NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

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

Contents:

- Royal College of Physicians
- NHS England

7 Expert personal statements from:

- Dr Martin Eatock – clinical expert, nominated by Pfizer
- Mark Zwanziger – patient expert, nominated by the Net Patient Foundation

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

Premeeting briefing
Everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression

This slide set is the premeeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Assessment Group (AG) report.

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the AG before the company has checked the AG report for factual inaccuracies.

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting.

Section 1: Background

Content	Slide number
Disease background and management	3 - 4
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Neuroendocrine tumours (NETs)

- Heterogeneous group of rare tumours that develop from the gastrointestinal tissue, pancreas, lung and thyroid
- Approximately 45-65% of NETs occur in the gastrointestinal tissue, approximately 3-7% in the pancreas and 10% in the lungs
- Can be 'functional' or 'non-functional
- Grade of the tumour gives an idea of how quickly it will develop

  low (grade 1) } **well differentiated**
  moderate (grade 2) }
  high grade tumours (grade 3) - **poorly differentiated**

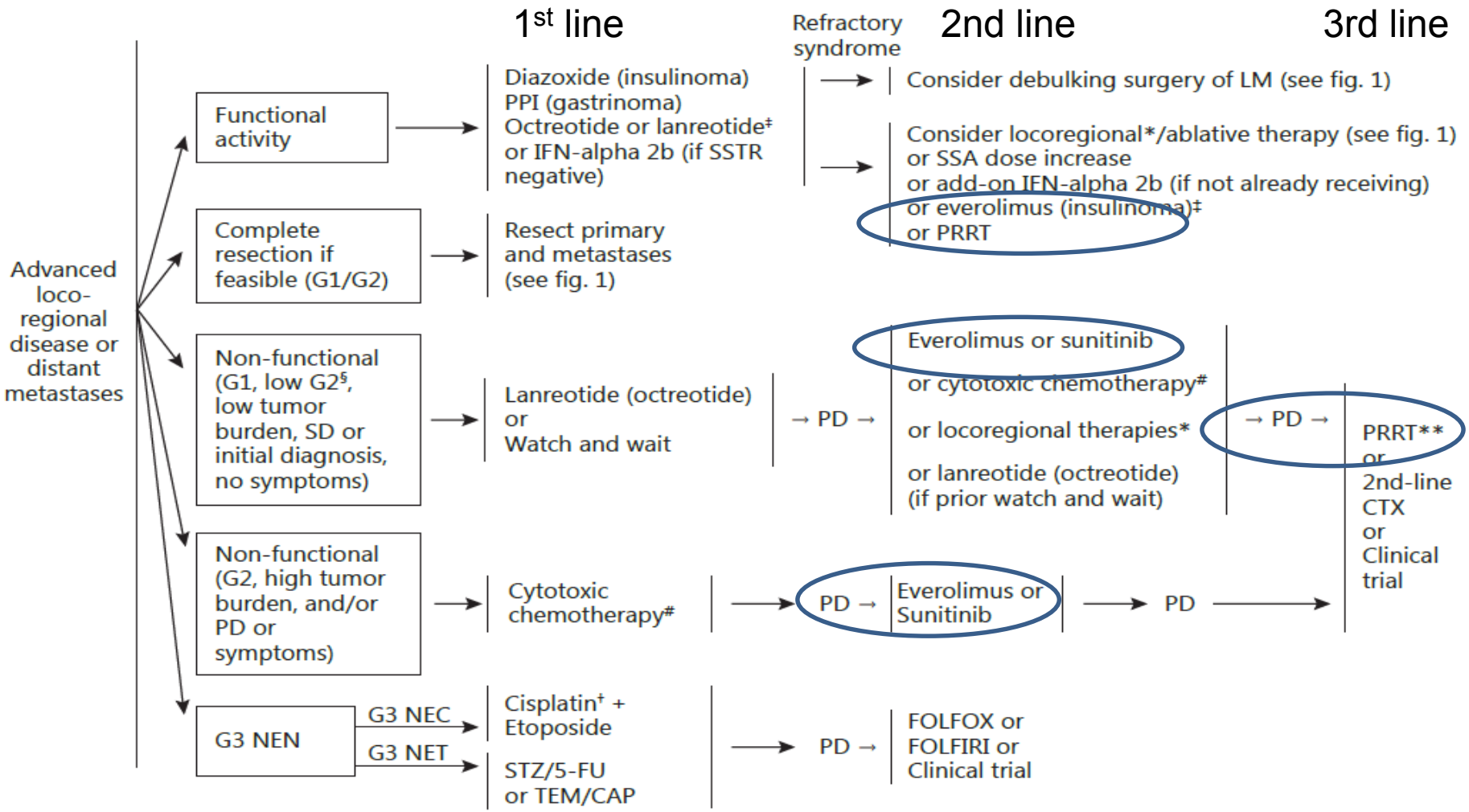
- Ki-67 proliferative index (Ki-67 index) is also used as a prognostic measure for grading parameters for NETs

  Grade 1 is equivalent to a Ki67 index of up to 3%
  Grade 2 is equivalent to a Ki67 index between 3-20%
  Grade 3 is equivalent to a Ki67 index beyond 20%

Neuroendocrine tumours
(Management)

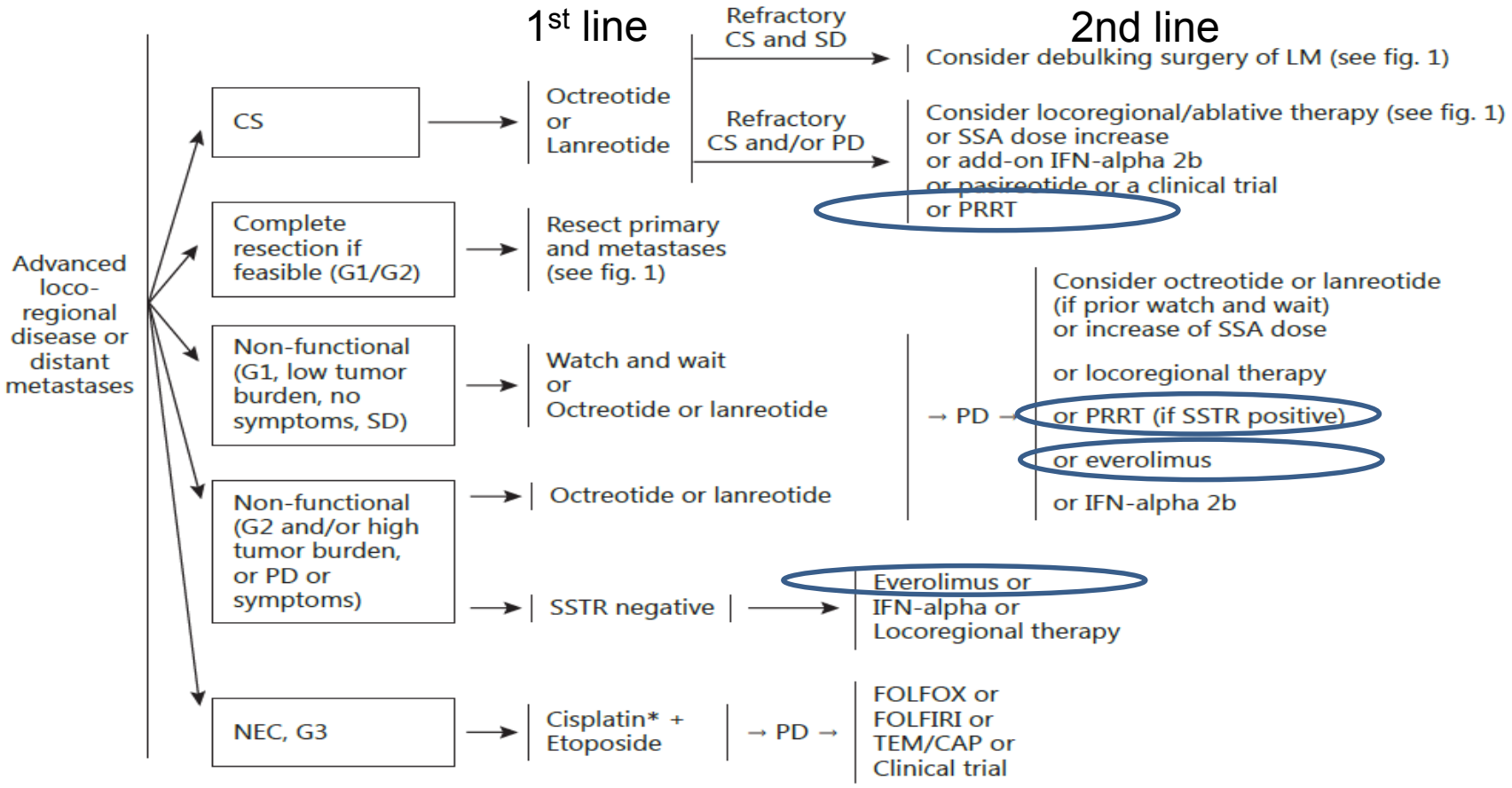
- No NICE guidance on neuroendocrine tumours
- Surgery is the only curative treatment
- Options for treating neuroendocrine tumours that have progressed include
  - somastatin analogues (e.g octreotide, lanreotide)
  - chemotherapy regimens (using combinations of streptozocin, 5-fluorouracil, doxorubicin, temozolomide and capecitabine)
  - radionuclides (e.g lutetium-177 – previously on the CDF)
  - everolimus (previously on the CDF)
  - Sunitinib (currently on the CDF)
- Treatment pathways for pancreatic and GI NETs presented on next slides
- Limited data for lung NETs.
  - ENETS guidelines recommends everolimus for progressive lung NETs

Treatment pathway: Pancreatic NETs



Source: Novartis submission, figure 3.1, page 29
Original source: Pavel et al 2016, ENETs-recommended treatment algorithm

Treatment pathway: GI NETs



Abbreviations: 5-FU: 5-fluorouracil, CAP: capecitabine, CS: carcinoid syndrome, CTX: chemotherapy, FOLFIRI: folinic acid, 5-FU, irinotecan, FOLFOX: folinic acid, 5-FU, oxaliplatin, IFN: interferon, LM: liver metastases, NEN: neuroendocrine neoplasm, PD: progressive disease, PRRT: peptide receptor radionuclide therapy, SD: stable disease, SSA: somatostatin analogue, SSTR: somatostatin receptor, STZ: streptozotocin, TEM: temozolomide.

