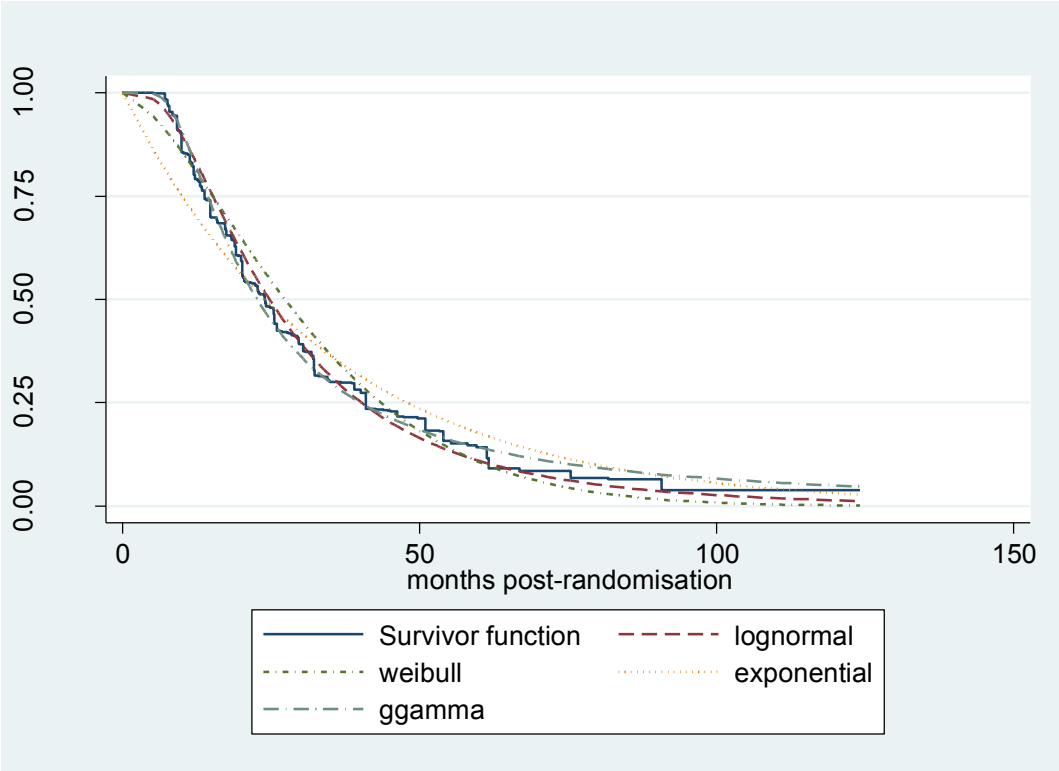
Table 14 Baseline characteristics pre and pots-matching ERASMUS whole GI-NETs cohort to RADIANT-4 GI subpopulation

Baseline variable	ERASMUS (before matching)	ERASMUS (after matching)	RADIANT-4 (reference population)*
N	245	245	175
ESS	N/A	74.7	N/A
Age (median)	61	62	62
Female	52.6	54.8	54.8
ECOG >1	62.2	21.7	21.7
Previous SSA	36.5	60.3	60.3
Previous surgery	1.9	74.3	74.3
Previous chemotherapy	12.8	16.5	16.5
Tumour class:			
Bronchial	7.9	19.5	34.0
Foregut (excl. bronchial)	4.5	3.2	4.2
Midgut	82.6	65.7	65.7
Hindgut	4.9	11.6	18.1
MAIC weights range	N/A	0.05-11.2	N/A

Note: N sample size; ESS: effective sample size after matching, N/A Not applicable. *Baseline characteristics reported in the ASCO poster by Singh et al. (Singh et al. 2016).

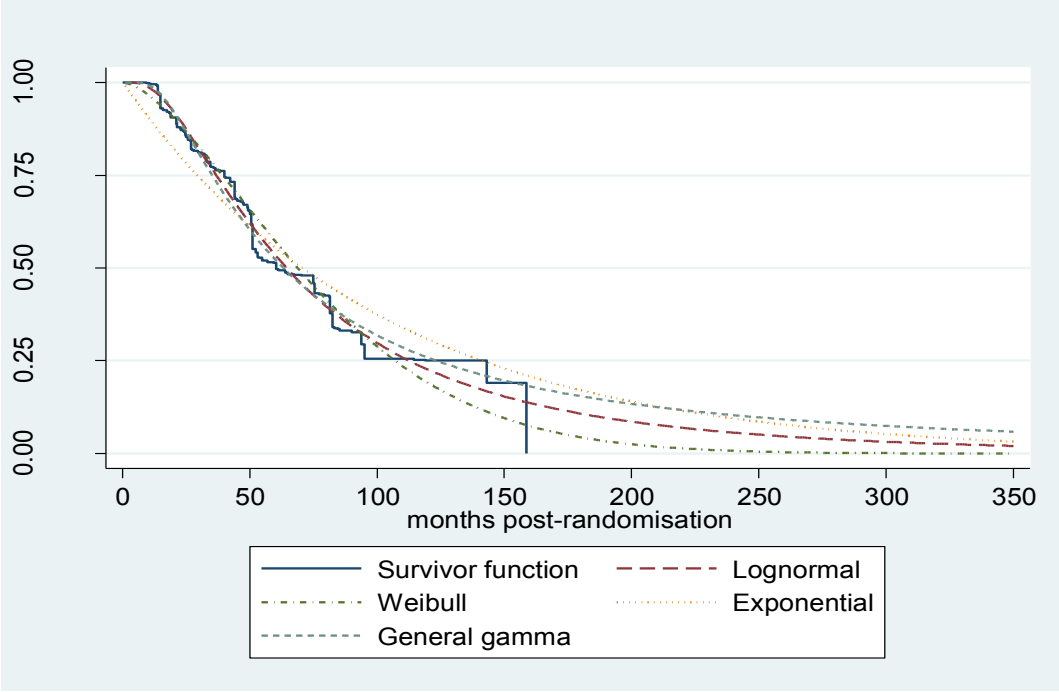
After applying weights to the ERASMUS GI sample, the generalised gamma and the lognormal distribution had the closest fit to the time to disease progression or death data (AIC: 475 and 485, BIC: 482 and 489, respectively). The Weibull form fitted the data better than the exponential and Gompertz functions (AIC: 526, 566, 557; BIC: 530, 568, 561; BIC).

Figure 7 MAIC-weighted K-M and parametric fits to PFS with 177Lu-DOTATATE: GI



Of the best-fitting functions to the data, which became sparse beyond 100 months after randomisation (when one third of the sample was still alive), the generalised gamma function provided the most optimistic extrapolation, the Weibull function provided the most conservative one, with the exponential and lognormal functions providing projections in the middle of the predicted range. It is worth noting that the exponential underestimates survival in the early period up to 50 months, and then overestimate it from 50 to 140 months.

Figure 8 MAIC-weighted K-M and parametric fits to OS with 177Lu-DOTATATE: GI



These outcomes were achieved at a cumulative mean dose intensity of 94.6% after weighting (24.99/29.60 GBq or 756.62/800.0 mCi) of the four planned infusions (95.2% before weighting).

3.3.2.1.3 GI midgut

Since we had no information available on baseline characteristics of GI midgut patients from RADIANT-4 we matched the baseline characteristics of ERASMUS GI Midgut subgroup to those of GI NETs in RADIANT-4. Patients in the Midgut NETs group accounted for 117 (66.8%) out of the 175 GI NETs patients in RADIANT-4 (Singh et al. 2016). The results must therefore be interpreted with this caveat in mind.

Table 15 Baseline characteristics pre and pots-matching ERASMUS GI midgut-NETs cohort to RADIANT-4 GI subpopulation

Baseline variable	ERASMUS (before matching)	ERASMUS (after matching)	RADIANT-4 (reference population) *
N	108	108	175
ESS	N/A	33.1	N/A
Age (median)	61	62	62
Female	47.2	54.8	54.8
ECOG >1	70.4	21.7	21.7
Previous SSA	78.7	60.3	60.3
Previous surgery	57.4	74.3	74.3
Previous chemotherapy	10.2	16.5	16.5
MAIC weights range	N/A	0.03-7.12	N/A

Note: N sample size; ESS: effective sample size after matching, N/A Not applicable. * Since no information on baseline characteristics was available for the GI midgut subgroup of RADIANT-4 matching was performed to the baseline characteristics of whole GI RADIANT-4 patients (Singh et al. 2016).

Figure 9 MAIC-weighted K-M and parametric fits to PFS with 177Lu-DOTATATE: GI midgut

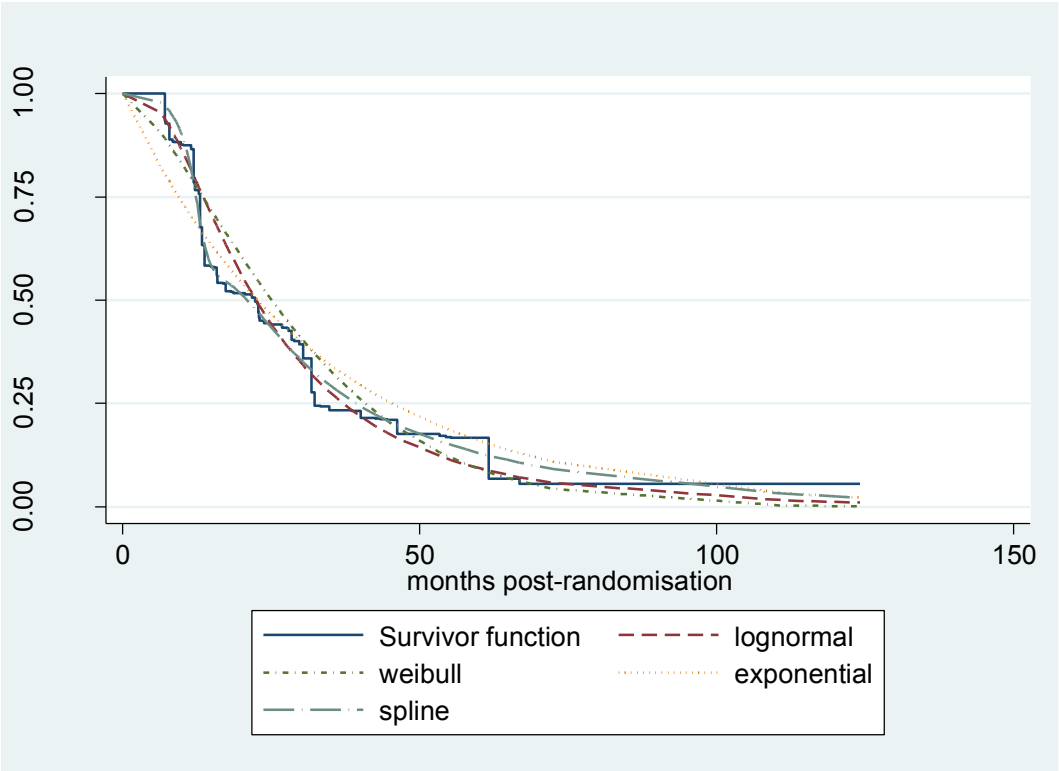
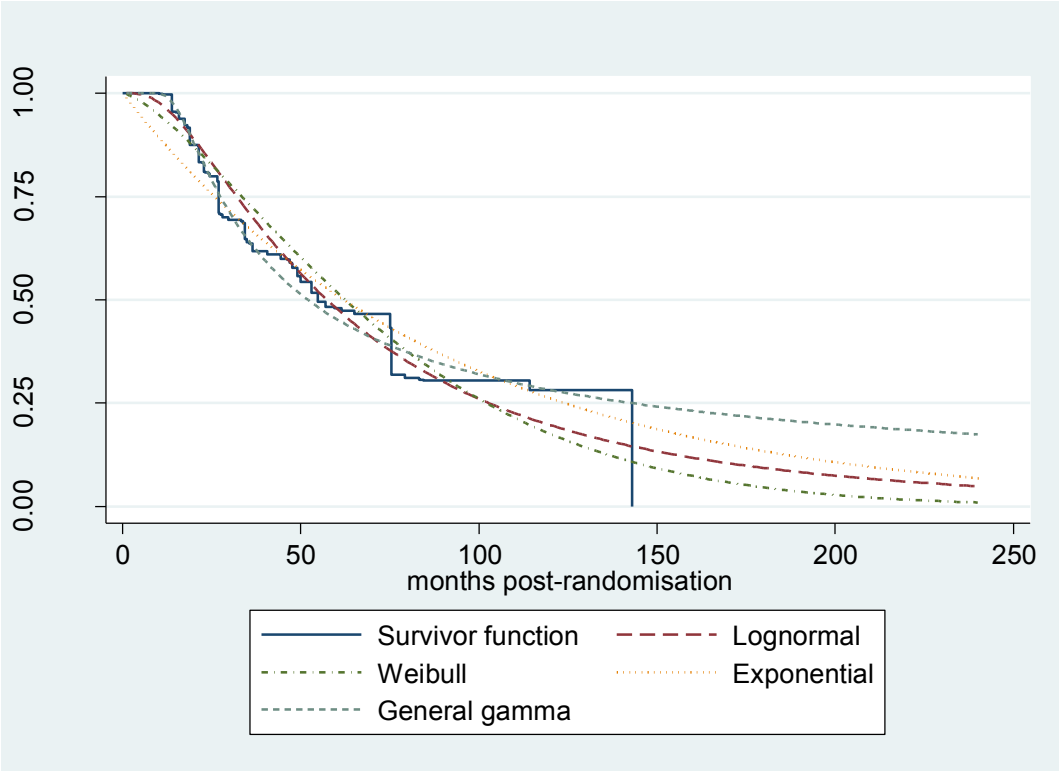


Figure 10 MAIC-weighted K-M and parametric fits to OS with 177Lu-DOTATATE: GI midgut

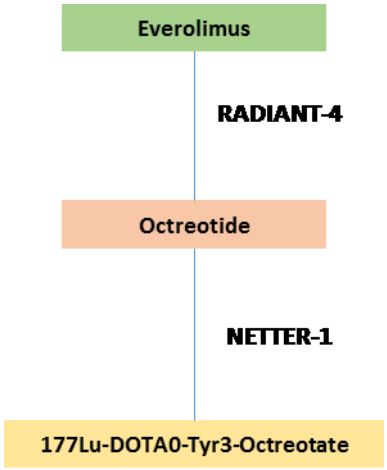


3.3.2.2 By AAA Ltd.

3.3.3 New indirect comparison in GI-NETs (New datasets and approach to MTC, and a new MAIC)

AAA Ltd have updated their GI-NET network meta-analysis (Figure 11). They have used data from an updated analysis of NETTER-1 and removed RADIANT-2 from the analysis. The outcomes assessed were PFS and OS.

Figure 11 Network Meta-Analysis schematic for GI-NETs used by AAA



AAA Ltd. noted the following limitation to their NMA:

- RADIANT-4 only included patients with non-functioning NETs whilst NETTER-1 included patients with both functioning and non-functioning NETs.
- NETTER-1 only include patients that were somatostatin receptor positive whilst it was not reported in RADIANT-4 whether the patients were positive or negative.

We would like to highlight the following additional limitations to their NMA:

- The NMA hinges on the assumption that control arm of NETTER-1, where individuals received Octreotide 60mgs is the same as the control arm of RADIANT-4, where individuals received Placebo and BSC. In the AGs original report, we looked to identify RCTs that compared Octreotide to Placebo, in order to verify whether this assumption was appropriate. We were unable to identify any such studies and therefore concluded that this is a very strong assumption.
- RADIANT-4 included patients with GI-NETs and Lung NETs. For the outcome PFS, AAA Ltd. were able to use data that reported the subgroup of those with GI-NETs from RADIANT-4, whilst for the outcome OS, they have used data from the RADIANT-4 population that contains individuals with both GI and Lung NETs. They

have miss-reported in their updated submission that the tumour locations from RADIANT-4 were mid-gut.

– The tumour locations of GI-NETs (RADIANT-4) are different to that of mid-gut NETs (NETTER-1). Table 16, taken from the previous AG report, presents the tumour locations of individuals recruited to NETTER-1 and RADIANT-4. The locations are not particularly comparable and may impact effectiveness when comparing between NETTER-1 and RADIANT-4.

Table 16 tumour locations for NETTER-1 (Mid Gut NETs) and RADIANT-4 (GI NETs)

	NETTER-1		RADIANT-4	
	177Lu-DOTATATE	Octreotide 60mg	Everolimus + BSC	Placebo + BSC
Tumour location	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Jejunum	6/116 (5.2)	9/113 (8.0)	16/142 (11.3)	6/70 (8.6)
Ileum	86/116 (74.1)	82/113 (72.6)	47/142 (33.1)	24/70 (34.3)
Appendix	1/116 (0.9)	2/113 (1.8)	1/142 (0.7)	0/70 (0)
Right Colon	3/116 (2.6)	1/113 (0.9)	NA	NA
Duodenum	1/116 (0.9)	1/113 (0.9)	8/142 (5.6)	2/70 (2.9)
Ileum+ Caecum	1/116 (0.9)	1/113 (0.9)	NA	NA
Ileum + Caecum + Colon	0/116 (0)	1/113 (0.9)	NA	NA
Mesentery	5/116 (4.3)	3/113 (2.7)	NA	NA
Midgut	1/116 (0.9)	1/113 (0.9)	NA	NA
Small bowel	10/116 (8.6)	11/113 (9.7)	NA	NA
Unknown	2/116 (1.7)	1/113 (0.9)	23/142 (16.2)	13/70 (18.6)
Rectum	NA	NA	25/142 (17.6)	15/70 (21.4)
Stomach	NA	NA	7/142 (4.9)	4/70 (5.7)
Colon	NA	NA	5/142 (3.5)	3/70 (4.3)
Other	NA	NA	5/142 (4.2)	2/70 (2.9)
Caecum	NA	NA	4/142 (2.8)	1/70 (1.4)

3.3.4 Indirect comparison in GI-NETs

3.3.4.1 By AG (old report)

Previously, in the AG report (section 4.7.4), we used the Bucher method to indirectly compare Everolimus to 177Lu-DOTATATE. We highlighted the two assumptions with this ITC.

- Placebo + BSC (as used by RADIANT-4) can be considered equivalent care to Octreotide 60mg (as used by NETTER-1)
- GI NETs (the population in RADIANT-4) is the same as Mid Gut NETs (the population in NETTER-1)

Table 17 reports the results originally presented in the AG report.

Table 17 Indirect Treatment Comparison using Bucher for Everolimus vs 177Lu-DOTATATE for PFS and OS for individuals with GI-NETs

Intervention	Comparator	Data source	HR (95%CI)
HRs (95% CIs) for (central review of) disease progression or death in GI NETs			
Everolimus+BSC	Placebo+BSC	RADIANT-4 (from AG data request to Novartis)	0.56 (0.37, 0.84)
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1 (from AG data request to AAA)	[redacted]
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG	0.37 (0.19, 0.69)
HRs (95% CIs) for OS in GI NETs			
Everolimus+BSC	Placebo+BSC	RADIANT-4 (from AG data request to Novartis)	[redacted]
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1 (from AG data request to AAA)	[redacted]
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG	[redacted]
ORs (95% CIs) for response rates in GI NETs			
Everolimus+BSC	Placebo+BSC	RADIANT-4 (from AG data request to Novartis)	[redacted]
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1 (from AG data request to AAA)	
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG	[redacted]

3.3.4.2 By AAA Ltd.

The data that was used by AAA Ltd. for the NMA for PFS is the same as the data used by the AG in the previous report.

The HR for 177Lu-DOTATATE vs Everolimus calculated by AAA Ltd. was 2.69 (95%CI 0.07, 93.28), this is the reciprocal value to the results calculated by the AG (0.37 (95%CI 0.19, 0.69).

The data that was used by AAA Ltd. for the NMA of OS is different to the data used by the AG in the previous report. AAA Ltd. have used updated data for 177Lu-DOTATATE and the hazard ratio is now 0.54 (95% CI 0.33, 0.86),(16) whilst the data they have used for Everolimus is from a population that contains Lung and GI-NETs patients (0.64, 95%CI 0.4, 1.05).(22) Their hazard ratio for 177Lu-DOTATATE vs Everolimus was 1.20 (95%CI 0.03, 43.73).

3.3.4.3 By AG (new analysis)

The AG have updated their analysis for OS in GI-NETs using the new data from NETTER-1 (16) and the previous data from RADIANT-4 that includes just GI-NETs (AG data request to Novartis). We have used two HRs provided by AAA for NETTER1, firstly the HR estimated by the Kaplan Meier method (unadjusted unstratified and stratified) and secondly following adjustment for crossover, using the HR estimated by the RPSFT method (unadjusted unstratified and stratified). Table 18 reports these new results.

Table 18 Indirect Treatment Comparison using Bucher for Everolimus vs 177Lu-DOTATATE for OS for individuals with GI-NETs

Intervention	Comparator	Data source	HR (95%CI)
HRs (95% CIs) for OS in GI NETs			
Everolimus+BSC	Placebo+BSC	RADIANT-4 (from AG data request to Novartis)	[redacted]
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1(16), using Kaplan Meier Method	0.54 (0.33, 0.86) unstratified 0.54 (0.33, 0.87) stratified
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1(16) using RPSFT method	0.50 (0.31, 0.80) unstratified 0.49 (0.30, 0.80) stratified
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG using NETTER1 Kaplan Meier Method	0.95 (0.40, 2.23) unstratified 0.95 (0.40, 2.24) stratified
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG using NETTER1 RPSFT method	0.88 (0.37, 2.06) unstratified 0.86 (0.36, 2.04) stratified

3.3.5 New adjustment for cross-over in NETTER-1

The above new OS results of adjusting for treatment crossover in NETTER-1 submitted by the company to NICE were not accompanied with relevant methodological information to be able to judge its quality. In particular, it was not reported whether the RPSFT adjustment had been conducted with or without re-censoring, nor how well the method had performed, which would require showing that removing the effect of 17Lu-DOTATATE from both arms of NETTER-1 (or, alternatively, modelling its effect on the octreotide 60mg arm if all patients had received it from the beginning of the trial) produced very similar OS Kaplan-Meier curves (White et al. 2002).(23)

Consequently, the AG requested from AAA the data and analysis files used to obtain the company's OS results of adjusting from treatment crossover in the octreotide 60 mg arm to 177Lu-DOTATATE in NETTER-1. AAA provided the data without the analysis files, and in AG's own analysis of those data we reproduced the RPSFT results produced by the company. Using data on the randomised sample (n=231) with the 30 June 2016 cut-off date used by AAA to produce their intention to treat (ITT) and RPSTF hazard ratios we obtain similar effectiveness results in the crossover-adjusted analysis of 177Lu-DOTATATE than AAA's (HR 0.471 vs. 0.488). The slight difference is due to the fact that AAA modelled the effect of time on treatment exposure, whereas AG estimated the effect of any treatment exposure.

Table 19 Comparison of 177Lu-DOTATATE versus Oct 60mg for OS with and without adjustment for treatment crossover in GI midgut-NETs (Full Analysis Sample, n=231)

	AAA				AG			
	HR	P value	95%CI)		HR	P value	95%CI)	
				Unstratified				
Analysis ITT	0.536	0.0094	0.333	0.864	0.537	0.131	0.333	0.865
Adjusted	0.497*	0.0036	0.308	0.804	0.516**	0.009	0.313	0.850
No treatment**	Not reported				1.0008			
				Stratified				

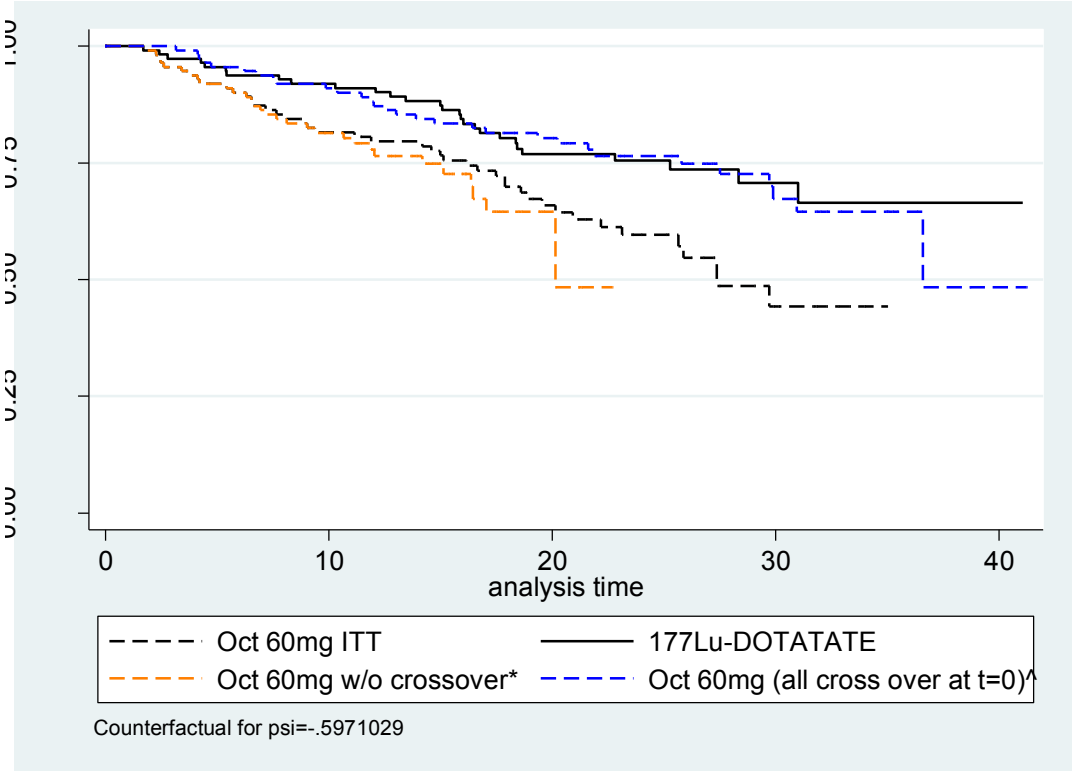
ITT	0.537	0.0102	0.332	0.868	0.538	0.131	0.333	0.870
Adjusted	0.488*	0.0033	0.300	0.795	0.471**	0.010	0.265	0.836
No treatment**	Not reported				0.9901			

* Method of adjustment: Rank preserving structural failure time (RPSFT) model based on time on (177Lu-DOTATATE) treatment exposure ** RPSFT model based on any (177Lu-DOTATATE) treatment exposure with re-censoring, implemented in Stata 14.1 by the programme strbee (White et al. 2002); test-based confidence interval ** this is a check on performance of the adjustment for cross-over: after removing the effect of 177Lu-DOTATATE from both trial arms, the hazard ratio is indistinguishable from 1

Adjusting for crossover from the octreotide 60mg to the experimental arm results in larger predicted overall survival differences between the two trial arms than observed in NETTER-1. Re-censoring the data to avoid bias in the RPSFT model estimate from administrative censoring (Robins and Tsiatis 1991), limits the available data to 20 months after randomisation, as opposed to the observed 35 months in NETTER-1. The predicted overall survival in the octreotide 60mg arm in the hypothetical (counterfactual) scenario that all patients crossed over from the start of the trial (discontinuous blue line in Figure 12) appears to match the observed Kaplan-Meier survival curve of the 177Lu-DOTATATE arm in NETTER-1.

It must be noted that RPSFT estimates of NETTER-1 are likely to underestimate the effectiveness of 177Lu-DOTATATE because the method does not address the problem highlighted in section 2.2.2 above, namely that such targeted treatment was given alongside a lower dose of octreotide than that used in the control arm, which was treated with octreotide 60mg.

Figure 12 ITT and crossover-adjusted overall survival in NETTER-1



Source: Analysis by AG. *Cross-over adjustment by the Rank Preserving Structural Failure Time (RPSFT) model with re-censoring (24). ^Check that the RPSFT model predicts similar treatment outcomes on both trial arms when modelling start of 177Lu-DOTATATE treatment at time 0.