Source: Pavel *et al.* 2016

Source: Novartis submission, figure 3.1, page 29

Original source: Pavel et al 2016, ENETs-recommended treatment algorithm

Impact on patients and carers

NET Patient foundation and Patient expert comment

- There is a high unmet need in patients with lung NETs, and patients with GI NETs who have progressed following current therapy as there is no NICE guidance in this disease area
- A diagnosis of GEP-NET and the use of subsequent treatments has a significant impact on patients and their families in many ways
- NETs are very challenging tumours to treat due to the complexity and variety of clinical behaviours
- They can vary greatly, depending upon their site of origin and functionality
- Symptoms associated with NET hormonal hypersecretion may impair patients' QoL and in some instances can be life-threatening (e.g. severe diarrhoea and hypokalaemia in VIPomas) (Ramage et al. 2012)
- GEP-NETs are often at an advanced stage at the time of diagnosis and are often deemed incurable
- Historically, treatments often improved symptoms but not always overall survival
- Although the development of new treatments has improved progression-free survival but has also increased toxicity
- Patient's experience with Lu177 DOTATATE has been positive with significant improvement to length of life and quality of life

Clinical perspectives

British Institute of Radiology and British Nuclear Medicine Society

- Majority of well differentiated NETS express somatostatin receptors on their surface which can be targeted by somatostatin receptor based radionuclide therapy
- Lu-177 DOTATATE is an effective treatment and place in treatment algorithms is recommended by several international guidelines including ENETS Consensus Guidelines (2016)
- Lu-177 DOTATATE is promoted as second-line therapy for disease progression after first-line therapy with SSA's.
- The guidelines also recommend its use as third-line therapy after Everolimus in non-midgut NETs
- In patients with progressive disease Lu-177 DOTATATE stabilises disease and prolongs survival and side effects are uncommon
- QOL of life analysis in 39 consecutive patients at the Royal Free London NHS Foundation Trust demonstrated a significant improvement in QOL in patients treated with Lu-177 DOTATATE in neuroendocrine tumours
- Lu-177 DOTATATE is a safe and efficacious treatment for patients with metastatic neuroendocrine tumours
- Number of centres in the UK already providing Lu177 DOTATATE
- No further resources would be required for provision of Lu177 DOTATATE

DETAILS OF THE TECHNOLOGIES			
Technology	Lutetium-177 DOTATATE (Lutathera)	Everolimus (Afinitor)	Sunitinib (Sutent)
Marketing authorisation	• [redacted]	• unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease • unresectable or metastatic, well-differentiated (grade 1 or grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease	• unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults
Administration	Intravenous Infusion (IV)	Oral	Oral
Acquisition cost	• [redacted] • A single cycle comprising four administrations of 7.4 GBq. The recommended interval between two infusions is eight weeks (± 1 week).	• The list price for everolimus is £2,673.00 for 30 x 10 mg everolimus tablets • A confidential PAS is available	• Pack of 28, 12.5 mg capsules £784.70. • Pack of 29, 25 mg capsules £1,569.40. • Pack of 28, 50 mg capsules £3,138.80.
Cost of a course of treatment	• [redacted]	• List price is expected to be between £23,495.67 and £24,912.36 • A confidential PAS is available and details are presented in a confidential appendix	• Monthly cost of 37.5 mg/day of sunitinib is £2354.10 at list price.

The decision problem

Final scope issued by NICE		AG comments
Population	People with progressed unresectable or metastatic neuroendocrine tumours (according to the specific locations covered by the existing and anticipated marketing authorisations of the interventions)	The AG population is consistent with the NICE scope
Intervention	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • Lutetium-177 DOTATATE (neuroendeocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)	The AG included all of these interventions
Comparators	• the technologies listed above will be compared with each other where appropriate • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care	The AG consulted with clinicians and were told that interferon alpha was not commonly used within UK clinical practice. Therefore, it was not included
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life	The AG considered and included all of these outcome measures

Section 2: Clinical effectiveness evidence

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Pancreatic NETs: Clinical Trials

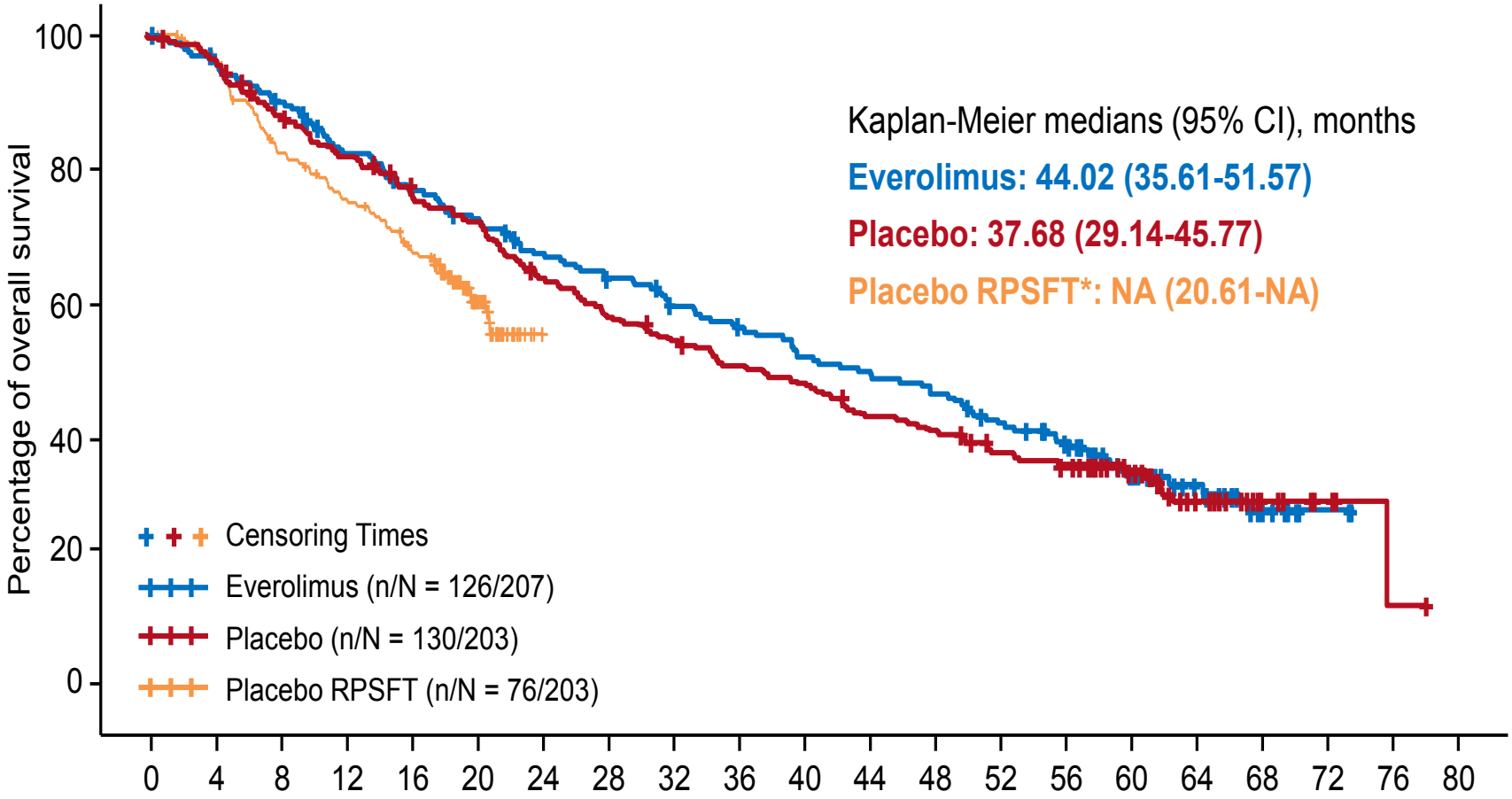
Trial	RADIANT-3 – everolimus plus BSC Vs. placebo plus BSC	A6181111 – sunitinib plus BSC Vs. placebo plus BSC
Design	• Double-blind, randomised, placebo-controlled phase III	• Randomised, double-blind, phase 3 study
Population	• Patients with advanced, progressive, low- or intermediate-grade P-NETs	• Patients with progressive well-differentiated P-NETs
Outcomes	• Primary endpoint - PFS (locally assessed according to RECIST) • Secondary endpoints - OS, DoR, ORR and safety	• Primary endpoint – PFS • Secondary endpoints - OS, ORR, TTR, DoR, EORTC QLQ-C30 (HRQoL)
Other	• Concurrent SSA use allowed (37.7 % and 39.9% in the everolimus and placebo arms respectively) • Crossover from the placebo arm to the treatment arm was 73%	• SSA use permitted both before and during the trial • Cross-over allowed (at disease progression) in one of two separate, open-label extension studies • 69% placebo patients crossed over to sunitinib

RADIANT-3 Results

Novartis submission, tables 4.3 – 4.5 (pages 37 – 44)

Outcomes	Local assessment		Adjudicated central review	
Progression-free survival (PFS)				
	Everolimus + BSC (n=207)	Placebo + BSC (n=203)	Everolimus + BSC (n=207)	Placebo + BSC (n=203)
PFS, median, months HR [p-value]	**11.0** (8.4 – 13.9)	**4.6** (3.1 – 5.4)	**11.4**	**5.4**
	0.35 (95%, 0.27–0.45)		**0.34** (95%, 0.26 – 0.44)	
Overall survival (OS) with adjustment for cross-over (Final OS analysis, March 2014, open label phase)				
OS, median, months HR [p-value]	**44.02**	**37.68**	-	
	0.94 (95%, 0.73–1.20)			
Tumour response rates				
Partial response	**10** (4.8)	**4** (2.0)	• Results from the central reviews were similar to those reported for the local review • Compared with placebo, everolimus was associated with a superior response profile according to RECIST	
Stable disease	**151** (72.9)	**103** (50.7)		
Progressed disease	**29** (14.0)	**85** (41.9)		

RADIANT-3 Overall Survival



No. of patients still at risk

Everolimus	207	194	181	163	152	142	130	122	112	105	97	93	87	77	67	39	22	10	2	0	0
Placebo	203	195	175	162	150	140	123	113	104	96	91	81	77	68	64	45	25	10	6	1	0
Placebo RPSFT	203	189	159	143	125	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Source: Novartis submission, figure 4.7, page 45

RADIANT-3 subgroup analyses

PFS subgroup analysis			
Covariate	**Subgroup**	**N**	**HR (95% CI)**
Tumour grade:	Well differentiated	341	**0.41** (0.31, 0.53) P<0.001
	Moderately differentiated	65	**0.21** (0.11, 0.42) P<0.001
Previous chemotherapy	Yes	189	**0.34** (0.24,0.49) P<0.001
	No	221	**0.41** (0.29,0.58) P<0.001
Previous long-acting SSA use	Yes	203	**0.40** (0.28,0.57) P<0.001
	No	207	**0.36** (0.25,0.51) P<0.001
OS subgroup analysis			
Covariate	**Subgroup**	**N**	**HR (95% CI)**
Previous chemotherapy	Yes	189	
	No	221	**0.78** (0.61, 1.01) P=0.056
Previous long-acting SSA use	Yes	203	
	No	207	**1.15** (0.89, 1.49) P=0.288
Sources: Assessment report, tables 29 – 30, page 96			

A6181111 Results (1)

Pfizer submission, section 4.7, pages 42 - 50

Outcomes	Investigator assessment		Independent review	
	Sunitinib (n=86)	Placebo (n=85)	Sunitinib (n=86)	Placebo (n=85)
Progression-free survival				
PFS, median, months	**11.4** (7.4 – 19.8)	**5.5** (3.6 – 7.4)	**12.6** (11.1 - 20.6)	**5.8** (3.8 - 7.2)
HR [p-value]	**0.418** (95% CI: 0.263, 0.662)		**0.315** (0.181, 0.546)	
Overall survival				
OS unadjusted for cross over, median, months	**38.6** (25.6 – 56.4)	**29.1** (16.4 – 36.8)	-	
HR [p-value]	**0.73** (0.50 – 1.06)			
Adjustment for crossover, median, months – RPSFT (placebo)	-	**13.2** (11.3 – 16.5) **HR 0.34** (0.14 – 1.28)	-	
Censoring at crossover – IPCW (placebo)	-	**16.3** (12.5 – 24.3) **HR 0.40** (0.23 – 0.71)	-	

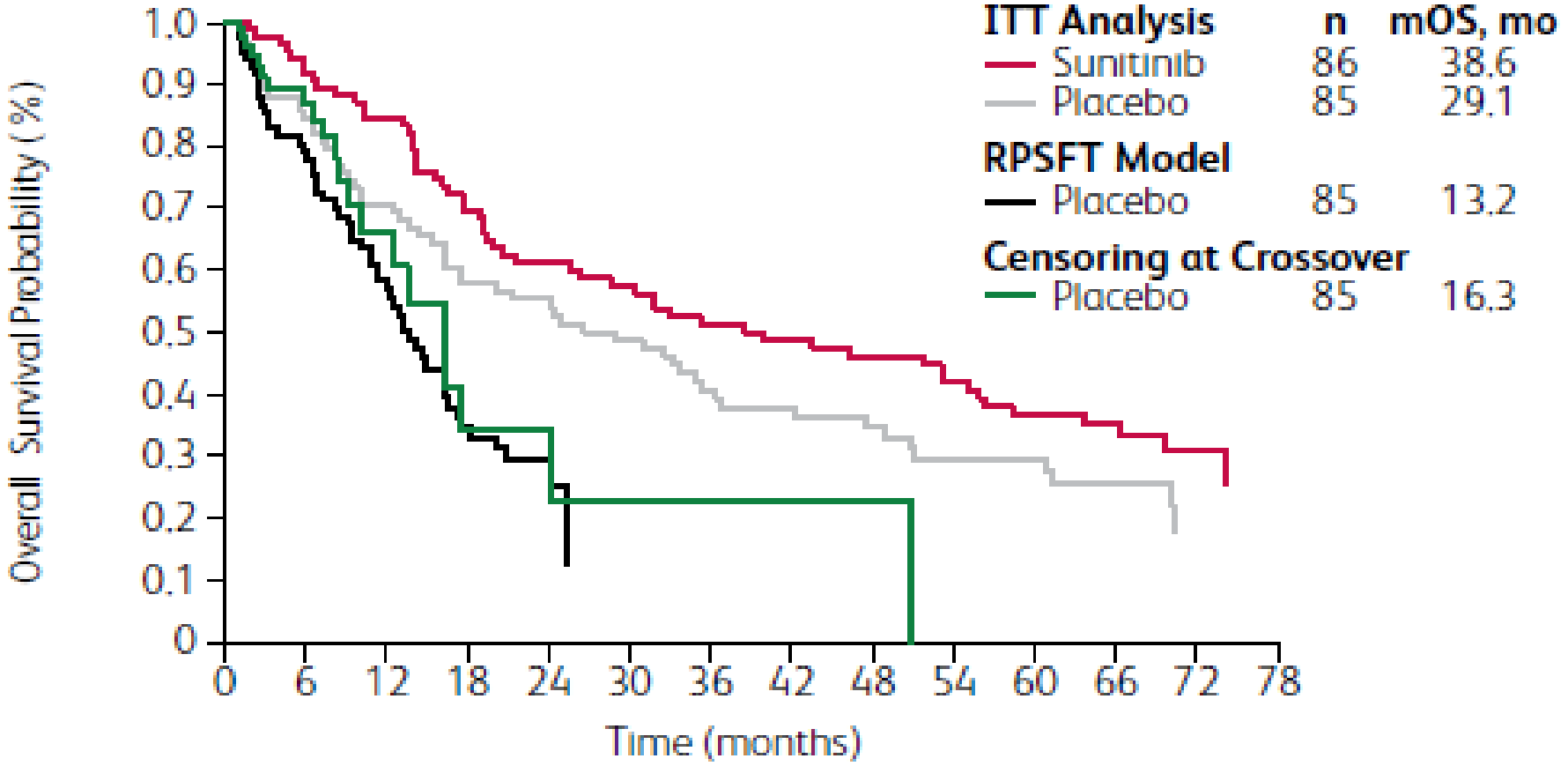
A6181111 Results (2)

Pfizer submission, section 4.7, pages 42 - 50

	Sunitinib (N = 86)	**Placebo (N = 85)**
Progression-free survival (PFS) ITT population		
Number censored	**56** (65.1%)	**34** (40.0%)
Probability of being event free at 6 months (95% CI)	**71.3%** (95% CI, 60.0%, 82.5%)	**43.2%** (30.3%, 56.1%)
Overall-survival (OS) ITT population		
Number censored	**77** (89.5%)	**64** (75.3%)
Probability of survival at 6 months (95% CI)	**92.6%** (95% CI: 86.3%, 98.9%)	**85.2%** (95% CI: 77.1%, 93.3%)
Tumour response rates ITT population		
Complete response (CR)	**2** (2.3%)	**0** (0.0%)
Partial response (PR)	**6** (7.0%)	**0** (0.0%)
Stable/no response (SD)	**54** (62.8%)	**51** (60.0%)

A6181111 Overall Survival

Kaplan-Meier estimate of overall survival with and without adjustment for crossover, final analysis, ITT population (source: Raymond et al. 2016[11])



Source: Pfizer submission, figure 6 (page 48)

A6181111 subgroup analyses

PFS subgroup analysis (using cox proportional hazards)			
Covariate	**Subgroup**	**N**	**HR (95% CI)**
Tumour functionality	Functioning	86	**0.26** (0.13, 0.54)
	Not Functioning	46	**0.75** (0.30, 1.84)
No. of previous systemic regimens	0 or 1	121	**0.33** (0.19,0.59)
	≥2	50	**0.61** (0.27,1.37)
Previous use of SSA	Yes	68	**0.43** (0.21,0.89)
	No	103	**0.41** (0.22,0.75)
Sources: Assessment report, table 28, page 96			

GI and Lung NETs: Clinical Trials

Trial	RADIANT-4: everolimus plus BSC Vs. placebo plus BSC	NETTER-1: 177Lu-DOTATATE plus octreotide 30mg Vs. octreotide LAR (60 mg)
Design	• Double-blind, randomised, placebo-controlled phase III trial	• Stratified, open, randomised, comparator-controlled, parallel-group phase III
Population	• Patients with advanced, progressive, low- or intermediate-grade GI and Lung NETs	• Patients with inoperable, progressive (as determined by RECIST Criteria), somatostatin receptor positive, midgut NETs of the small bowel
Outcomes	• Primary endpoint - PFS (locally assessed according to RECIST) • Secondary endpoints - OS, DoR, ORR and safety	• Primary endpoint - PFS Independent Review Centre (IRC) • Secondary endpoints – OS, DoR, ORR, TTP, safety, tolerability and HRQoL
Other	• Crossover after progression was not allowed • More than half had previous SSA therapy (mostly for tumour control) • Quarter received prior chemo • HRQoL: FACT-G questionnaire	• All patients received prior therapy • Concomitant systemic therapy was not permitted