3.4 New Survival Analyses from the AG

3.4.1 Indirect comparison in P-NETs

The time-to-event analyses presented in section 3.3.2.1.1 led us to select two functional forms for the extrapolation of progression-free survival outcomes in ERASMUS, the Weibull form (base case analysis), and the lognormal (sensitivity analysis) distributions. For extrapolating overall survival in ERASMUS we adopted the exponential (base case analysis) and lognormal (sensitivity analysis) distributions. By selecting these distributions we applied the same distributions across all treatments; i.e. 177Lu-DOTATATE, sunitinib, everolimus and BSC in the base case analysis and scenario analyses (see Assessment Report section 7.1.5.3.2 on the analysis used to select the distributions for sunitinib, everolimus and BSC). Nevertheless, that the lognormal function fit the ERASMUS data better than the exponential function.

3.4.2 Indirect comparison in GI-NETs

The time-to-event analyses presented in section 3.3.2.1.2 led to the choice of the exponential function to extrapolate the PFS and OS outcomes with 177Lu-DOTATATE in ERASMUS in the base case analysis. In sensitivity analysis we instead adopted the

lognormal distribution. Given that these functions had been previously chosen to provide the best fit to the data for competing treatments as described in our Assessment Report ID858, these choices of parametric functions to extrapolate outcomes thus ensured that all treatments being compared were modelled using the same distribution function in both base case and sensitivity analyses. It must be noted that the lognormal function provided a better fit to the progression free and overall survival data in ERASMUS.

3.5 Summary of Clinical Effectiveness Evidence

- The identification of the new data provided by the company is not systematically identified
- The updated data provided by the company for NETTER-1 and ERASMUS is unpublished
- The focus on just one non-RCT (ERASMUS) is unjustified, since there are a further seven non-RCT studies published with relevant data
  - None of the other treatments (Sunitinib or Everolimus) have had their non-RCT evidence reviewed
- P-NETs
  - Evidence for pancreatic NETs was provided from ERASMUS, a single arm, non-RCT trial conducted primarily with Dutch patients. The company provided very limited data surrounding the baseline population characteristics of the 133 individuals with P-NETs
- GI NETs
  - Evidence for GI NETs was provided from NETTER-1, an RCT which compared 177Lu-DOTATATE 30mg Octreotide LAR against 60mg Octreotide LAR.
  - The data provided from NETTER-1 was unpublished, since it was the most up to date data the company had (30 June 2016; these data include 2 additional patients randomised after the previous cut-off date of 24 July 2015) .
  - The company provided a scenario analysis where treatment cross-over was accounted for using the RPSFT method.
  - The company updated the data used for Sunitinib by incorporating results from the paper Faivre et al., 2017.(17) The data provided in this paper had already been used by the AG in their previous report, since Pfizer had previously provided us with the update.
  - The company updated their indirect comparison between RADIANT-4 (Everolimus) and NETTER-1 (177Lu-DOTATATE). The following assumptions were made for this analysis:

        - The control arm of RADIANT-4 (Placebo + BSC) is the same as the control arm of NETTER-1 (Octreotide LAR 60mg)
        - The population from RADIANT-4 (non-functioning GI and Lung NETs) is the same as NETTER-1 (functioning and non-functioning mid gut only NETs)
            - Novartis provided data for GI only NETs from RADIANT-4, these data was not available to AAA Ltd.

– Finally, a word of caution is warranted regarding the quality of the evidence from the indirect comparisons of outcomes of 177Lu-DOTATATE from single arm trials presented in this section, including those produced by the AG, which inform the economic evidence discussed in the next section. These 'unanchored' MAIC analyses do not permit some basic validity testing, for example by comparing that the matched control arms have similar outcomes and Kaplan –Meier curves. In terms of the ERASMUS data in particular this trial did not have an adequate recorded baseline measures of grade and stage, which are the most important prognostic factors and treatment effect modifiers, as advised by our clinical experts. Thus it is likely that estimates of relative treatment effects on PFS and OS outcomes for treatments in P-NETs, GI-NETs and especially GI-midgut NETs may be subject to confounding.

4 Economic Evaluation

4.1 Critique of the Company's New Economic Evaluation

In this section, we critique the changes to the economic aspects of their evaluation, up to and including the updated information to February 2018, and remark on any newly arising issues. A critique of the clinical effectiveness aspects, including their survival analyses, is provided in the earlier Section 2.3.

4.1.1 Resourcing costing issues raised by the AG in relation to the original economic analysis

Regarding those issues not pertaining to clinical effectiveness we raised five areas of concern in respect to the company's model (all were applicable to both the P-NETS and GI NETS analyses)

1. No comparison was made with a strategy of best supportive care.
2. Treatment with everolimus and sunitinib was assumed to continue until disease progression, potentially overestimating their use.
3. Treatment after progression was over-simplified to octreotide in every patient (all strategies), potentially overestimating the use of octreotide and underestimating the use of other resources during this stage of disease.
4. The cost burden of resource requirement for the administration of 177Lu-DOTATATE was low compared to expert opinion collected by the AG.
5. The cost burden of serious adverse events included considerable imprecision due to low unit costing of serious adverse events and application well beyond the expected mean duration of treatment (all strategies).

4.1.2 Summary of AAA's revisions to the economic analysis and remaining contentions

The company made changes to their original model to address some of the issues raised earlier in the critique by the AG but also in response to subsequent requests (specifically the update of the survival analyses by use of MAIC of outcomes in ERASMUS with those from trials of competitor treatments in P-NETS and GI NETs).

From the economic perspective, a BSC strategy was included by AAA in their modelling of both pancreatic and GI populations (point 1 above); and adjustments were made to dose intensity for everolimus and sunitinib (relating to point 2 above).

We therefore highlight the following concerns that remain outstanding in the company's modelling of 177Lu-DOTATATE in pancreatic and GI NETs populations: the potential overestimation of treatment with everolimus and sunitinib; the potential overestimation of octreotide post-progression; and the potential underestimation of the cost of administration

of 177Lu-DOTATATE. Overestimation of everolimus and sunitinib treatment pre-progression would favour 177Lu-DTATE in comparisons of cost-effectiveness with these drugs; and underestimation of 177Lu-DOTATATE administration cost would favour 177Lu-DOTATATE in comparisons with everolimus, sunitinib and BSC.

Further, the company's definition of BSC, their new strategy, is significantly different to the definition adopted in the AG's modelling. The AG's approach is premised on the observed rates of resource utilisation in the RADIANT-3 (pancreatic NETs) and RADIANT-4 (GI-NETs) RCTs; whereas the company's definition is premised on the design of NETTER-1, i.e. All patients are treated with high dose SSRA (60mg octreotide). Our approach to SSRA usage is as a background and supportive therapy, used either-side of progression according to patient need, with utilisation rates as observed in the trial sources of effectiveness data for modelling cost-effectiveness. In contrast AAA's approach is to use SSRAs as a direct comparator in its own right, equating it explicitly and directly to BSC. This approach is extended into the post-progression phase of disease, in which the company model all patients to receive octreotide at low dose irrespective of the preceding treatment. Utilisation rates in the RADIANT trials show low level residual use of SSRAs at this stage of disease. The contrast in the way SSRAs are modelled by ourselves and the company can be seen in the table below (Table 20).

Table 20 Use of SSRAs in AG and Company models

Disease and stage	Strategy	Proportion using SSRAs – AG model	Proportion using SSRAs – AAA model
Pancreatic NETs			
Pre-progression	BSC	39.90%(LD)	100.00%(HD)
	Active treatments	37.70%(LD)	0.00%
Post-progression	BSC	2.00%(LD)	100.00%(LD)
	Active treatments	2.02%(LD)	100.00%(LD)
Whole/midgut GI NETs			
Pre-progression	BSC	1.03%(LD)	100.00%(HD)
	Active treatments	1.95%(LD)	0.00%
Post-progression 1st cycle	BSC	22.74%(LD)	100.00%(LD)
	Active treatments	29.80%(LD)	100.00%(LD)
Post-progression Subsequent cycles	BSC	1.03%(LD)	100.00%(LD)
	Active treatments	1.95%(LD)	100.00%(LD)

Key: BSC = Best Supportive Care; HD = High dose; LD = Low dose; SSRA = Somatostatin Receptor agonist. Active treatments were Everolimus, Sunitinib, and 177Lu-DOTATATE

The AG has undertaken tests of alternative plausible approaches to disease management in respect to SSRA therapy in the form of scenario analyses (Sections 4.3.5 and 4.3.6). These should be considered alongside the base case results since expert clinical option is that the

AG estimates of SSRA in the base case for BSC, post-progression, and concomitant to active treatment, may be low relative to clinical practice.

Separate to these issues with the company model described above, which are not new, there is now a question over the estimate of 177Lu-DOTATATE dose intensity. Having changed to ERASMUS instead of NETTER-1 as the source trial for effectiveness data on 177Lu-DOTATATE used in indirect comparisons (both in P-NETS and GI NETS), the dose intensity estimate in the model should also change. This is important since the input parameter increases from 86.4% to the range 94.4%-97.8%. Having not made this change, the company model will overestimate the cost-effectiveness of 177Lu-DOTATATE.

4.1.3 Critique of AAA's new submitted economic analyses

AAA submitted two types of economic analyses for 177Lu-DOTATATE. One set of analyses compared it against treatments for pancreatic and overall gastrointestinal patients using ERASMUS data which were matched-adjusted for indirect comparison with the trials evaluating sunitinib (for P-NETS only) and everolimus relative to BSC. In addition, it evaluated its sponsored treatment relative to octreotide 60mg for GI midgut NETs based on the results of the head-to-head NETTER-1 trial. The primary analyses used the MIAC-based estimates.

We have highlighted the issues derived from the effectiveness analyses that informed the company's economic evaluation based on indirect comparisons in section 3.3. The main issue with the effectiveness data used in economic analyses relates to the small effective sample sizes resulting from their MAIC analyses after restricting them to ERASMUS Dutch patients. The second problem arises from the fact that the company modelled relative treatment effects after imposing the assumption of proportional hazards, without any statistical testing for those assumptions. The AG instead preferred to model relative treatment effects by fitting separate curves to each arm using proportional hazards and accelerated failure time functions, while following the principle that parametric functions used to extrapolate outcomes should be common to all treatments. Further, specifically with regard to the economic analysis of the GI case, the main limitation of the company's evidence is the lack of OS outcome data. Since the company did not have such data, in their economic modelling they adopted the assumption that life expectancy at the time of disease progression was the same across treatments, so that quantity of life benefits was effectively determined by PFS outcomes in their model of GI NETs.

In terms of the cost side, the main issue was the adoption of implausible costing assumptions, as discussed in 4.1.2 above. The problem is most evident in the economic analysis presented by AAA in their submission of December 2017 where effectiveness data

from MAIC of ERASMUS to the BSC trial arm of A6181111 was used to produce an incremental cost per QALY gained of 177Lu-DOTATATE vs. Octreotide 60mg. This high dose of course was not used in that trial or indeed in the RADIANT-3 trial also used by AAA to derive MAIC-based ICERs for 177Lu-DOTATATE relative to octreotide 60mg (see section 5.2 of AAA submission to NICE December 8 2017).

The economic evaluation of treatments in GI-midgut based on the head-to-head comparison submitted by the company to NICE is based on the highest quality of evidence provided by the company in terms of relative effectiveness, although it suffers from serious flaws on the costing analysis side, as discussed in the previous section. This analysis adjusts for treatment cross-over in the octreotide 60mg arm although data are immature as median overall survival in the experimental arm is not yet reached by the end of follow-up. With these limitations in mind, the analysis by the company produces an ICER of £28,284. Given the implausible costing assumptions in the company's analysis this casts doubt that the true ICER is below £30,000. Due to time limitations the AG did not undertake their own independent evaluation based on the head-to-head NETTER-1 trial.

4.1.4 Comparison of new estimates versus previous (See also Section 3)

The cost-effectiveness analyses in the Assessment Report [ID858] of P-NETS and Whole GI NETS was extended to include a new 177Lu-DOTATATE strategy based on the data available from ERASMUS. This strategy had already been presented for a midgut NETs population. So the treatments now being compared in P-NETS are:

- Everolimus plus BSC (referred to as the Everolimus strategy)
- Sunitinib plus BSC (referred to as the Sunitinib strategy)
- 177Lu-DOTATATE plus BSC (referred to as the 177Lu-DOTATATE strategy)
- BSC only;

and the treatments compared in Whole GI NETS and Midgut NETS are:

- Everolimus plus BSC (referred to as the Everolimus strategy)
- 177Lu-DOTATATE plus BSC (referred to as the 177Lu-DOTATATE strategy)
- BSC only.

The main Assessment Report included an economic evaluation of:

- 177Lu-DOTATATE (referred to as the 177Lu-DOTATATE strategy)
- Everolimus plus BSC (referred to as the Everolimus strategy)

- BSC only

in the midgut NETs RADIANT-4 patient population, based on indirect comparison by Bucher matching of the 177Lu-DOTATATE arm in NETTER-1 to RADIANT-4. Since the NETTER-1 and RADIANT-4 midgut populations may not be comparable (Yao et al. 2018), we have produced new analysis comparing the same treatments but based instead on MAIC of the ERASMUS midgut to the RADIANT-4 midgut population.

The source and data used for treatment arms other than 177Lu-DOTATATE are as described previously in the main Assessment Report [ID858]. The ERASMUS data provided by AAA was used to populate model parameters of 177LU-DOTATATE on mean dose intensity, PFS, and OS, and to estimate the maximum follow up time of Kaplan-Meier PFS and OS curves, which marked the start of background mortality adjustment in the model. The extrapolating survival functions and parameter values used in the base case and scenario analyses are presented in Table 23. In the base case analysis, the choice of parametric survival functions for 177Lu-DOTATATE was the same as the functions used for the competing treatments in the base case analysis as described in the Assessment Report [ID858]. The best-fitting alternative parametric functions were used in scenario analysis subject to the requirement that the same functions be used for alternative treatments.