RADIANT-4 results: GI and Lung NETs combined

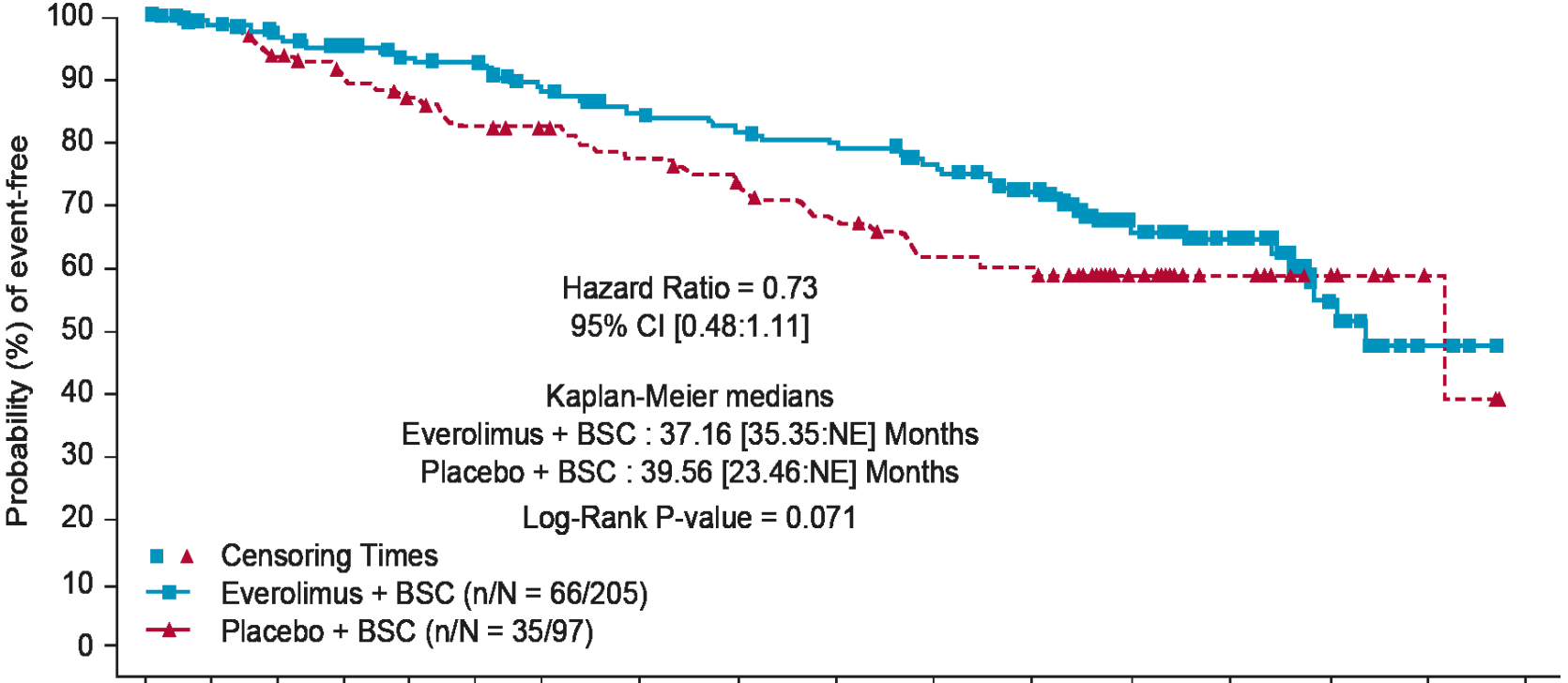
Novartis submission, tables 5.4 and 5.5 (pages 66 – 74)

Progression-free survival (PFS) - central review (Primary data cut, November 2014)		
	Everolimus + BSC (n=207)	Placebo + BSC (n=203)
PFS, median, months HR [p-value]	**11.0** (9.2 – 13.3)	**3.9** (3.6 – 7.4)
	0.48 (95%, 0.35 – 0.67)	
Overall survival (OS) (Secondary data cut, November 2015)		
OS, median, months HR [p-value]	**37.16** (35.35 – NE)	**39.56** (23.46 – NE)
	0.73 (95%, 0.48 – 1.11)	
Tumour response rates (n %) - central review (Primary data cut, November 2014)		
Partial response (PR)	**4** (2.0)	**1** (1.0)
Stable disease (SD)	**165** (80.5)	**62** (63.9)
Progressed disease (PD)	**19** (9.3)	**26** (26.8)

The AG stated that there is little evidence of a difference in PFS within subgroups according to treatment history, previous chemotherapy, previous SSA and tumour grade

RADIANT-4 Overall survival: GI and Lung NETs

Kaplan-Meier plot for OS estimates: secondary data cut-off (30th November 2015)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	15	18	21	24	27	30	33	36	39	42
Everolimus + BSC	205	195	185	180	173	171	160	148	142	138	130	115	76	42	19	3	0
Placebo + BSC	97	94	86	80	75	70	67	62	57	51	45	43	28	18	10	3	0

-[1] P-value is obtained from the stratified log-rank test.

Source: Novartis submission, figure 5.12, page 73

RADIANT-4 results: GI NETs only

Assessment report, tables 47- 49 (page 110)

Progression-free survival (PFS) - central review		
	Everolimus + BSC (n=118)	Placebo + BSC (n=57)
PFS, median, months	**13.1** (9.2, 17.3)	**5.4** (3.6, 9.3)
HR [p-value]	**0.56** (0.37, 0.84)	
Overall survival (OS)		
OS, median, months	[redacted]	[redacted]
HR [p-value]	[redacted]	
Tumour response rates (n %)		
Stable disease (SD)	[redacted]	[redacted]
Progressed disease (PD)	[redacted]	[redacted]

RADIANT-4 results: Lung NETs only

Assessment report, tables 52 - 54 (page 112)

Progression-free survival (PFS)		
	Everolimus + BSC (n=63)	Placebo + BSC (n=27)
PFS, median, months	**42** (CI not recorded)	**18** (CI not recorded)
HR [p-value]	**0.50** (0.28-0.88)	
Overall survival (OS)		
OS, median, months	[redacted]	[redacted]
HR [p-value]	[redacted]	
Tumour response rates (n %)		
Partial response (PR)	[redacted]	[redacted]
Stable disease (SD)	[redacted]	[redacted]
Progressed disease (PD)	[redacted]	[redacted]

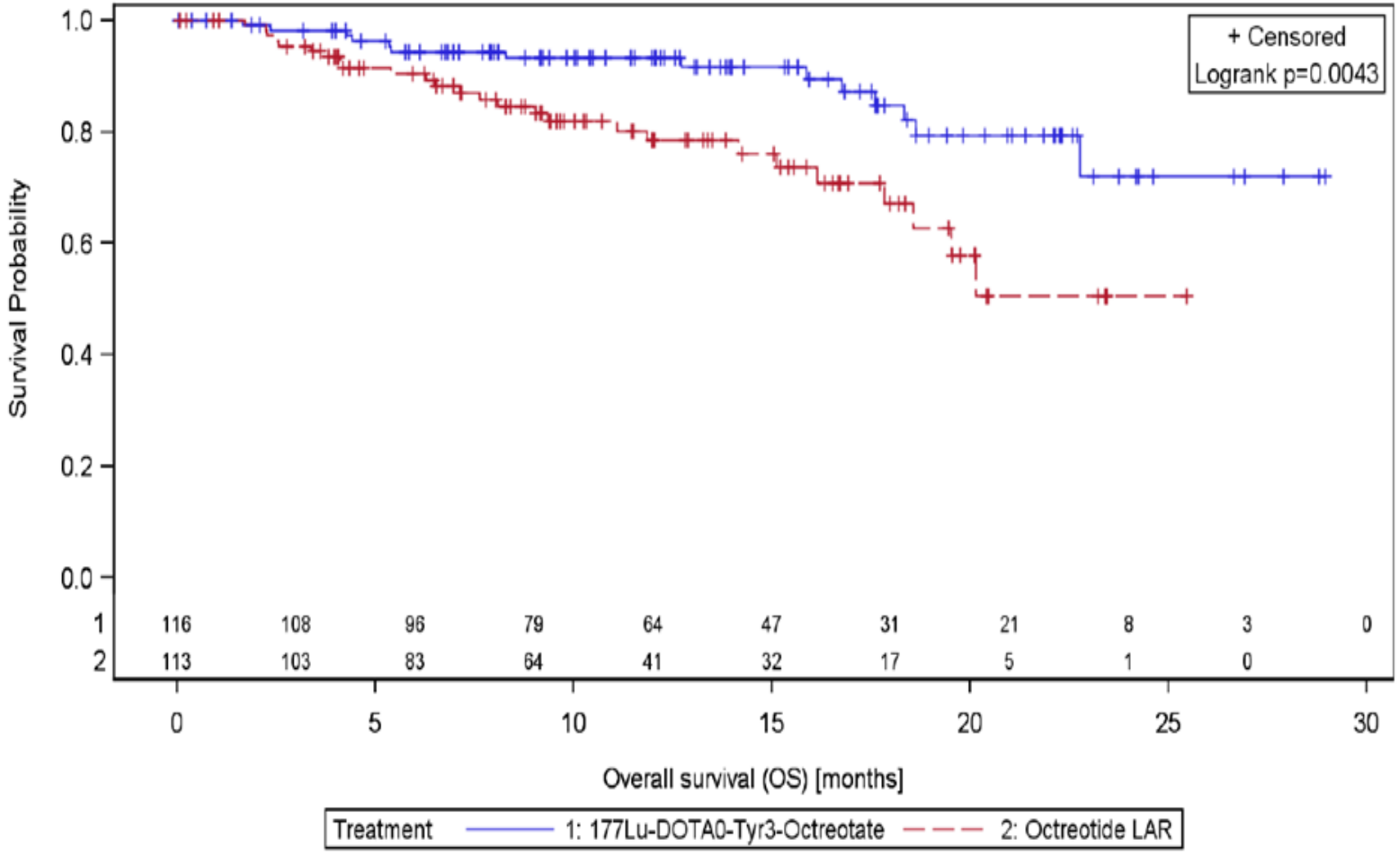
NETTER-1 Results

AAA submission, tables 13 and 14, page 50 –53

Outcomes	Independent IRC	
Progression-free survival (PFS)		
	177 Lu-DOTATATE + Placebo (n=116)	Octreotide LAR (n=113)
PFS, median, months HR [p-value]	Not reached	8.4
	0.25 (95%, 0.13 – 0.33)	
Patients with events (n)	23	68
Censored patients (n)	93	45
Overall survival (OS) (Interim analysis)		
OS, median, months HR [p-value]	Not reached	Not reached
	0.398 (95%, 0.207 – 0.766)	
Patients with events (n)	14	26
Censored patients (n)	102	87
Objective response rate (ORR)		
Overall response rate (all patients)	15.5%	2.7%
	(95%, 10.4 – 25.4)	(95%, 0.0 – 6.3)

NETTER-1 Overall Survival

OS interim analysis, full analysis set



Source: AAA submission, figure 10, page 52

Health-related quality of life (HRQoL)

- Everolimus (RADIANT-3 and RADIANT-4)
  - **RADIANT-3**
    - Not collected
  - **RADIANT-4**
    - Everolimus had longer median time to definitive deterioration in HRQoL using FACT-G but not statistically significant
- **Lu-177 DOTATATE (NETTER-1)**
  - Measured using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
  - Mean EORTC QLQ-30 global health status score was slightly improved compared with baseline in the 177Lu-DOTATATE arm at each assessment up to week 108
  - HRQoL results show that treatment with 177Lu-DOTATATE does not negatively affect the patient's HRQoL compared with octreotide LAR
- **Sunitinib (A6181111)**
  - Measured using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3).
  - No statistically significant difference between the sunitinib and placebo groups at any time
  - Baseline EORTC QLQ-C30 scores were comparable with no clinically significant differences

Adverse events (1)

- **RADIANT-3**
  - Most common treatment related AEs occurring in ≥20% of patients were rash (52.5%), stomatitis (53.9%), diarrhoea (48%) and fatigue (44.6%)
  - 13 incidences of treatment discontinuation due to treatment related AE with everolimus compared to 2 with placebo plus BSC
- **RADIANT-4**
  - Serious AEs reported for everolimus and BSC were 42.1% and 19.4% respectively
  - Most common serious AEs related to everolimus were stomatitis (55.0%), diarrhoea (41.1%), peripheral oedema (38.6%), fatigue (37.1%), and rash (30.2%)
  - Treatment related SAE: 20.8% for everolimus and 6.1% for placebo
  - Most common treatment-related AEs (of any grade) reported by patients receiving everolimus were stomatitis (63%), diarrhoea (31%), fatigue (31%), infections (29%), rash (27%), and peripheral oedema (26%)
  - 69 deaths in the trial 20.3% for everolimus and 28.6% for placebo arm

Adverse events (2)

- **NETTER-1**
  - 177Lu-DOTATATE was relatively well tolerated
  - Incidence of AE and SAE judged to be treatment-related higher with 177Lu-DOTATATE than with octreotide LAR
  - Incidence of grade 3-5 AEs with 177Lu-DOTATATE was low
  - Incidences of Grade 3-5 AEs was comparable except for vomiting and lymphopenia
  - 5 incidences of treatment discontinuation due to treatment related AE with 177Lu-DOTATATE compared with 0 for octreotide
- **A6181111**
  - AEs were more common in the sunitinib group
  - Proportion experiencing SAEs was greater in the placebo group (41.5%, versus 26.5% with sunitinib)
  - Most common treatment-related AEs reported in the sunitinib arm were diarrhoea, nausea and asthenia, all of which were experienced by at least 30% of patients
  - 35 and 15 people (42% and 18%) from the sunitinib and placebo groups respectively, temporarily discontinued from treatment due to adverse events

Review of clinical trials by AG (1)

RADIANT 3, RADIANT 4 and A6181111

- 6 systematic reviews and 3 trials were included in the AG review: RADIANT-3, RADIANT-4 and A6181111

- No studies were found for comparing everolimus or sunitinib to interferon alpha or chemotherapy (comparators included in the scope)

- Additional search to find RCTs that compared chemotherapy to best supportive care (BSC) or placebo (to inform an ITC)
  - No studies were identified

- All 3 trials double blind - low risk of bias in all

- Populations for the 3 trials all in line with the licensed indication for each treatment and with final scope

- Limited information for current prevalence of NETs to assess generalisability
  - The applicability of the results in the UK setting was unclear

Review of clinical trials by AG (2)

RADIANT 3, RADIANT 4 and A6181111

- Baseline characteristics similar between the two arms for the 3 trials
  - Overall, differences in baseline characteristics unlikely to affect clinical effectiveness results
- All a priori outcomes reported in the protocols were reported in the trials
  - ITT analysis performed in all trials
- Changes in participant numbers for reported AEs were poorly reported by all 3 trials
- Proportions of individuals who had received previous treatments were variable between RADIANT-3 and A6181111
- High levels of crossover in RADIANT-3 and A6181111 (73% and 69%)
- Information on subsequent treatment is important but unknown

Review of clinical trials by AG (3)

NETTER-1

'Normally, we would not report in detail the results of the NETTER-1 RCT, because it concerns a comparator which is not in the NICE Scope. However, we do this here on request from NICE, as it is the pivotal trial that will underpin the anticipated marketing authorisation for lutetium and informs our economic analysis for lutetium'

- NETTER-1 separated out P-NETs and GI-NETs
- No participants had P-NETs
- It is unclear if octreotide 60mg can be assumed to be equivalent to placebo and placebo + octreotide 30mg

Section 3: Indirect and Mixed Treatment Comparisons

Everolimus vs sunitinib (P-NETs)

Novartis submission

- Bucher indirect comparison using data from RADIANT-3 and A6181111
- PFS local investigator assessment – **HR 0.83** (0.49, 1.42)
- PFS blinded independent review committee - **HR 1.08** (0.59, 1.99)
- OS ITT analysis – **HR 1.32** (0.81, 2.16)
- OS RPSFT-adjusted analysis – **HR 1.40** (0.17, 11.72)
- No significant difference in SSA use between everolimus and sunitinib
- Higher rate of grade 3/4 AEs for sunitinib compared with everolimus
- Results from a published matched-adjusted indirect comparison (MAIC) also presented, but the Bucher ITC results was preferred for the economic model

Comments from Assessment Group

- Inconsistent results for PFS between central review and local review
- Wide confidence intervals for all results highlighting uncertainties
- Very different results when using crossover unadjusted and adjusted results
- Results for response rates are associated with wide confidence intervals suggesting little difference between the two treatments
- Unclear why the Bucher had been used over the MAIC, however, they have similar results and Bucher has more mature data

Sunitinib vs everolimus (P-NETs)

Pfizer submission

- MAIC using patient-level data from A6181111 and aggregate data from RADIANT-3
- PFS:
  - [redacted]
  - [redacted]
- OS:
  - [redacted]
  - [redacted]

Comments from Assessment Group

- MAIC here could not adjust for differences in study design across trials
- RADIANT-3 and A6181111 populations were similar (but differences existed)
  - Termination/trial size/imaging frequency
- Balanced baseline characteristics in RADIANT-3
- Imbalanced baseline characteristics in A6181111
  - more prior use of chemotherapy and less use of radiotherapy
- Small sample size (which after matching halved in size)

177Lu DOTATATE vs everolimus vs sunitinib (P-NETs)

AAA submission

- Mixed treatment comparison including results from NETTER-1, RADIANT-3 and A6181111
- PFS MTC analysis
  - 177Lu DOTATATE vs everolimus: **HR 0.60** (0.04, 9.92)
  - 177Lu DOTATATE vs sunitinib: **HR 0.50** (0.03, 8.60)
- OS MTC analysis
  - 177Lu DOTATATE vs everolimus: **HR 0.38** (0.07, 2.28)
  - 177Lu DOTATATE vs sunitinib: **HR 0.98** (0.15, 6.46)

Comments from Assessment Group

- No justification that octreotide LAR 60mg is equivalent to placebo, placebo + octreotide (30mg) and placebo + BSC
- NETTER-1 should be excluded from the P-NETs network: does not contain any patients with P-NETs
- No consideration of treatment switching for the trials included
- Wide confidence intervals suggesting uncertainty
- Models used not reported in the submission and so no comparison of any differences in point estimates

177Lu DOTATATE vs everolimus (GI-NETs)

AAA submission

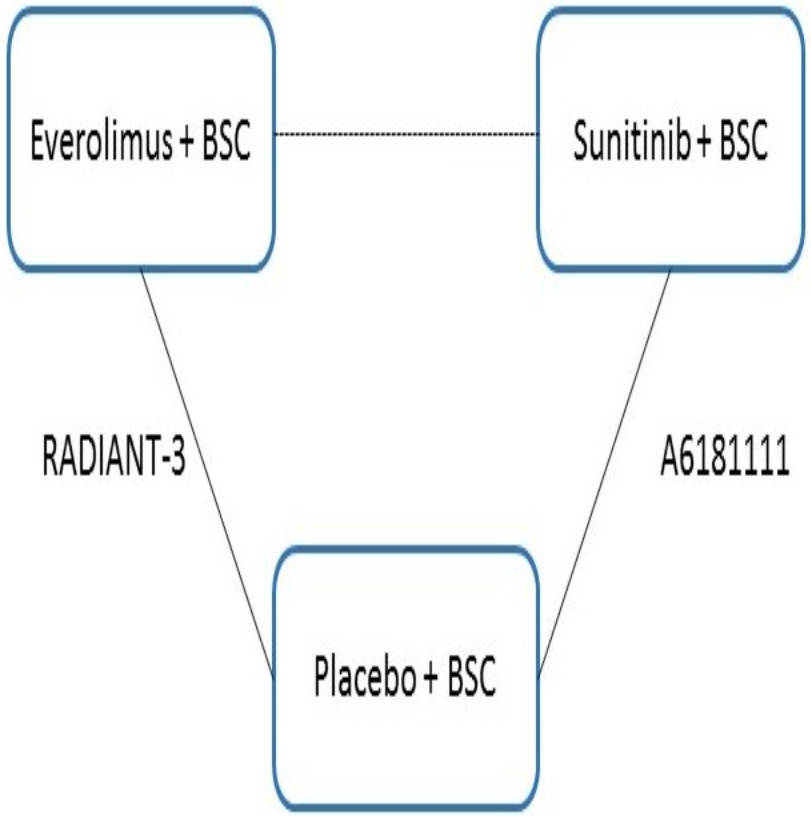
- Indirect treatment comparison comparing results from NETTER-1 and RADIANT-4
- PFS MTC analysis:
  - 177Lu DOTATATE vs Everolimus: **HR 0.43** (0.05, 4.24)
- OS MTC analysis:
  - 177Lu DOTATATE vs Sunitinib: **HR 0.43** (0.09, 2.12)

Comments from Assessment Group

- No justification that octreotide LAR 60mg is equivalent to placebo placebo+octreotide (30mg) and placebo+BSC
- RADIANT-2 should be excluded: population all have functioning tumours (outside MA for everolimus for GI-NETs)
- For GI NETs populations for OS differ across the three studies
- No consideration of treatment switching for the trials included
- Wide confidence intervals suggesting uncertainty
- not reported in the submission and so no comparison of any differences in point estimates

Everolimus Vs Sunitinib (P-NETs)

Assessment Group



- RADIANT-3 and A6181111 are comparable to allow an ITC
- Bucher method used – but no analyses for heterogeneity between the trials or inconsistency (only 2 trials)
- Outcomes – PFS, OS, RR, AEs
- Higher proportion of SSA use in RADIANT-3 (40%) compared to A6181111 (28%),
  - Not thought that this would affect the relative effectiveness of the treatments
- ITC should be interpreted with caution

Source: Assessment report, figure 17 (page 98)

ITC – PFS results (P-NETs)

AG Report

HRs (95% CIs) for **(local review)** disease progression or death in P-NETs			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus	Placebo	RADIANT-3	[redacted]
Sunitinib	Placebo	A6181111	[redacted]
Everolimus	Sunitinib	Calculated by AG ITC	[redacted]
Source: Assessment report, table 31 (page 99)			

HRs (95% CIs) for **(central review)** disease progression or death in P-NETs			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus+BSC	Placebo+BSC	RADIANT-3	[redacted]
Sunitinib+BSC	Placebo+BSC	A6181111	[redacted]
Everolimus+BSC	Sunitinib+BSC	Calculated by AG	[redacted]
Source: Assessment report, table 32 (page 99)			