The assumptions, methods, data, and sources relating to the pre- and post- progression cost of drug acquisition, drug administration, monitoring and medical management, adverse events, as well as for the end-of-life period, are described in the main Assessment Report [ID858], in Section 7.1.5.6. Deviations to the base case made within this evaluation are described in the next section 4.2, AG revisions to the economic analysis.

The values used for populating PFS and OS model parameters were obtained from the time to event analyses presented in section 3.3.2 (25, 26) The survival parameter values used in the model are presented in Table 21 and Table 22 for P-NETs, whole GI NETs. These parametric functions and values were used to extrapolate outcomes beyond the end of the trial follow-up of the respective trial, at which point background mortality adjustment was applied in P-NETs, for scenario analysis, and in the base case analysis for overall GI NETs and GI midgut NETs,

Table 21 Parameter values used in the model for 177Lu-DOTATATE in P-NETs

Intervention	Outcome	Model	Parameter	Estimate (Standard error)	Analysis	Method	Source
177Lu-DOTATATE	PFS	Weibull[1]	Scale	0.0003 (0.001)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			Shape	1.818 (0.204)			
177Lu-DOTATATE	PFS	Lognormal	Mean	4.879 (0.087)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.669 (0.076)			
177Lu-DOTATATE	OS	Exponential	Scale	0.009 (0.002)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
177Lu-DOTATATE	OS	Log-normal	Mean	4.163 (0.180)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.811 (0.127)			

Note: PFS progression free survival; OS overall survival. [1] Weibull cumulative survival function: exp(-Scale*time^shape).

Table 22 Parameter values used in the model for 177Lu-DOTATATE in GI-NETs

Intervention	Outcome	Model	Parameter	Estimate (Standard error)	Analysis	Method	Source
177Lu-DOTATATE	PFS	Exponential	Scale	0.029 (0.221)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
177Lu-DOTATATE	PFS	Lognormal	Mean	3.208 (0.)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.722 (0.050)			
177Lu-DOTATATE	OS	Exponential	Scale	0.010 (0.001)	Base case	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
177Lu-DOTATATE	OS	Log-normal	Mean	4.186 (0.123)	Scenario	MAIC to RADIANT-3	Estimated by AG from ERASMUS data provided by AAA
			SD	0.828 (0.089)			

Note: PFS progression free survival; OS overall survival.

Figure 13 Progression Free Survival in AG model

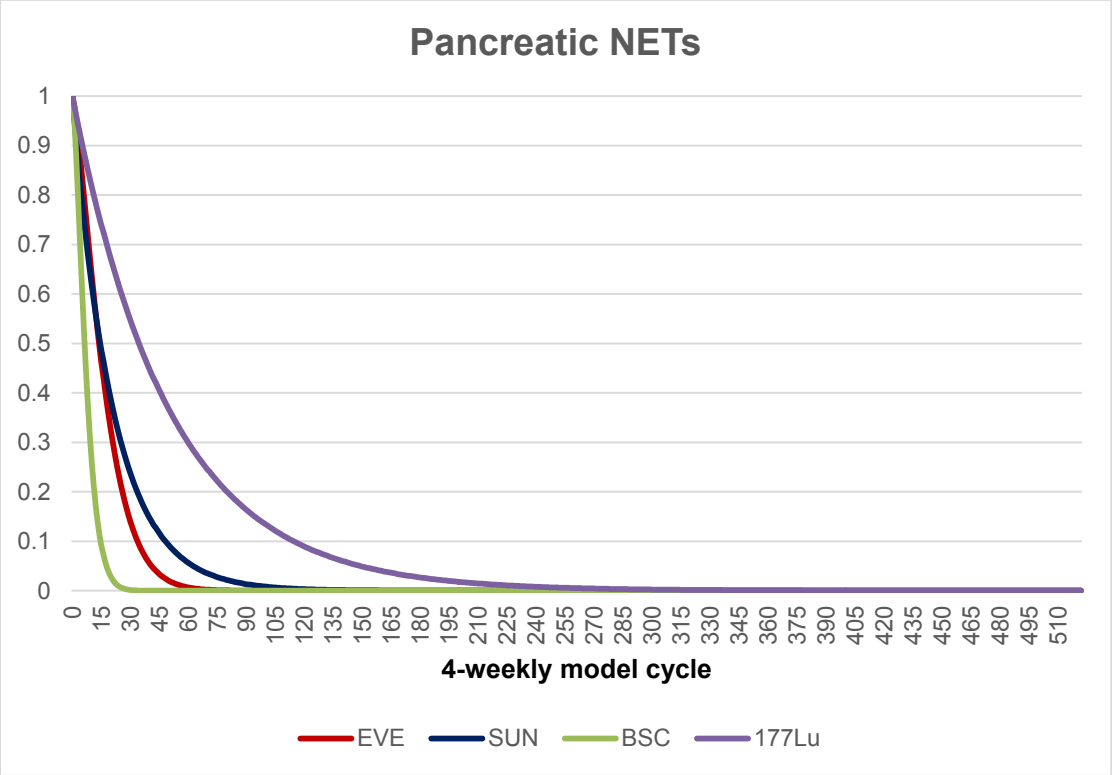


Figure 14 Overall Survival in AG model

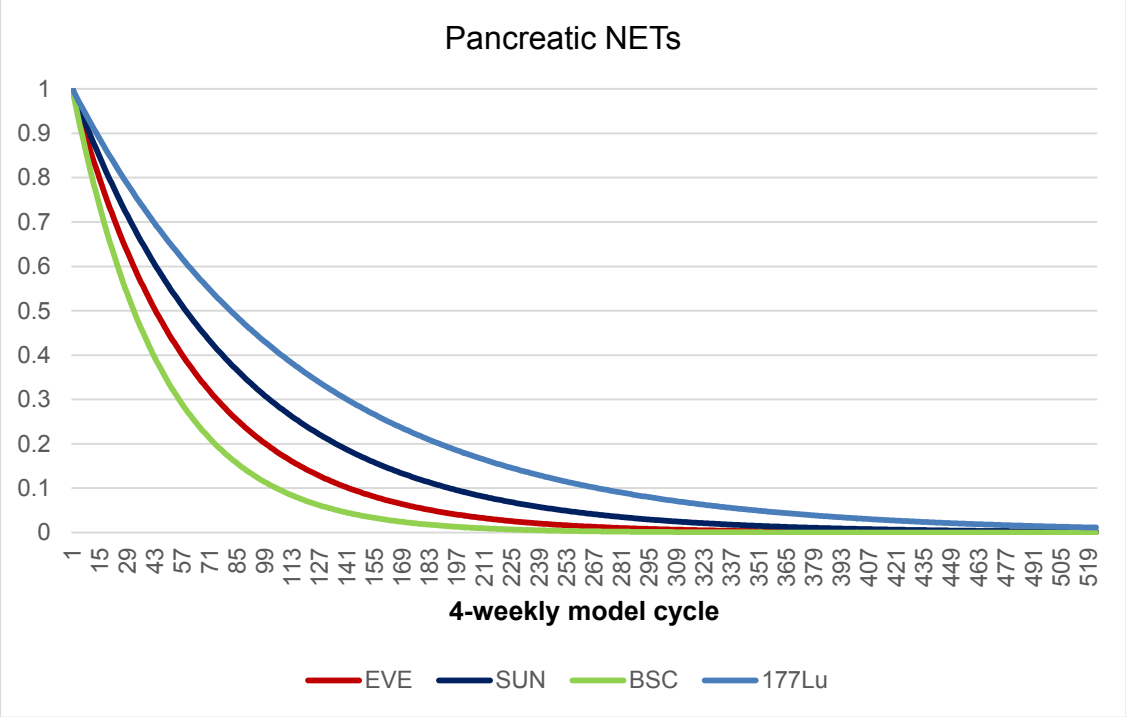
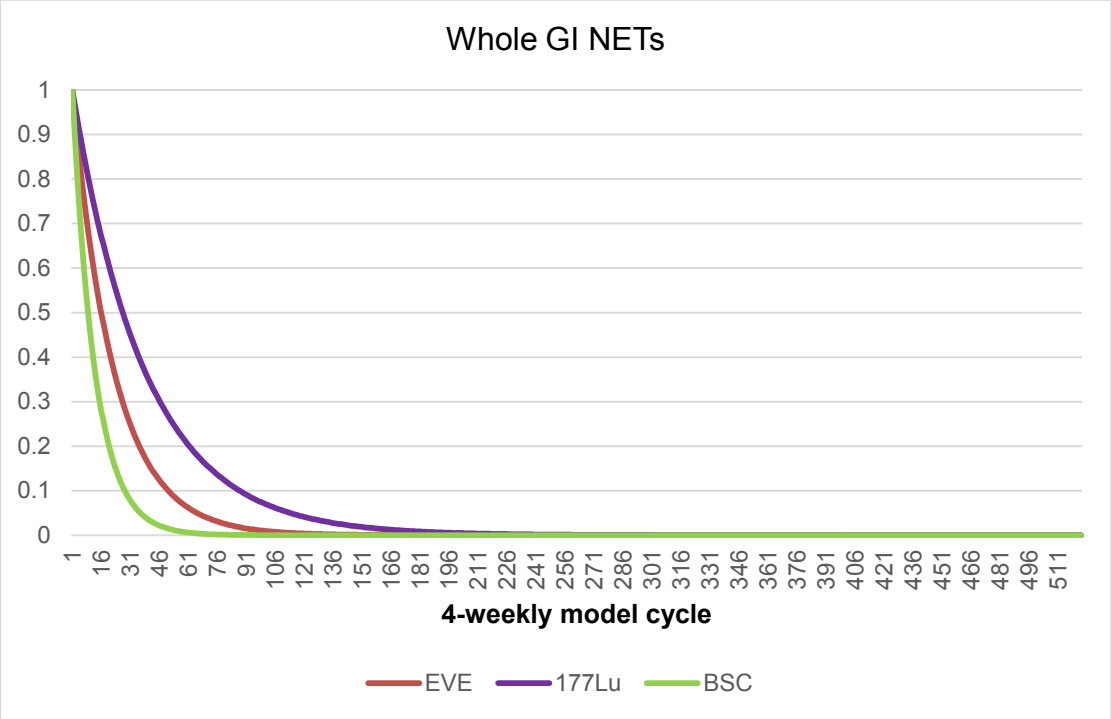
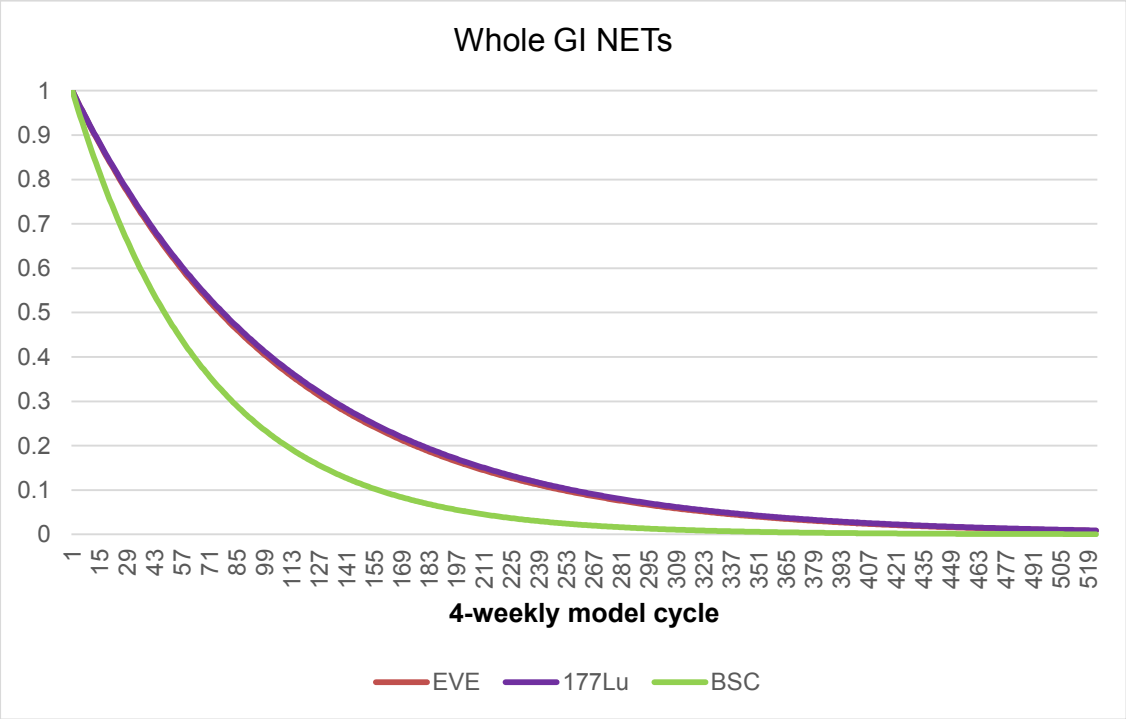


Figure 15 Progression Free Survival in AG model



* Note: These curves do not reflect the effect of background mortality which was applied in the base case analysis in the model.

Figure 16 Overall Survival in AG model



* Note: These curves do not reflect the effect of background mortality which was applied in the base case analysis in the model.

4.2 AG revisions to the economic analysis

4.2.1 Cost of 177Lu-administration

In a change to the original base case, to reduce potential double counting of consumed resources for those patients who require overnight stay (admission), we used the national average cost of an elective inpatient excess bed day instead of the national average cost of a non-elective inpatient short stay.(27) The result is a reduction in the weighted unit cost of 177Lu-DOTATATE administration from £1,063.07 to £811.77.

4.2.2 Dose intensity of 177Lu-DOTATATE

For consistency with our source of effectiveness data, i.e. the ERASMUS dataset in MAIC based survival analyses, we have calculated and adopted the mean relative dose intensity of 177Lu-DOTATATE in the ERASMUS population. This has increased the previous base case estimate of 86.4%, which originated from NETTER-1, to 94.4% in P-NETs, 94.6% in Whole GI NETs, and 97.8% in midgut NETS, obtained from MAIC analyses described above.