ITC – OS results (P-NETs)

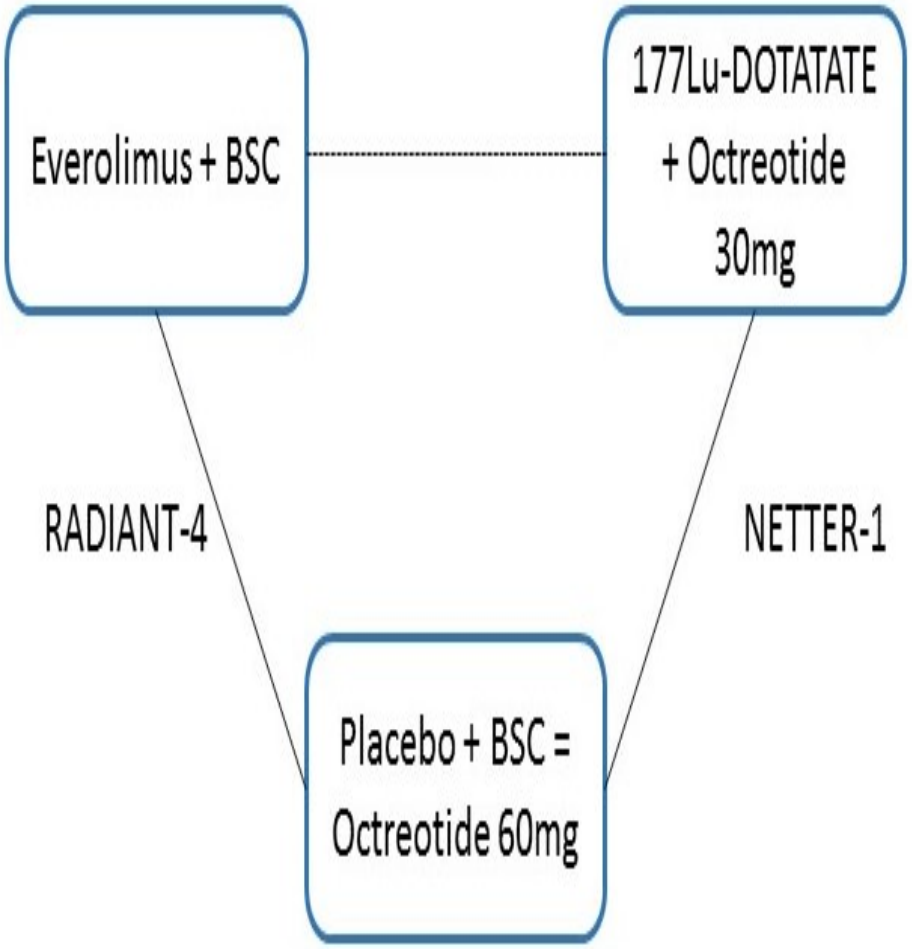
AG Report

HRs (95% CIs) OS in P-NETs based on published HRs from RADIANT-3 and A6181111 **(crossover unadjusted)**			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus	Placebo	RADIANT-3	[redacted]
Sunitinib	Placebo	A6181111	[redacted]
Everolimus	Sunitinib	Calculated by AG	[redacted]
HRs (95%CI) for death P-NETs based on final follow-up data **(crossover unadjusted)**			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus	Placebo+BSC	RADIANT-3	[redacted]
Sunitinib	*Placebo+BSC*	A6181111	[redacted]
Everolimus	*Sunitinib+BSC*	Calculated by AG	[redacted]
HRs (95%CI) for death P-NETs **(crossover adjusted RPSFT)**			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus	Placebo+BSC	RADIANT-3	[redacted]
Sunitinib	*Placebo+BSC*	A6181111	[redacted]
Everolimus	*Sunitinib+BSC*	Calculated by AG	[redacted]

Sources: Assessment report, table 33 (page 99), Source: Assessment report, table 34 (page 100) and Assessment report, table 35 (page 100)

Lutetium-177 Vs everolimus (GI-NETs)

Assessment Group



- AG assumed that placebo+BSC can be considered equivalent to octreotide 60mg
- RADIANT-4 does not report outcomes for the subgroup of participants with GI NETs only (only combined group of GI+lung NETs)
- Different tumour locations included under term GI in the two RCTs
  - NETTER-1 only midgut NETs
  - RADIANT-4 fore-, mid- and hind-gut NETs
- Bucher used to indirectly compare everolimus to 177Lu-DOTATATE for GI NETs: central review PFS, OS , RR and various AEs
- Analyses for heterogeneity or inconsistency between trials was not possible
- ITC should be treated with caution

Source: Assessment report, figure 28 figure 29 (page 141 and 142)

ITC – PFS & OS results (GI-NETs)

AG Report

HRs (95% CIs) for (**central review** of) disease progression or death in GI NETs			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus+BSC	Placebo+BSC	RADIANT-4	**0.56** (0.37, 0.84)
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1	**0.21** (0.13, 0.33)
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG ITC	**0.37** (0.19, 0.69)
Source: Assessment report, table 67 (page 144)			

HRs (95% CIs) for OS in GI NETs			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus+BSC	Placebo+BSC	RADIANT-4	[redacted]
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1	**0.40** (0.21, 0.77)
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG ITC	[redacted]
Source: Assessment report, table 68 (page 145)			

Cost effectiveness evidence

Note. results in these slides do NOT reflect the unapproved and approved patient access schemes for sunitinib and everolimus respectively (List prices used for all the technologies)

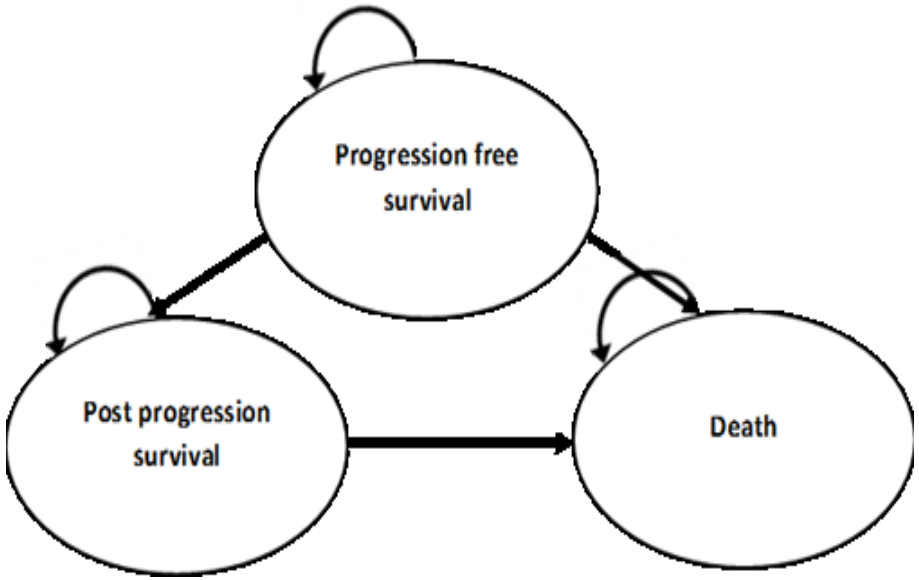
Please see AG's confidential appendix for results relating to PAS details

COMPANY MODELS

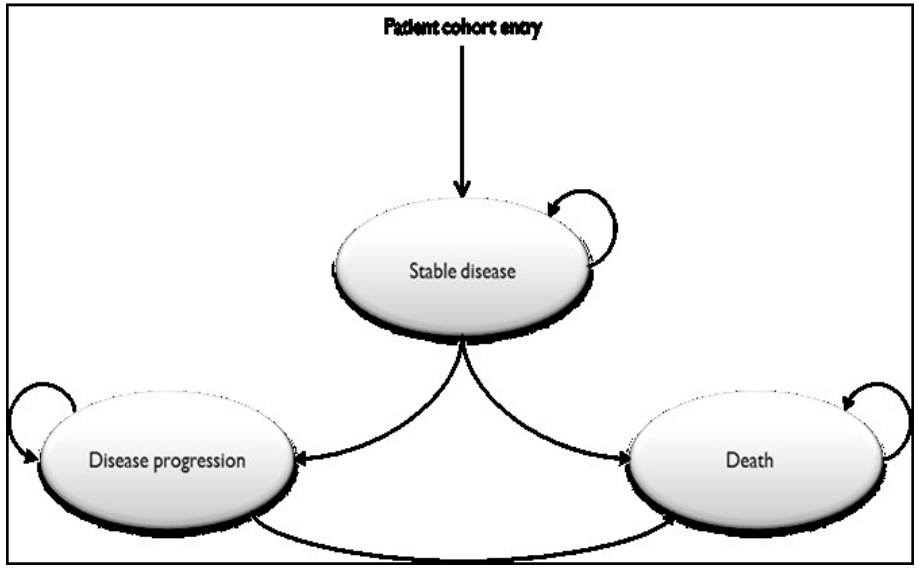
1. Novartis
    a. Pancreatic NETs
    b. GI/Lung NETs
2. AAA
    a. GI NETs
    b.Pancreatic NETs

*Pfizer did not submit an economic analysis for this appraisal

Company model structures



AAA
(Source: Company submission, figure 15, page 113)



Novartis
(Source: Company submission, figure 6.1,page 84)

Base case results from Novartis

Novartis P-NETs Results							
Technology	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Inc costs (£)**	**Inc LYG**	**Inc QALYs**	**ICER (£/QALY)**
Sunitinib	38,568.97	4.177	2.711	-	-	-	-
Everolimus	36,933.11	4.177	2.733	-1,635.86	0.000	0.021	**DOMINANT**
Source: Novartis submission, table 6.16, page 109							

Novartis GI and Lungs Results							
Technology	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Inc costs (£)**	**Inc LYG**	**Inc QALYs**	**ICER (£/QALY)**
BSC alone	25,817.42	4.775	3.508	-	-	-	-
Everolimus plus BSC	59,720.14	5.793	4.285	33,902.72	1.018	0.777	**£43,642.24**
Source: Novartis submission, table 7.17, page 1							