The mean proportion of people who are alive and disease free (i.e. the area under the parametric PFS curve) under the 177Lu-DOTATATE arm over the first seven four-weekly model cycles, the period during which 177Lu-DOTATATE administration is scheduled, places a cap on the mean cumulative dose that is consumed in the model. For the base case analysis (which use an exponential PFS curve) that cap is 93.3%, 90.7%, and 90.8% in P-NETs, whole GI, and GI midgut, respectively. Therefore the effective relative dose intensity in the model are equal to the values just described times the cap imposed by the PFS distribution in the model. In sensitivity analysis where we assume 100% dose intensity the cap becomes the effective relative dose intensity, which thus becomes closer to the ERASMUS values we estimated from MAIC in section 3. Also note that the use of lognormal PFS curves changes the caps, which become 99.8%, 99.2%, and 98.7%, for P-NETs, GI NETs and GI midgut NETs, and again bring the effective relative dose intensity closer to the values we estimated from ERASMUS.

Therefore the base case assumptions of relative dose intensity tend to slightly underestimate costs from the point of view and 177Lu-DOTATATE, due to premature attrition of patients from treatment, and in this sense represent a slightly optimistic analysis.

4.2.3 Application of background mortality in the GI analyses

In the base case analysis of strategies for the treatment of patients with GI NETs we made adjustment in the survival analysis for background mortality (Table 23). This was applied because of the short period of follow-up in the supporting indirect comparison of progression and mortality; in cases where a substantial extrapolation is fitted to a short period of

observation the impact of death from other causes on relative health benefit can be significant. In this revised economic analysis by the AG we have for each strategy matched the point of adjustment to the point at which the last in-trial event is recorded.

Table 23 Length of follow-up under 177Lu-DOTATATE in ERASMUS from data provided by AAA

	Outcome	Length of trial follow-up in months (Kaplan-Meier)
P-NETs	PFS	90
P-NETs	OS	150
GI	PFS	125
GI	OS	150
GI (midgut)	PFS	140
GI (midgut)	OS	140

4.3 Results

The deterministic model was selected as the primary analysis.

In section 4.3.1 below the base case analysis estimates of costs and QALYs of each treatment arm as well as incremental results are presented. These are followed by the probabilistic results, section 4.3.3. Presented below these are the results of relevant scenario analyses, each which an incorporated description, section 4.3.5 and 4.3.6.

Finally we have placed AG and Company results alongside one another for comparison in section 4.3.7.

4.3.1 Base case results for treatment strategies by tumour location

177Lu-DOTATATE is estimated to produce the longest life expectancy across treatments for P-NETS, Whole GI and Midgut NETs patient populations. It was also the most effective and most costly option in all three tumour location groups, producing 4.2, 4.8 and 4.4 discounted QALYs, and £91,784, £90,071 and £89,790 discounted costs, respectively (Table 24). Drug acquisition is the cost driver accounting for 73% (£67 345) of its total (£91,784) in P-NETS, 69% (£61,918) of its total (£90,071) in whole GI NETs and 71% (£63,673) of its total (£89,790) in GI midgut.

Table 24 Base-case strategy results for Pancreatic NETs (deterministic discounted QALY and cost means, costs in £s)

	Pancreatic NETS				Whole GI NETs			Midgut NETs		
	BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus	177Lu-DOTATATE
Life years*										
Pre-progression	0.570	1.279	1.601	3.814	0.901	1.644	2.878	1.434	2.069	2.726
Post-progression	2.893	3.413	4.787	5.003	3.999	5.168	5.029	2.940	3.104	4.369
Total	**3.463**	**4.692**	**6.388**	**8.717**	**4.900**	**6.812**	**7.907**	**4.374**	**5.172**	**7.096**
QALYS										
Pre-progression	0.381	0.813	0.997	2.207	0.705	1.192	2.003	1.102	1.479	1.914
Post-progression	1.534	1.692	2.241	2.050	2.404	2.891	2.656	1.767	1.797	2.354
Total	**1.914**	**2.505**	**3.238**	**4.257**	**3.109**	**4.082**	**4.805**	**2.869**	**3.276**	**4.268**
Costs pre-progression										
Drug acquisition	2,003	25,547	22,216	63,689	405	29,813	61,918	634	30,353	63,673
Drug administration	510	1,104	1,308	2,840	3	168	2,784	4	170	2,864
Medical management	184	776	952	2,116	2,201	4,758	8,012	3,440	5,909	7,625
AEs	15	132	89	89	34	171	171	105	287	85
Total	2,712	27,559	24,566	68,733	2,642	34,910	72,885	4,184	36,719	74,247
Costs post-progression										
Drug acquisition	4,660	6,113	8,120	7,483	2,523	4,610	4,278	1,855	2,879	3,787
Drug administration	1,106	1,468	1,949	1,797	10	23	21	7	14	18
Medical management	3,394	3,759	4,993	4,601	7,862	9,520	8,778	5,780	5,907	7,771
End-of-life care	3,889	3,747	3,565	3,321	3,721	3,515	3,403	3,779	3,688	3,485
Total	13,049	15,087	18,627	17,202	14,115	17,697	16,479	11,422	12,488	15,063
Total Costs	**15,761**	**42,646**	**43,192**	**85,935**	**16,757**	**52,607**	**89,364**	**15,606**	**49,207**	**89,309**

Key: AEs = Adverse events (Serious); BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours; QALY = Quality-Adjusted Life Year. *Life years are presented as undiscounted.

4.3.2 Base case results for treatment strategy comparisons by tumour location

In P-NETS, 177Lu-DOTATATE has an incremental ICER of £29,956 relative to BSC, £24,714 relative to everolimus, and of £41,967 relative to the second most effective alternative, sunitinib (Table 25).

Table 25 Base-case incremental results for Pancreatic NETs (deterministic discounted QALY and cost means, costs in £s)

	177Lu-DOTATATE versus BSC	177Lu-DOATATE versus Everolimus	177Lu-DOTATATE versus Sunitinib
Life years gained*			
Pre-progression	3.244	2.535	2.213
Post-progression	2.110	1.590	0.216
Total	5.353	4.125	2.428
QALYS gained			
Pre-progression	1.827	1.394	1.210
Post-progression	0.516	0.358	-0.192
Total	2.343	1.752	1.018
Costs pre-progression			
Drug acquisition	61,685	38,142	41,472
Drug administration	2,330	1,735	1,532
Medical management	1,932	1,340	1,163
AEs	74	-43	0
Total	66,021	41,174	44,167
Costs post-progression			
Drug acquisition	2,823	1,370	-636
Drug administration	690	329	-153
Medical management	1,207	842	-391
End-of-life care	-568	-426	-244
Total	4,153	2,115	-1,424
Total Costs	70,174	43,289	42,743
ICER – lifetime horizon	**29,956**	**24,714**	**41,967**
ICER – until progression	36,144	29,537	36,499

Key: AEs = Adverse events (Serious); BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours; QALY = Quality-Adjusted Life Year. *Life years are presented as undiscounted.

In whole GI NETs, 177Lu-DOTATATE has an incremental ICER of £46,870 relative to BSC and of £63,792, relative to the second most effective alternative, everolimus (Table 26).

Table 26 Base-case incremental results for Whole GI NETs (deterministic discounted QALYs and cost means, costs in £s)

	177Lu-DOTATATE versus BSC	177Lu-DOATATE versus Everolimus
Life years gained*		
Pre-progression	1.977	1.235
Post-progression	1.030	-0.139
Total	3.007	1.096
QALYS gained		
Pre-progression	1.297	0.811
Post-progression	0.252	-0235
Total	1.549	0.576
Costs pre-progression		
Drug acquisition	61,513	32,105
Drug administration	2,782	2,617
Medical management	5,811	3,254
AEs	137	0
Total	70,243	37,975
Costs post-progression		
Drug acquisition	1,755	-362
Drug administration	11	-2
Medical management	917	-742
End-of-life care	-318	-112
Total	2,364	-1,218
Total Costs	72,607	36,758
ICER – lifetime horizon	**46,870**	**63,792**
ICER – until progression	54,154	46,841

Key: AEs = Adverse events (Serious); BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio: NETs = Neuroendocrine Tumours; QALY = Quality-Adjusted Life Year. *Life years are presented as undiscounted.

In midgut GI NETs, 177Lu-DOTATATE has an incremental ICER of £52,690 relative to BSC and of £40,423, relative to the second most effective alternative, everolimus (Table 27).

Table 27 Base-case incremental results for 'Midgut GI' NETs (deterministic discounted QALYs and cost means, costs in £s)

	177Lu-DOTATATE versus BSC	177Lu-DOATATE versus Everolimus
Life years gained*		
Pre-progression	1.292	0.658
Post-progression	1.429	1.266
Total	2.722	1.923
QALYS gained		
Pre-progression	0.812	0.435
Post-progression	0.587	0.557
Total	1.399	0.992
Costs pre-progression		
Drug acquisition	63,039	33,319
Drug administration	2,860	2,694
Medical management	4,184	1,716
AEs	-20	-202
Total	70,063	37,528
Costs post-progression		
Drug acquisition	1,932	908
Drug administration	11	4
Medical management	1,991	1,864
End-of-life care	-294	-202
Total	3,640	2,575
Total Costs	73,704	40,102
ICER – lifetime horizon	**52,690**	**40,423**
ICER – until progression	86,299	86,298

Key: AEs = Adverse events (Serious); BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio: NETs = Neuroendocrine Tumours; QALY = Quality-Adjusted Life Year. *Life years are presented as undiscounted.

4.3.3 Probabilistic Sensitivity Analysis

Allowing for sampling uncertainty in model parameter values results in probabilistic mean ICER estimates of £29,434 versus BSC, £24,300 versus everolimus, and £40,428 versus sunitinib in P-NETS. These are respectively 2%%, 2%, and 4% lower than the deterministic estimates. In the Whole GI NETS population, the probabilistic ICER is £48,692 versus BSC and £65,317 versus everolimus which are respectively 4% and 2% above the deterministic estimate. For GI midgut NETS the PSA results are within 1.5% of the deterministic (Table 28). Results of the individual simulation are presented on the cost-effectiveness plane for the P_NETS comparison in Figure 17, and the Whole GI comparisons in Figure 18.

Table 28 PSA of base case model by Strategy comparison and NETs location (probabilistic discounted QALY and cost means, costs in £s)

	Pancreatic NETS			**Whole GI NETs**		**Midgut NETs**	
	177Lu-DOTATATE versus:			177Lu-DOTATATE versus:		177Lu-DOTATATE versus:	
	BSC	Everolimus	Sunitinib	BSC	Everolimus	BSC	Everolimus
PSA ICER	29,434	24,300	40,428	48,692	65,317	53,416	40,589
Deterministic ICER	29,956	24,714	41,967	46,870	63,792	52,690	40,423

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours.

Figure 17 PSA simulations for pancreatic NETS on the cost-effectiveness plane

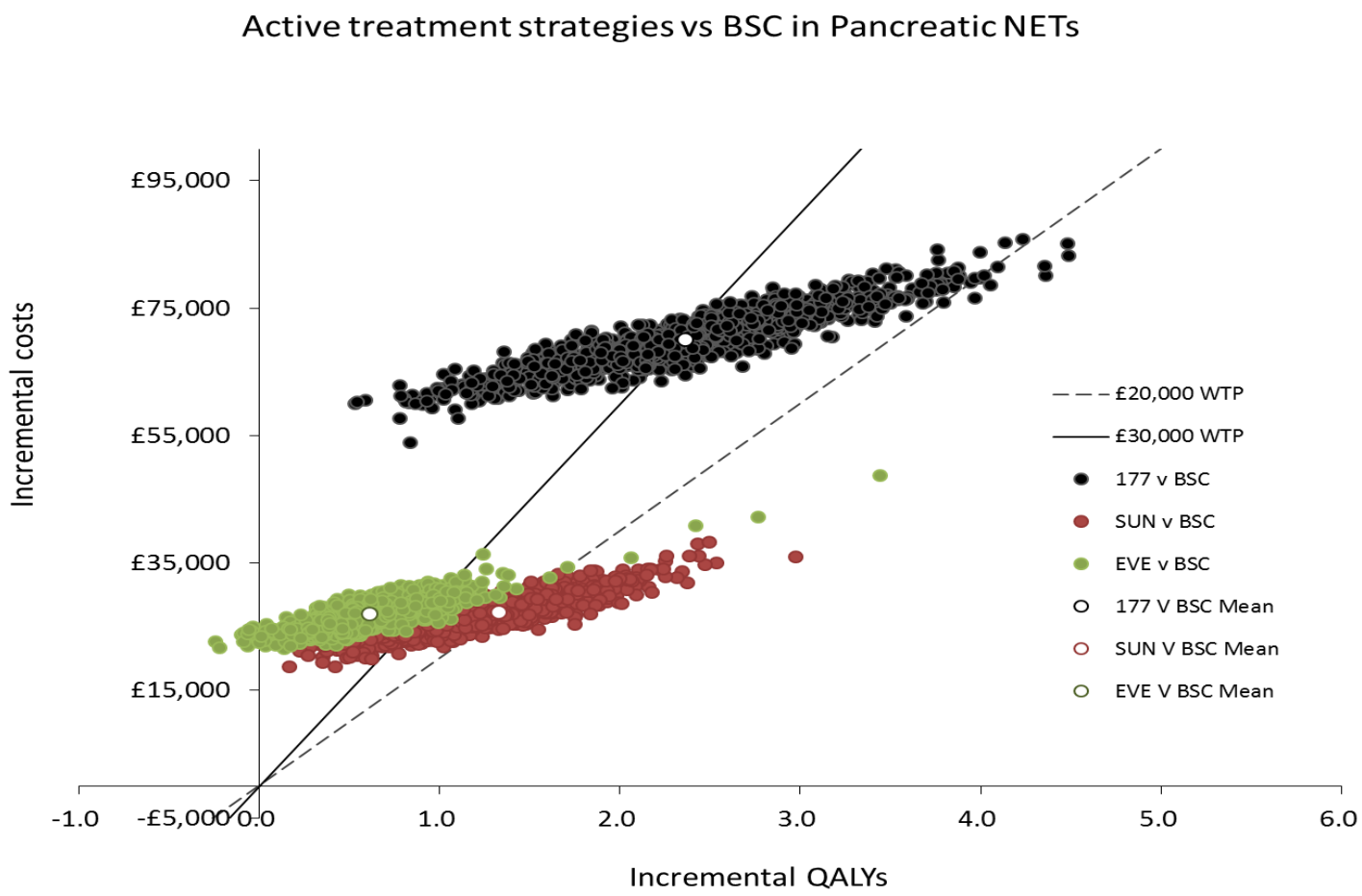


Figure 18 PSA simulations for Whole GI NETS on the cost-effectiveness plane

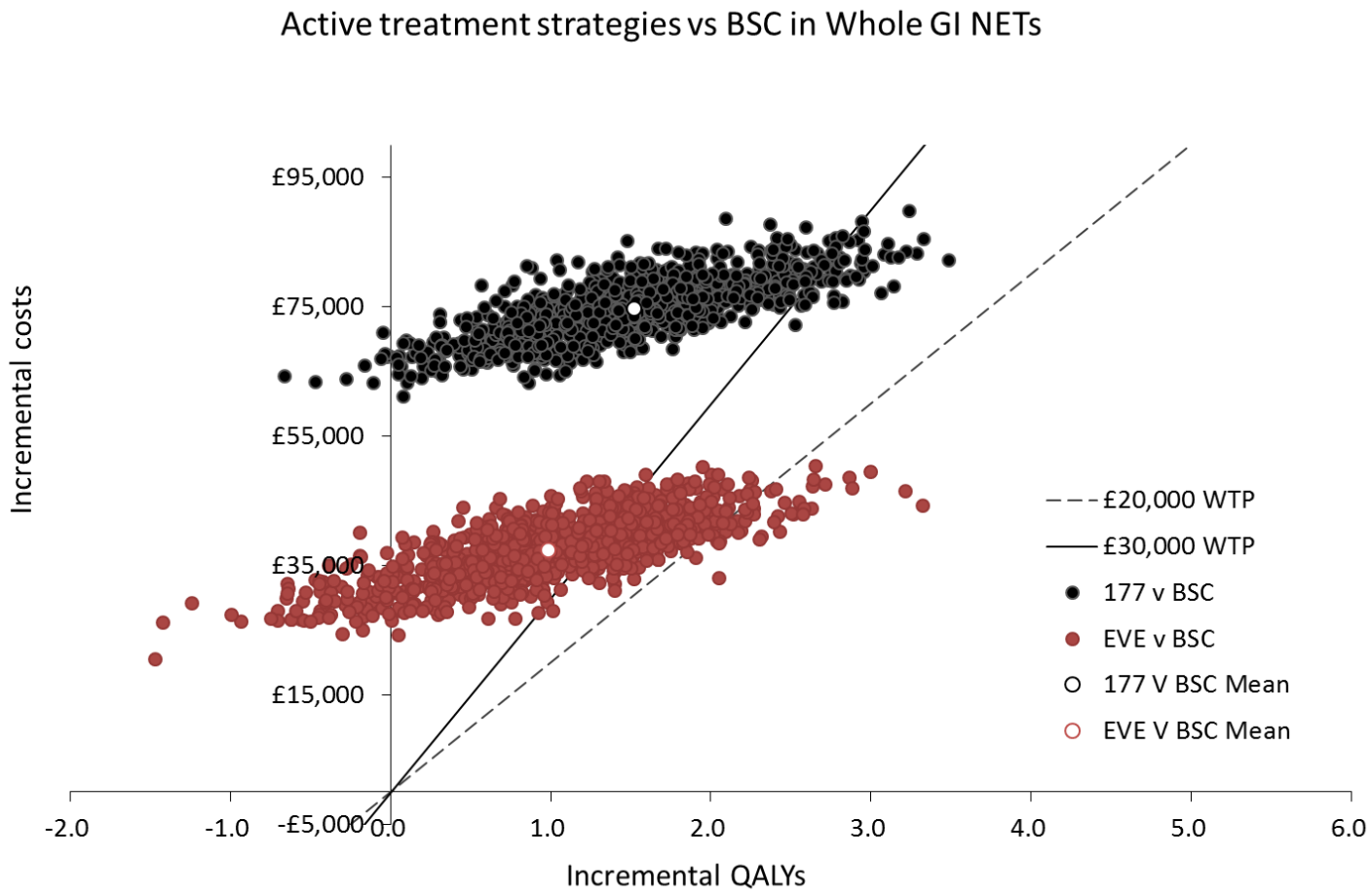


Figure 19 Cost Effectiveness Acceptability Curve (CEAC) for comparisons of 177Lu-DOTATATE in Pancreatic NETS

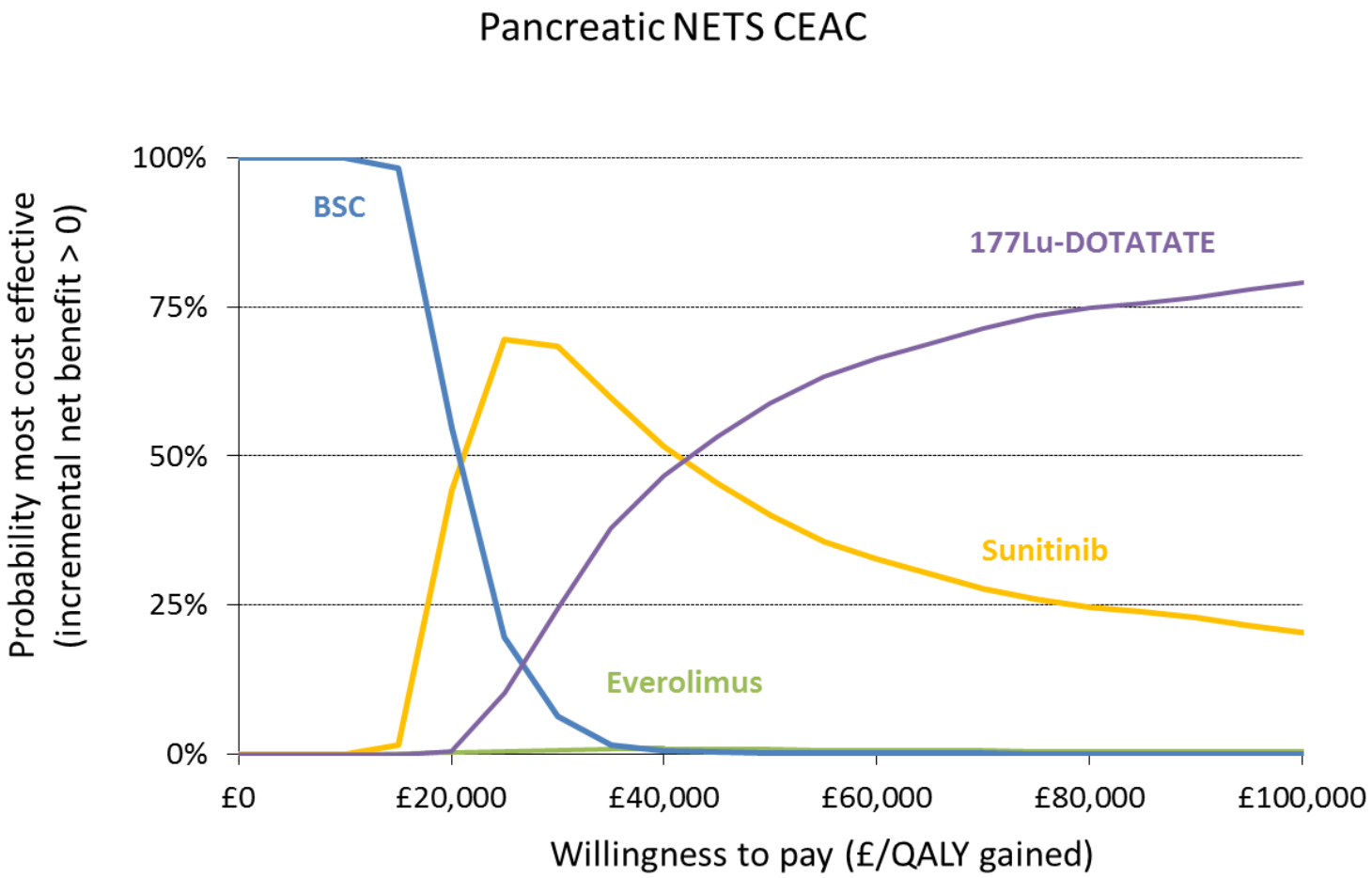
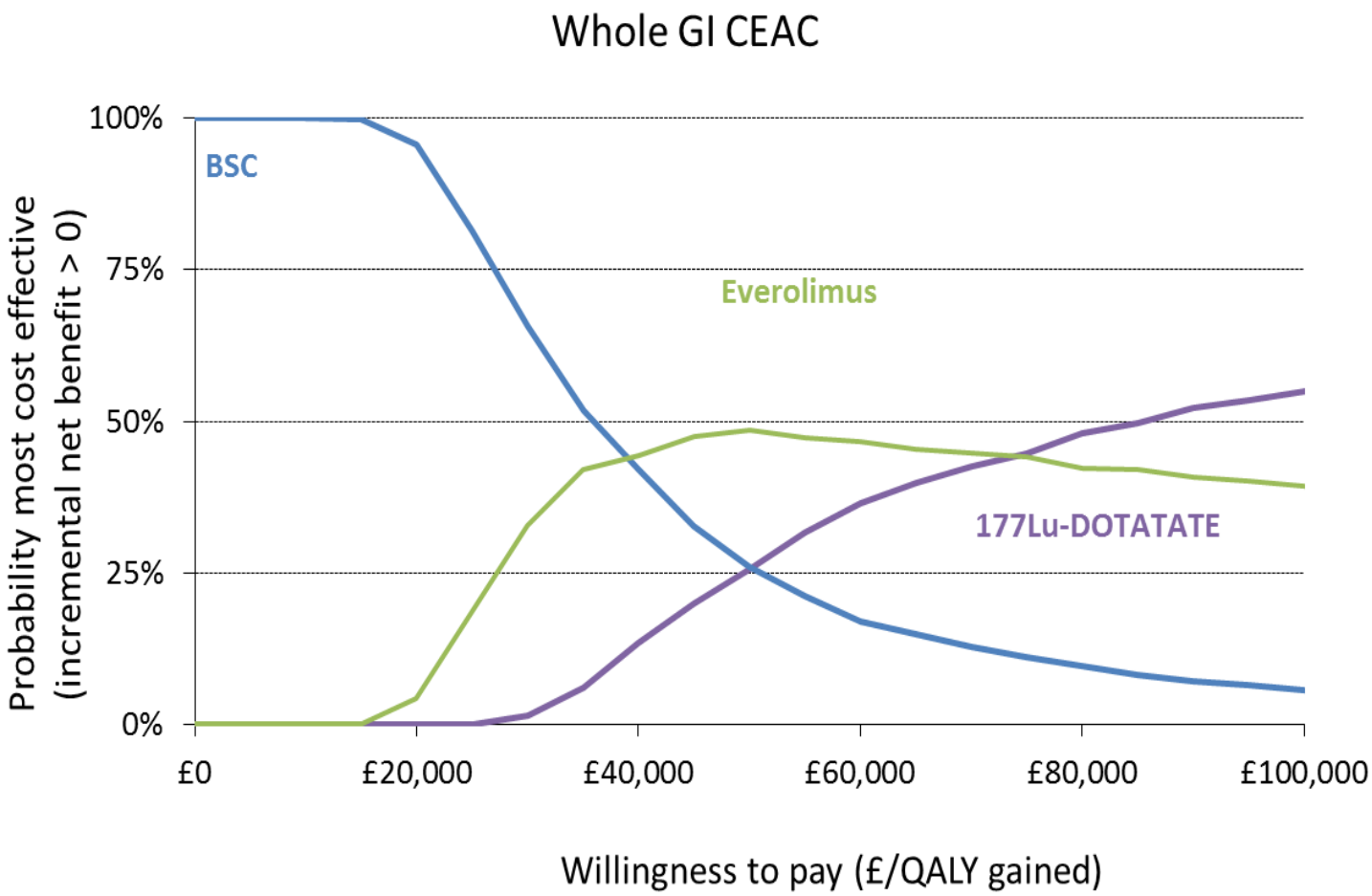


Figure 20 Cost Effectiveness Acceptability Curve (CEAC) for comparisons of 177Lu-DOTATATE in Whole GI NETS



4.3.4 No discounting of future costs and QALYs

Table 29 Effect of no discounting, ICERs by Strategy comparison and NETs location (deterministic discounted QALY and cost means, costs in £s)

	Pancreatic NETS			Whole GI NETs		'Midgut' NETs	
	177Lu-DOTATATE versus:			177Lu-DOTATATE versus:		177Lu-DOTATATE versus:	
	BSC	Everolimus	Sunitinib	BSC	Everolimus	BSC	Everolimus
No discount ICER	22,996	18,546	29,242	35,212	45,194	39,896	29,710
Deterministic ICER	29,956	24,714	41,967	46,870	63,792	52,690	40,423

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours.

4.3.5 Univariate Scenario Analyses in Pancreatic NETs

Presented below (Table 30 to Table 36) are a series of univariate deterministic scenario analyses which employ plausible alternative assumptions or input estimates.

Table 30 Full dose intensity in pre-progression in Pancreatic NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Dose intensity of Everolimus, Sunitinib and 177Lu-DOTATATE at 100%

The base case uses includes estimates of dose intensities for everolimus, sunitinib and 177Lu-DOATATE from clinical trials, these are all below 100%. In this scenario we remove this assumption and estimate cost-effectiveness at full dose intensity.