AG's critique of Novartis P-NETs model

- Did not meet NICE reference case as it excluded BSC as a comparator
- As HRQoL for everolimus was not collected in the trial, it was based on vignettes of stable disease (described by professionals descriptions)
- OS data: adjusted for crossover using RPSFT
  - RPSFT assumption that people derive the same benefit from targeted therapy whether given at initial diagnosis or after progression is questionable
  - A sensitivity analyses looking at a reduction in benefit should have been performed
- Bucher ITC used evidence which was outdated
  - When using new data: AG adjusted OS HR for everolimus vs sunitinib of **0.51** instead of the **0.72** (Novartis)
- *AE data from A6181111 was different to data submitted by Pfizer
  - Using Pfizer data: pooled AE OR: **4.47** becomes **1.37**, therefore reducing differences in costs and disutilities of AEs between sunitinib and everolimus
- The way effectiveness and safety evidence was combined in the model inadequately reflected the available information
- Assumption of equal OS and PFS efficacy was based on wide CI
  - This misrepresents the level of uncertainty on the data
- Assumption of same treatment duration was also incorrect (sunitinib likely to be lower)
- Choice between sunitinib and everolimus hinges on their relative effects on PFS and OS and drug acquisition costs
- High levels of uncertainty related to clinical effectiveness
- Disutility of adverse events is unlikely to be a significant factor but impossible to test the magnitude

Source: Assessment report, section 6.1.1.4.3

AG's critique of Novartis GI and Lung model

- Relies on the quality of RADIANT-4
- A major limitation is omission of 177Lu-DOTATATE as a relevant active comparator
- Lack of a separate analysis for GI patients and Lung patients
- Lack of resource data – data estimates were only taken from a sample of patients
- Not clear how robust the estimated costs of subsequent treatment use are likely to be because of issues such as administrative censoring
- Crossover was restricted, but 10 people did and no adjustment was done for this
- Estimation of the costs of subsequent treatments were not correct
- However, unlike P-NETs important data such as BSC treatment use, everolimus treatment duration and intensity, and incidence of Grade 3/4 AEs are well-reported
    - Due to these, reduced uncertainty in comparison to the P-NETs

Source: Assessment report, section 6.1.2.4.3

Base case results from AAA

AAA P-NETs Results							
Technology	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Inc costs (£)**	**Inc LYG**	**Inc QALYs**	**ICER (£/QALY)**
177Lu-DOTATATE	[redacted]	[redacted]	[redacted]				
Everolimus	[redacted]	[redacted]	[redacted]	£21,489	2.75	2.18	**£9,847.46**
Sunitinib	[redacted]	[redacted]	[redacted]	-£6,648	0.07	0.10	**Dominant**
Source: AAA submission, table 69 -70, page 154							

AAA GI-NETs Results							
Technology	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Inc costs (£)**	**Inc LYG**	**Inc QALYs**	**ICER (£/QALY)**
177Lu-DOTATATE	[redacted]	[redacted]	[redacted]	-	-	-	-
Everolimus	[redacted]	[redacted]	[redacted]	£28,099	1.77	1.42	**£19,816**
Source: AAA submission, table 68, page 153							

AG's critique of AAA GI and P-NET model

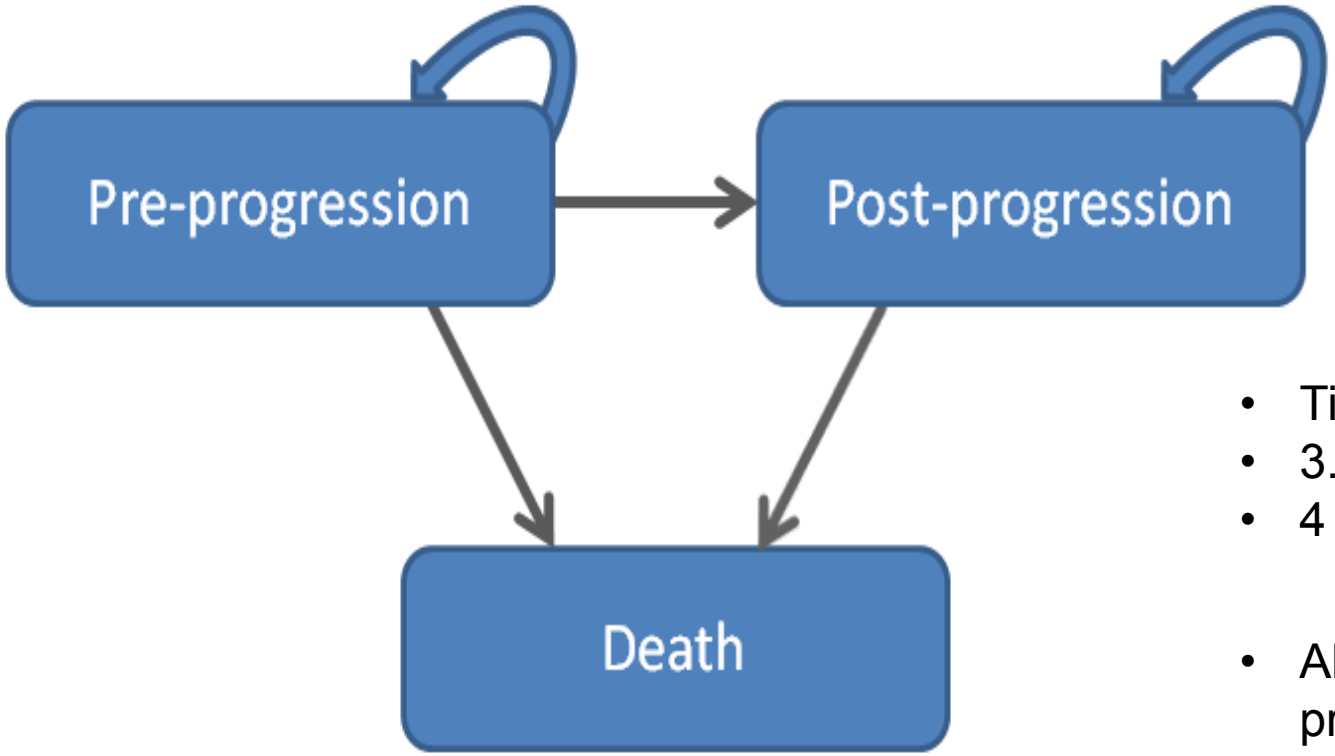
- Analyses correctly separated P-NETs and GI-NETs
- Structurally the model was well implemented and, straight-forward and easy to understand
- SAE were incorporated (but not well)
- Only minor wiring errors that did not have a large impact
- Similar to the Novartis P-NETs model, no comparison made to BSC
- MTC comparison uncertainties (significant because the results were used in the model)
- These uncertainties included the assumption that 60mg octreotide is clinically the same as placebo and placebo+ octreotide 30mg (GI + P-NETs)
- *Data from NETTER-1 used in P-NETs comparison
- *RADIANT-2 incorrectly included in the GI- NETs MTC
- No consideration of treatment switching in RADIANT-2, 3 or A6181111 (of which their was a significant amount)
- Treatment after progression over-simplified to octreotide across all strategies and up to death
- It was assumed in the model that everolimus and sunitinib were given until progression. This is incorrect and has an impact of costs and QALYs
- *Usage of 177Lu-DOTATATE is underestimated
- *Costing of SAE is inadequate

Source: Assessment report, section 6.2.1.3.3

ASSESSMENT GROUP (AG) MODEL

AG model structure

Structure of PenTAG cost-effectiveness model



- Time horizon = 40 years
- 3.5% discount rate
- 4 weekly cycle length

- All patients start in pre-progression state and transition to post-progression or death

Source: Assessment report, figure 40, page 223

AG model description

	Model	AG notes
Structure	Assumed that: • Patients receive active treatment until disease progression/earlier treatment discontinuation (SAE) as observed in the RCTs • Patients treated with BSC after progression	-
Population	Progressed unresectable or metastatic neuroendocrine tumours from 3 different patient populations according to tumour location: • P-NETs/GI+Lung NETs/GI only NETs	• Choice determined by the available clinical effectiveness RCT data • No subgroups considered as no evidence could be found
Interventions/comparators	• Everolimus • Sunitinib • 177Lu-DOTATATE (in scenario analyses only) • BSC	• All included in the scope • Chemotherapy/ interferon alpha • No evidence found – not included
Source: Assessment report, section 7.1 – 7.4, pages 220 - 225		

AG model comparisons and sources of data

Tumour location	Treatment	Treatment or Comparator	Type of data	Source of data
P-NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-3
	Everolimus	Sunitinib	Indirect comparison	RADIANT-3, A6181111
	Sunitinib	BSC	Head-to-head RCT	A6181111
GI NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4
	Everolimus	177Lu-DOTATATE	Indirect comparison	RADIANT-4, NETTER-1
	177Lu-DOTATATE	BSC	Head-to-head RCT	NETTER-1
GI and lung NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4
Source: Assessment report, table 116, page 225				

Model parameters

	Data source and estimate
Mean age	• PenTAG assumed that all patients are 60 at start of treatment • This was the average age of the trials identified • 63.7 and 61.7 used by AAA in GI and P-NETs respectively
Background mortality	• Not modelled in the base case but scenario analyses are provided • PFS/OS curves were expected to account for it • Background mortality rises as the cohort ages • AAA: modelled in stable state but not in progressed state • This could lead to double counting and under-estimation • Novartis: no inclusion of background mortality
Source: Assessment report, sections 7.1.5.1 and 7.1.5.2	

Base case survival curves – P-NETS

Baseline trial: RADIANT-3

Outcome	Treatment arm	Parametric model used
PFS	Everolimus plus BSC	Weibull model used because it made more reasonable assumption of progression and survival, although the log-logistic had the best fit to RADIANT-3 data
	BSC only	Weibull model used, although log-normal and gamma had the best fit to RADIANT-3 data (placebo arm)
	Sunitinib plus BSC	Exponential model used because it made more reasonable assumption of progression and survival, although the generalised gamma had the best fit to A6181111 data
	Adjustment for ITC	Sunitinib exponential model was adjusted using restricted means in order to derive PFS estimates that were comparable to those in RADIANT-3
OS	Everolimus plus BSC	Exponential model was used.15-year survival = 4% compared with 10% estimated with Novartis's log-normal for the everolimus arm
	BSC only	Exponential model used
	Sunitinib plus BSC	Exponential model used, although log normal had an equally good fit to the OS data from sunitinib in the A6181111 trial
	Adjustment for ITC	Sunitinib exponential model was adjusted to reflect the differences in OS between the placebo arms of A6181111 and RADIANT-3
Source: Assessment report, section 7.1.5.3		