						177Lu-DOTATATE versus:		
		BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	Sunitinib
Life-years*	Pre	0.570	1.279	1.601	3.814			
	Post	2.893	3.413	4.787	5.003			
QALYs	Pre	0.381	0.813	0.997	2.207			
	Post	1.534	1.692	2.241	2.050			
Costs	Pre	2,712	**31,076**	**26,211**	**72,609**			
	Post	13,049	15,087	18,627	17,202			
					Scenario Lifetime ICER	**31,610**	**24,919**	**44,157**
					c.f. Base case ICER	29,956	24,714	41,967

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 31 177Lu-DOTATATE dose intensity in Pancreatic NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Dose intensity of 177Lu-DOTATATE dose

The base case uses a dose intensity of 94.4%, an estimate derived from usage in ERASMUS, the reference trial of the MAIC. Another plausible estimate for the dose intensity of 177Lu-DOTATATE is that observed in NETTER-1, but adjusted for attrition death on treatment (93.3%).

						177Lu-DOTATATE versus:		
		BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	Sunitinib
Life-years*	Pre	0.570	1.279	1.601	3.814			
	Post	2.893	3.413	4.787	5.003			
QALYs	Pre	0.381	0.813	0.997	2.207			
	Post	1.534	1.692	2.241	2.050			
Costs	Pre	2,712	27,559	24,566	**63,196**			
	Post	13,049	15,087	18,627	17,202			
					Scenario Lifetime ICER	**29,425**	**24,004**	**40,747**
					c.f. Base case ICER	29,956	24,714	41,967

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours.*Life years are presented as undiscounted.

Table 32 Supportive treatment costs in Pancreatic NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Including the cost of supportive therapies bundled into the first cycle of treatment post-progression

In the base case analysis, the use of Chemoembolization, Radiotherapy and Chemotherapy (the cost of which were applied only to the first cycle post-progression) was not included despite observed utilisation post-progression in the RADIANT-3 trial. Here we have re-introduced these costs.

						177Lu-DOTATATE versus:		
		BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	Sunitinib
Life-years*	Pre	0.570	1.279	1.601	3.814			
	Post	2.893	3.413	4.787	5.003			
QALYs	Pre	0.381	0.813	0.997	2.207			
	Post	1.534	1.692	2.241	2.050			
Costs	Pre	2,712	27,559	24,566	68,733			
	Post	**13,589**	**15,519**	**19,057**	**17,471**			
					Scenario Lifetime ICER	**29,840**	**24,621**	**41,809**
					c.f. Base case ICER	29,956	24,714	41,967

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 33 Parametric curve choice for PFS in Pancreatic NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Using Accelerated failure time distributions

Statistical exploration and clinical validity drove the choice in the base case of the exponential parametric curve for the fitting and extrapolation of progression events across the life-time horizon. Here we test accelerated failure time selections (lognormal and loglogistic) as a plausible alternatives: the everolimus strategy follows loglogistic, and the 177Lu-DOTATATE and BSC strategies follow lognormal distributions. The sunitinib strategy is unchanged.

						177Lu-DOTATATE versus:		
		BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	Sunitinib
Life-years*	Pre	**0.620**	**1.933**	1.601	**3.154**			
	Post	**2.844**	**2.790**	4.787	**5.698**			
QALYs	Pre	**0.411**	**1.127**	0.997	**1.908**			
	Post	**1.506**	**1.407**	2.241	**2.348**			
Costs	Pre	**2,932**	**29,909**	24,566	**73,025**			
	Post	**12,889**	**13,167**	18,627	**19,214**			
					Scenario Lifetime ICER	**32,683**	**28,558**	**48,204**
					c.f. Base case ICER	29,956	24,714	41,967

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 34 Parametric curve choice for OS in Pancreatic NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Using Accelerated failure time distributions

Statistical exploration and clinical validity drove the choice in the base case of the Exponential parametric curve for the fitting and extrapolation of death events across the life-time horizon. Here we test accelerated failure time selections (lognormal and loglogistic) as plausible alternatives: the everolimus and 177Lu-DOTATATE strategies follow lognormal distributions. BSC and sunitinib are unchanged.

						177Lu-DOTATATE versus:		
		BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	Sunitinib
Life-years*	Pre	0.570	1.279	1.601	3.814			
	Post	2.893	**4.959**	4.787	**3.533**			
QALYs	Pre	0.381	0.813	0.997	2.207			
	Post	1.534	**2.160**	2.241	**1.579**			
Costs	Pre	2,712	27,559	24,566	68,733			
	Post	13,049	**18,172**	18,627	**14,081**			
					Scenario Lifetime ICER	**35,829**	**45,617**	**72,383**
					c.f. Base case ICER	29,956	24,714	41,967

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 35 No trial arm BSC cross-over adjustment for OS in Pancreatic NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Using naïve BSC RAD-3 and BSC A6181111 trial results (ITT). I.e. Without cross-over adjustment

This scenario explores the impact on the ICER 177Lu-DOTATATE versus BSC of not adjusting the outcomes of the BSC population for attrition to the active arms of the trials.

						177Lu-DOTATATE versus:		
		BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	Sunitinib
Life-years*	Pre	0.570	1.279	1.601	3.814			
	Post	**3.773**	3.413	**4.084**	5.003			
QALYs	Pre	0.381	0.813	0.997	2.207			
	Post	**1.945**	1.692	**1.951**	2.050			
Costs	Pre	2,712	27,559	24,566	68,733			
	Post	**15,420**	15,087	**17,202**	17,202			
					Scenario Lifetime ICER	**35,108**	24,714	**34,105**
					c.f. Base case ICER	29,956	24,714	41,967

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 36 Progression as measured by Local Assessment in Pancreatic NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Locally assessed outcomes instead of Central review

The base case model used the RADIANT-3 trial results according to Central review. This scenario analysis uses the alternative result set, as measured by local trial centre clinicians.

						177Lu-DOTATATE versus:		
		BSC	Everolimus	Sunitinib	177Lu-DOTATATE	BSC	Everolimus	Sunitinib
Life-years*	Pre	**0.533**	**1.221**	**1.456**	3.814			
	Post	**3.810**	**3.472**	**4.932**	5.003			
QALYs	Pre	**0.356**	**0.777**	**0.912**	2.207			
	Post	**1.967**	**1.726**	**2.321**	2.050			
Costs	Pre	**2,537**	**27,289**	**22,419**	68,733			
	Post	**15,550**	**15,311**	**19,154**	17,202			
					Scenario Lifetime ICER	**29,444**	**24,702**	**43,286**
					c.f. Base case ICER	29,956	24,714	41,967

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

4.3.6 Univariate Scenario Analyses in Whole GI NETs

The scenario analyses presented below (Table 37 to Table 49) explore plausible alternatives to base case assumptions or input estimates (sources).

Note that we have not presented scenario analyses of the Midgut NETs model since the results of the base case analysis of this sub-population show inferior cost-effectiveness of 177Lu-DOTATAE versus BSC compared to 177Lu-DOTATATE when used across the Whole GI population. Also, the quality of evidence supporting the analysis of midgut NETS is surpasses by that used for Whole GI NETS.

Table 37 Full dose intensity in pre-progression in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Dose intensity of Everolimus, Sunitinib and 177Lu-DOTATATE at 100%

The base case uses includes estimates of dose intensities for everolimus, sunitinib and 177Lu-DOATATE from clinical trials, these are all below 100%. In this scenario we remove this assumption and estimate cost-effectiveness at full dose intensity.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	2,642	**42,106**	**76,542**		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	**56,973**	**42,475**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 38 177Lu-DOTATATE dose intensity in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Dose intensity of 177Lu-DOTATATE dose

The base case uses a dose intensity of 94.6%, an estimate derived from usage in ERASMUS, the reference trial of the MAIC. Another plausible estimate for the dose intensity of 177Lu-DOTATATE is that observed in NETTER-1, but adjusted for attrition death on treatment (90.8%).

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	2,642	34,910	**73,261**		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	**47,112**	**64,443**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 39 Duration of everolimus treatment in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Mean duration of treatment with everolimus increased

The base case mean duration of everolimus treatment is 13.3 months, however in this scenario we test a longer duration based on the estimate from the midgut population; this is 16.3 months.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	2,642	**40,938**	72,885		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	56,973	**53,330**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 40 Increased resources for disease monitoring

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Alternative approach to disease monitoring utilisation rate

Disease monitoring in the base case in included for the whole period of disease until death, using . In this scenario

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	2,642	34,910	72,885		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	**48,314**	**65,120**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 41 First-cycle post-progression costs in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Including the cost of therapies bundled into the first cycle of treatment post-progression

In the base case analysis, the use of Chemoembolization, Radiotherapy and Chemotherapy (the cost of which were applied only to the first cycle post-progression) was not included despite observed utilisation post-progression in the RADIANT-3 trial. Here we have re-introduced these costs.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	2,642	34,910	72,885		
	Post	**15,883**	**21,601**	**19,189**		
				Scenario Lifetime ICER	**47,477**	**61,719**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 42 Alternative sources of utility estimates

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Alternative sources of utility estimates

In GI NETs the base case pre-progression utility estimates were based on a Novartis treatment arm analysis of RAD-4 for everolimus and BSC (0.767 and 0.807 respectively); and the ERASMUS study for 177Lu-DOTATATE (0.77). Post-progression the estimates for patients on all treatments were based on a Novartis pooled estimate of arms in RAD-4 (0.725). In this scenario a mix of alternative plausible sources are used: pre-progression a pooled RAD-4 analysis for everolimus and BSC (0.779), and the Guy's and St Thomas' registry for 177Lu-DOTATATE (0.79); post-progression the treatment arm analysis of RAD-4 for everolimus and BSC (0.714 and 0.747 respectively), and the ERASMUS study for 177Lu-DOTATATE (0.74).

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	**0.705**	**1.192**	**2.003**		
	Post	**2.404**	**2.891**	**2.656**		
Costs	Pre	2,642	34,910	72,885		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	**48,674**	**62,043**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 43 No background mortality in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Removing adjustment for background mortality in PFS and OS event rate

The treatment strategies of the GI analyses include in the base case an adjustment for the effect of all-cause age specific mortality in the background event rates. In this analysis this adjustment is removed, leaving a naïve rate.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	**0.902**	**1.652**	**2.883**		
	Post	**4.285**	**6.594**	**5..526**		
QALYs	Pre	**0.706**	**1.197**	**2.005**		
	Post	**2.535**	**3.491**	**2.800**		
Costs	Pre	**2,644**	**34,940**	**72,894**		
	Post	**14,661**	**20,558**	**17,177**		
				Scenario Lifetime ICER	**46,524**	**297,048**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 44 Parametric curve choice for PFS in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Using Lognormal instead of Weibull

Statistical exploration and clinical validity drove the choice in the base case of the Weibull parametric curve for the fitting and extrapolation of progression events across the life-time horizon. Here we test PFS estimates of the 177Lu-DOTATATE strategy by fitting the accelerated failure time distribution the lognormal. The other strategies are unchanged.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	**2.669**		
	Post	3.999	5.168	**5.282**		
QALYs	Pre	0.705	1.192	**1.898**		
	Post	2.404	2.891	**2.777**		
Costs	Pre	2,642	34,910	**78,037**		
	Post	14,115	17,697	**17,075**		
				Scenario Lifetime ICER	**50,061**	**71,765**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 45 Parametric curve choice for OS in Whole GI NETs

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Using Lognormal instead of Exponential

Statistical exploration and clinical validity drove the choice in the base case of the Exponential parametric curve for the fitting and extrapolation of death events across the life-time horizon. Here we test OS estimates of the 177Lu-DOTATATE strategy by fitting the accelerated failure time distribution the lognormal. The other strategies are unchanged.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	**4.242**		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	**2.360**		
Costs	Pre	2,642	34,910	72,885		
	Post	14,115	17,697	**15,050**		
				Scenario Lifetime ICER	**56,797**	**126,046**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 46 Alternative definition of BSC 1

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

BSC: No supportive therapies in stable disease except SSRAs, used with increased dose and prevalence (High dose Octreotide, 60mg, in 40% pts)

The base case simulation of the BSC strategy uses estimates taken from the observed rates of resource utilisation in the RAD-4 RCT, which was 1% of patients, using Octreotide 30mg. Expert clinical advice suggests this is a low estimate versus real-world usage in this population, so this sensitivity analysis presents a plausible alternative to the base case.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	**9,851**	34,910	72,885		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	**42,216**	63,792
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 47 Alternative definition of BSC 2

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

BSC: No supportive therapies in stable disease except SSRAs, used with increased dose and prevalence (High dose Octreotide, 60mg, in 100% pts)

The base case simulation of the BSC strategy uses estimates taken from the observed rates of resource utilisation in the RAD-4 RCT, which was 1% of patients, using Octreotide 30mg. Expert clinical advice suggests this is a low estimate versus real-world usage in this population, so this sensitivity analysis presents an alternative to the base case designed to demonstrate the extent of impact of high SSRA usage in BSC in stable disease. This scenario is one where SSRAs are essentially used as per the design of the comparator arm of NETTER-1, but note that SSRAs are not used here adjunct to 177Lu-DOTATATE, as was the design of NETTER-1.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	**21,203**	34,910	72,885		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	**34,888**	63,792
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 48 'Real world' SSRA approach

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Generally higher use of SSRAs versus base case

This scenario tests a general increase in SSRA usage versus the base case; when used with and without concurrent active treatment, and both pre and post progression. Estimates prevalence and dose of Octreotide is based on expert clinical opinion: Octreotide 30mg in 90% of pts pre-progression, reducing to 85% post-progression. This level is maintained whether or not pts are treated with other active treatments (i.e. 177Lu-DOTATATE or Everolimus).

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	**11,059**	**49,736**	**75,529**		
	Post	**44,468**	**53,948**	**49,904**		
				Scenario Lifetime ICER	**45,126**	**37,745**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

Table 49 177Lu-DOATATE administration as Day Case

Effected values are high-lighted bold. Estimates are deterministic discounted means, costs in £s.

Increase in the proportion of patients administered 177Lu-DOTATATE as Day case

This scenario assumes a greater number of patients will be able to leave hospital care following 177Lu-DOTATATE treatment and observation versus the base case. In the base case the estimate for the proportion of day case administrations was 10%, based on the average of estimates from two clinical experts in Nuclear medicine with experience of 177Lu-DOTATATE preparation and administration. Here we increase this proportion to 65% of patients, which may represent a plausible near future scenario.

					177Lu-DOTATATE versus:	
		BSC	Everolimus	177Lu-DOTATATE	BSC	Everolimus
Life-years*	Pre	0.901	1.644	2.878		
	Post	3.999	5.168	5.029		
QALYs	Pre	0.705	1.192	2.003		
	Post	2.404	2.891	2.656		
Costs	Pre	2,642	34,910	**72,695**		
	Post	14,115	17,697	16,479		
				Scenario Lifetime ICER	**46,747**	**63,461**
				c.f. Base case ICER	*46,870*	*63,792*

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. *Life years are presented as undiscounted.

4.3.7 Comparison of AG results with AAA deterministic base case results

Table 50 and

Table 51 present AG and company results for P-NETS and GI NETS, respectively, side-by-side. Company results are those produced and displayed by the company model (version submitted February 2018). Strategy selection are based on those that produce the base case ICERs described in the company's report (version submitted February 2018).

Unfortunately the results in P-NETS have an error in the calculations for the sunitinib strategy. We have presented the result in any case since we cannot present the results presented in the report because they cannot be substantiated by the model. As a result we cannot comment here on the comparison of sunitinib strategies between models

Pancreatic NETS

For P-NETS, as the figures in the last three columns of Table 50 show, AAA produced three different set of estimates of costs, QALYs and ICERs for 177Lu-DOTATATE, one set for each comparator (BSC, everolimus and sunitinib). The reason for having as many estimates of costs and health outcomes of its sponsored targeted therapy, is that AAA performed MAIC of the ERASMUS P-NETS sample to each of the two arms of RADIANT-3 separately, everolimus plus BSC and BSC only (AAA ID1224 submission to NICE December 8, 2018, Table 15), and to the sunitinib arm of A6181111. This complicates the interpretation of results since the numbers refer to at least two and possibly three different patient populations. Instead the AG matched the sunitinib arm by Bucher indirect comparison method and the ERASMUS arm by MAIC to the same population of RADIANT-3 as a whole (rather than each of the everolimus plus BSC and the BSC arms separately as the company did). It is worth noting how different AAA's cost and QALY estimates for 177Lu-DOTATATE are even between arms of the same RADIANT-3 trial population: the life years before progression for 177Lu-DOTATATE after MAIC re-weighting to match the BSC arm of RADIANT-3 is 3.063; versus 2.714 after MAIC re-weighting to match the everolimus arm of the same trial.

Table 50 Comparison of incremental summary results in Pancreatic NETs

(Discounted deterministic means, costs in £s. Company results are extracted from their model using the base case strategy descriptions given in their report)

		BSC		**Everolimus**		**Sunitinib**		**177Lu-DOTATATE**			
		AG	Company	AG	Company	AG	Company*	AG	Company (v BSC)	Company (v Evero')	Company (v Sun')*
Life years**	Pre	0.570	0.635	1.279	1.288	1.601	*0.173*	3.814	3.063	2.714	*14.480*
	Post	2.893	2.736	3.413	2.823	4.787	*0*	5.003	4.022	3.383	*0*
	Total	**3.463**	**3.372**	**4.692**	**4.111**	**6.388**	*0.173*	**8.817**	**7.085**	**6.098**	*14.480*
QALYS	Pre	0.381	0.511	0.813	1.000	0.997	*0.131*	2.207	2.415	2.140	*11,418*
	Post	1.534	2.163	1.692	2.231	2.241	*0*	2.050	3.179	2.674	*0*
	Total	**1.914**	**2.674**	**2.505**	**3.231**	**3.238**	*0.131*	**4.257**	**5.594**	**4.814**	*0*
Costs	Pre	2,712	16,153	27,559	33,511	24,566	*4,735*	68,733	65,090	64,213	*86,987*
	Post	13,049	36,316	15,087	37,462	18,627	*0*	17,202	54,197	45,592	*0*
	Total	**15,761**	**52,470**	**42,646**	**70,974**	**43,192**	*4,735*	**85,935**	**119,288**	**109,805**	*86,987*
ICER, 177Lu vs.		**29,956**	**22,883**	**24,714**	**24,526**	**41,967**	*7,287*	**-**	**-**	**-**	**-**

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. Company estimates are from the AAA model selections as driven by the results reported in the submission: **BSC** = Octreotide LAR (P-NETs –MAIC) (Faivre et al. 2016); **Everolimus** = Everolimus (P-NETs – MAIC); **Sunitinib** = Sunitinib (P-NETs – MAIC) [Faivre et al. 2016]; **177Lu** = Lutathera (P-NETs –MAIC). Note: Comparator selections in the company model are not independent, so 177Lu-DOTATATE strategy results are different with each choice of comparator. All three are presented. *These strategy results suggest an error in the model.Feb18 (and Jan18 version); the ICER given in the company report is £15,433. **Life years are presented as undiscounted.

By comparing the disaggregated pancreatic NETS strategy results within and across models (Table 50) the drivers behind the differences become apparent. In respect to 177Lu-DOTATATE, everolimus, and BSC, the models produce similar estimates of life-years gained for respective strategies as well as agree their ranking in effectiveness: each model predicting 177Lu-DOTATATE to produce the most QALYs, then everolimus then BSC. Whilst the AG model predicts slightly higher life year gains than the company model, the average disutility and discounting loss in the AG model is twice that of the company's (range of 0.45 to 0.49, versus 0.21). The resultant trend is for a lower QALY gain in the AG model across strategies. However, in respect to the ICERs, the ratio of costs to QALYs gained, there are large differences in costs between models and these are what drive the differences in ICERs. For P-NETS (and also GI NETS) the cause of the difference in costs between models arises largely from the way SSRAs are incorporated (see Section 2.6) I.e. in more patients and at greater doses in the company model.

The cost of BSC prior to progression in the company model, versus the AG model, is nearly 600% more costly. And post progression the difference approaches 300%. In the former instance the reason is that 100% of patients in in the BSC strategy receive high dose octreotide; versus 40% who receive low dose octreotide in the AG model (Table 20). Therefore, there is a considerable added drug cost in the company's estimate of BSC. Similarly, the high post-progression estimate in the company model is due to the added cost of octreotide (all patients go to low dose). However, these two dynamics have an opposing effect on the 177Lu-DOTATATE versus BSC ICER, since patients in the 177Lu-DOTATATE strategy live longer and consume resources (octreotide) post-progression for longer. Even so, when the AG model is adjusted to replicate the extreme utilisation of octreotide in BSC pre-progression, the ICER drops from the base case £29,565 per QALY gained, to £25,976 (compared to the company ICER of £22,883). The remaining difference in the ratio between the two models may arise from: a lower cost of administration of 177Lu-DOTATATE in the company model (ICER drops from £25,976 to £25,178); 177Lu-DOTATATE dose intensity (switching from ERASMUS to NETTER-1 dose intensity reduces the ICER further to £22,882); and variation in the methodology used to estimate health effect between the models (not quantified).

The ICERs for 177Lu-DOATATE versus everolimus across models are similar; the AG ICER is about £3,000 higher (£24,714 versus £24,526). Again, this margin may comprise effects from multiple areas, such as 177Lu-DOTATATE dose intensity (switching from ERASMUS to NETTER-1 intensities reduces the ICER to £21,553); 177Lu-DOATATE administration cost (using the company unit cost reduces the ICER further to £20,576); as well as variation in methods used to estimate health effect size.

It is not possible to compare between models the ICERs for 177Lu-DOATATE versus sunitinib for the reasons mentioned above.

Whole GI NETS

As was the case with the ICER results in the P-NETs analysis, the AG's GI-NETS analysis when compared to the company's produced higher ICERs: for both 177Lu-DOTATATE versus BSC, and 177Lu-DOTATATE versus everolimus. Although here we see that the differences are larger and the AG estimates fall above the conventional threshold for cost-effectiveness: £46,870 per QALY gained in the AG analysis versus £20,741 (56% lower), and £63,672 versus £22,227 (65% lower), for comparisons versus BSC and everolimus respectively. The reasons for these large differences may be explained in the comparison with BSC by the company's definition of BSC (I.e. high dose octreotide for all, leading to large costs); and in the comparison with everolimus, by the company's low estimate of its effectiveness. The AAA model estimates a whole QALY less per person over a lifetime following treatment with everolimus, compared to the AG model. The large discrepancy in survival estimates for everolimus and 177Lu-DOTATATE produced by the company and AG is explained by the fact that the company's results were derived from using OS data from the GI/Lung RADIANT-4 patient group, whereas the AG had access to the data for the GI only patient group in RADIANT-4, as provided by Novartis as part of responses to the Assessment Report for ID858. This meant that AAA severely underestimated the proportional amount of life extension past disease progression in the BSC and in the everolimus plus BSC arms of RADIANT-4 in GI patients. For example, according to AG estimates patients live on average 2.75 times the mean number of years lived without progression under 177Lu-DOTATATE-treated vs. 4.14 times under everolimus. In contrast, the company's estimates based on GI and lung patients, are respectively 1.83 versus 2.3. When other differences in assumptions/input estimates are changed in the AG model to match those in the company model, (to ubiquitous high dose octreotide use in BSC pre-progression; lower 177Lu-DOTATATE administration cost and dose intensity), the ICERs versus BSC and everolimus fall to £42,205 and £51,251 respectively. However, when the adjustment for background mortality (specific to the GI-NETS analysis) is removed, these ICER increase to £42,904 and £234,962.

Sensitivity analyses of AG results, including changing the survival curves for all treatments, support the observation that AAA's results are severely limited by their lack of data in the GI only population.

Table 51 Comparison of incremental summary results in Whole GI NETs

(Discounted means, costs in £s) AAA model version February 2018, with updated GI-NETs MAIC analysis

		BSC		Everolimus		177Lu-DOTATATE	
		AG	Company	AG	Company	AG	Company
Life years*	Pre	0.901	1.671	1.644	1.728	2.878	2.794
	Post	3.999	2.328	5.168	2.272	5.029	2.328
	Total	**4.900**	**3.999**	**6.812**	**4.000**	**7.907**	**5.123**
QALYS	Pre	0.705	1.325	1.192	1.310	2.003	2.216
	Post	2.404	1.724	2.891	1.683	2.656	1.724
	Total	**3.109**	**3.049**	**4.082**	**2.992**	**4.658**	**3.940**
Costs	Pre	2,642	42,488	34,910	44,599	72,885	60,500
	Post	14,115	30,900	17,697	30,159	16,479	31,375
	Total	**16,757**	**73,388**	**52,607**	**74,757**	**89,364**	**91,875**
ICER, 177Lu vs.		**46,870**	**20,741**	**63,792**	**22,227**	**-**	**-**

Key: BSC = Best Supportive Care; ICER = Incremental Cost Effectiveness Ratio; NETs = Neuroendocrine Tumours. Company estimates are from the AAA model selections as driven by the results reported in the submission: **BSC** = Octreotide LAR (GINET - MAIC); **Everolimus** = Everolimus (GINET – MAIC); **177Lu** = Lutathera (GINET – MAIC). The 177Lu strategy was not selected with Octreotide 30mg (in line with reported base case result), and the BSC care strategy was selected as high dose 60mg octreotide (in line with reported base case result). *Life years are presented as undiscounted.

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Appendix 1. Results including Patient Access Schemes

This appendix is supplied as a separate document entitled **'Neuroendocrine tumours (metastatic, unresectable, progressive) - 177 Lu-DOTATATE [ID1224] Appendix 1 Results with Patient Access Schemes CONFIDENTIAL.**'

Progression free survival: Matched-adjusted indirect comparison (MAIC) HR (95% CI)

	Pancreatic[1]	Whole GI[2]	GI midgut[2,3]
177Lu-DOTATATE vs			
Everolimus	0.20 (0.11, 0.34)	0.38 (0.21, 0.66)	0.65 (0.34, 1.23)
Sunitinib	0.22 [4] (0.10, 0.48)	N/A	N/A
BSC	0.07 (0.04, 0.12)	0.21 (0.12, 0.38)	0.43 (0.21, 0.85)

[1] RADIANT-3 as reference population. [2] RADIANT-4 as reference population. [3] Matching was to baseline characteristics of whole GI subgroup (66% of which were midgut only) of RADIANT-4, since no baseline data were available for the whole GI subgroup. [4] Estimates based on Bucher indirect comparison of HR for sunitinib vs. BSC in A6181111 (0.32, 95% CI: 0.18-0.55; Faivre et al. 2017) and the MAIC HR for 177Lu-DOTATATE vs BSC arm in RADIANT-3 in the table. N/A: Data not available

Overall survival: Matched-adjusted indirect comparison (MAIC) HR (95% CI)

	Pancreatic[1]	Whole GI[2]	GI midgut[2]
177Lu-DOTATATE vs			
Everolimus	0.54 (0.33, 0.88)	0.55 (0.27, 1.11)	N/A[4]
Sunitinib	0.65 [3] (0.16, 2.54)	N/A	N/A
BSC	0.22 (0.10, 0.50)	0.34 (0.16, 0.69)	N/A[5]

[1] RADIANT-3 as reference population. [2] RADIANT-4 as reference population. [3] Estimates based on Bucher indirect comparison of HR for sunitinib vs. BSC in A6181111 (0.34, 95% CI: 0.14, 1.28; Faivre et al. 2017) and the MAIC HR for 177Lu-DOTATATE vs. BSC arm in RADIANT-3 presented in the table. The study by Faivre et al. provides Kaplan-Meier curves for the A6181111 trial, 5 years after study closure (Faivre et al. 2017). Kaplan-Meier curves used for the BSC arms in RADIANT-3 and A6181111 trials were adjusted for cross-over using the RPSFT model. [4] In the economic model, the everolimus arm was assumed to have the same outcomes as everolimus in Whole GI. [4] In the economic model, the BSC arm was assumed to have the same outcomes as BSC arm in Whole GI. N/A: Data not available.