Base case survival curves – GI and Lung

Baseline trial: RADIANT-4

Outcome	Treatment arm	Parametric model used
PFS	Everolimus + BSC	Weibull model used, although the log-normal had the best fit to RADIANT-4 data
	BSC only	Weibull model used, although the cubic spline function had the best fit to the PFS data of the placebo arm in RADIANT-4
OS	Everolimus + BSC	Exponential distributions separately fitted to OS data in the everolimus arm and placebo arm of RADIANT-4 Only extrapolations of the exponential and log-logistic distributions seemed plausible
	BSC only	High degrees of uncertainty are visible for the follow-up period of patients in the placebo arm of RADIANT-4 Exponential curve used here
Source: Assessment report, section 7.1.5.3		

Base case survival curves – GI (midgut only)

Baseline trial: RADIANT-4

Outcome	Treatment arms	Parametric model used
PFS	Everolimus + BSC	Exponential distribution used as it had the best statistical fit (although poor fits to the hazard rates)
	BSC only	Exponential distribution was used although generalised gamma and log normal had similar hazard rates compared to the trial
PFS	Lutetium plus BSC (octreotide 30mg)	Exponential distribution used as its PFS rates were in the middle of the other possible distributions Adjustment applied for difference in expected PFS between the control arms of NETTER-1 and RADIANT-4
OS	Everolimus + BSC	Exponential distribution used (the same OS curve as estimated in the GI and Lung population)
	BSC only	Adjusted exponential function fitted to the OS data from the everolimus arm of RADIANT-4 in the GI/Lung population
	Lutetium plus BSC (octreotide 30mg)	Exponential model was used.15-year survival = 22% (Once adjusted 25%) compared with 3% for the Weibull Adjustment applied for the difference in expected OS between the control arms of NETTER-1 and RADIANT-4 OS data from NETTER-1 immature, comparison of 177Lu-DOTATATE with everolimus very uncertain
Source: Assessment report, section 7.1.5.3		

Adverse events

- P-NETs
  - Estimated from AG ITC using related Grade 3/4 AEs of ≥2% incidence in any active treatment arm

- GI/Lung NETs
  - Probabilities from Novartis model were used (as they were taken from IPD)

- GI (midgut) NETs
  - Everolimus plus BSC and BSC only - grade 3/4 AEs rates for the everolimus and placebo arm reported in a conference poster by RADIANT-4 investigators were used
  - 177Lu-DOTATATE - grade 3/4 AE rates reported in the AAA submission were used

HRQoL

Utilities in pancreatic NETs - Interventions: Everolimus, Sunitinib; Comparator: BSC only						
	Pre-progression			Post-progression		
Treatment	Everolimus + BSC	Sunitinib + BSC	Placebo	Everolimus	Sunitinib	Placebo
N	N/A	86	85	N/A	86	85
Mean utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	0.021	0.021	0.023	0.046	0.046	0.046
Source	Assumed equal to Sunitinib+BSC (taken from A6181111)	Analysis by the AG from IPD from A6181111 provided by manufacturer	Analysis by the AG from IPD from A6181111 provided by manufacturer	Assumed same as sunitinib+BSC (taken from A6181111)	Analysis by the AG from IPD from A6181111 provided by manufacturer	Analysis by the AG from IPD from A6181111 provided by manufacturer
Alternative values*	**0.749**	**0.749**	**0.771**	**0.612**	**0.612**	**0.612**
Source	Swinburn et al. (2012) times ratio of sunitinib to BSC in A6181111	Assumed the same as everolimus	Swinburn et al. (2012) - AE adjusted	Swinburn et al. (2012)	Assumed the same as everolimus	Swinburn et al. (2012)

HRQoL (2)

Utilities in gastrointestinal NETs - Interventions: Everolimus and 177Lu-DOTATATE						
	Pre-progression			Post-progression		
Treatment	Everolimus + BSC	Placebo + BSC	177Lu-DOTATATE	Everolimus + BSC	Placebo + BSC	177Lu-DOTATATE
N	837	281	227	238	143	111
Mean utility	**0.767**	**0.807**	**0.77**	**0.725**	**0.725**	**0.725**
SE	0.010	0.015	0.005	0.010	0.010	0.010
Source	Treatment arm analysis using IPD from RADIANT-4 (Novartis, 2016).		Erasmus study (AAA Ltd., 2016)	Pooled analysis of individual patient data from RADIANT-4 (Novartis, 2016)		Assumed the same as everolimus (RADIANT-4)
Alternative values	**0.779**		**0.79**	**0.714**	**0.747**	**0.740**
Source	(Novartis, 2016) – Pooled analysis		Guy's and St Thomas registry (AAA Ltd., 2016)	Treatment arm specific analysis Novartis, (2016)		Erasmus study (AAA Ltd., 2016)

Resources and costs

- SSAs use based on the proportions reported in clinical trials (assumed an equal split between lanreotide and octreotide)
  - SSA usage post progression is the same for everolimus and sunitinib
- Proportion receiving SSA's taken from RADIANT-3 in P-NETs (23% and 19% for everolimus and BSC respectively)
  - Proportion receiving SSA's taken from RADIANT-4 for GI+Lung NETs and GI only
- Variation across treatments for their administration: 177Lu-DOTATATE is resource intensive - IV delivered requiring specialist oversight vs tablet form for everolimus and sunitinib
- AG concluded for 177Lu-DOTATATE current standard practice is to admit patients overnight, which is a further cost
- Costs from other therapies include: analgesics, anti-emetics, and anti-diarrhoeals
- Costs of chemotherapy in the post-progression state (see next slide)
- Other costs included are:
  - Medical management and disease monitoring
  - Resource/ hospital resource use
  - Supportive procedures
  - Cost of adverse events
  - Cost of end of life

Resources and costs – other treatments

- See below for chemotherapy use post progression. In absence of data for sunitinib it was assumed to be the same as for everolimus

Use of chemotherapy post-progression in RADIANT-3		
Treatment	Proportion of patients	Number of cycles
5-flourouracil	21.9%	2.5
Doxorubicin	28.1%	1.66
Streptozocyn	31.3%	2.14

Use of chemotherapy post-progression in RADIANT-4			
Treatment	Arm	Proportion	Number of cycles
5-flourouracil	EVE + BSC	2.8%	1.45
	BSC	1.1%	
Streptozocyn	EVE + BSC	2.8%	1.45
	BSC	1.1%	
Temozolomide	EVE + BSC	14.2%	3.08
	BSC	11.4%	
Capecitabine	EVE + BSC	14.2%	3.08

Base case results – P-NETs

	Sunitinib	Everolimus	BSC	Sunitinib vs Everolimus	Everolimus vs BSC	Sunitinib vs.BSC
Life years (mean, undiscounted)	6.39	4.69	3.46	1.70	1.23	2.93
QALYs (mean, discounted)	[redacted]	[redacted]	[redacted]	0.73	0.59	1.32
Costs (mean, discounted)	£43,192	£42,646	£15,761	£546	£26,885	£27,431
ICER (Cost / QALY)				**£745**	**£45,493**	**£20,717**

Source: Assessment report, table 149, page 269
See table 150, page 270 of the assessment report for detailed base case results

- Drug acquisition cost = major driver of total costs
- Difference in QALY outcomes – largely from difference in survival time in post-progression health state between everolimus and sunitinib (1.58 vs 0.52)
  - HRQoL in this state is the same for both treatments
- Sunitinib+BSC extendedly dominate everolimus+BSC
- Relevant comparison – sunitinib vs BSC – ICER = **£20,717**

Base case results – GI + Lung NETs and GI only

GI+Lung NETs	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	6.21	4.82	1.39
QALYs (mean, discounted)	3.74	3.05	0.69
Total costs (mean, discounted)	£47,334	£16,526	£30,809
ICER (Cost / QALY)			**£44,557**
Source: Assessment report, table 151, page 271 See table 152, page 271 of the assessment report for detailed base case results			

GI only NETs	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	7.50	7.05	0.44
QALYs (mean, discounted)	4.37	4.19	0.17
Total costs (mean, discounted)	£55,842	£21,119	£34,723
ICER (Cost / QALY)			**£199,233**
Source: Assessment report, table 151, page 271 See table 152, page 271 of the assessment report for detailed base case results			

Base case results – Lung NETs

GI only NETs	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	5.12	2.96	2.16
QALYs (mean, discounted)	3.18	1.99	1.19
Total costs (mean, discounted)	£49,168	£12,249	£36,920
ICER (Cost / QALY)			**£31,016**
Source:			

Base case results – GI (midgut) NETs

	Everolimus	177Lu-DOTATATE	BSC	Everolimus vs. BSC	177Lu-DOTATATE vs. everolimus	177Lu-DOTATATE vs. BSC
Life years (mean, undiscounted)	5.75	6.66	4.90	0.85	0.91	1.76
QALYs (mean, discounted)	3.57	4.19	3.11	0.45	0.63	1.08
Total costs (mean, discounted)	£52,018	£83,667	£16,628	£35,390	£31,649	£67,039
ICER (Cost /QALY)				**£78,330**	**£50,499**	**£62,158**
Source: Assessment report, table 155, page 272 See table 156, page 273 of the assessment report for detailed base case results						

Scenario analyses

P-NETs	GI+Lung-NETs	GI (midgut) NETs
PFS data using local investigator assessment for everolimus (instead of central independent review)	PFS data using local investigator assessment for everolimus (instead of central independent review)	Disease monitoring intensity
OS data from ITT analysis instead of the RPSFT-adjusted	Alternative set of utility values	Accounting for first cycle costs of subsequent treatment
Alternative set of utility values	Alternative set of OS and PFS curves	0% discount rate to costs and benefits
Alternative set of OS and PFS curves	Background mortality adjustments to OS and PFS curves	
Background mortality adjustments to OS and PFS curves	Accounting for first cycle costs of subsequent treatment	
Accounting for first cycle costs of subsequent treatment	0% discount rate to costs and benefits	
0% discount rate to costs and benefits		
Source: Assessment report, section 7.2.3		

Scenario analyses – results
PFS and OS trial data

PFS data for everolimus using local investigator assessment (instead of central review)			
Tumour location	**Treatment**	**Treatment or comparator**	**ICER**
Pancreas	Everolimus	BSC	£45,511
	Sunitinib	BSC	£19,586
GI and lung	Everolimus	BSC	£44,252
Source: Assessment report, table 157, page 274			

Using the ITT data from the A6181111 and RADIANT-3 trials in P-NETs (instead of RPSFT adjusted)		
Treatment	**Treatment or comparator**	**ICER**
Everolimus	BSC	£136,455
Sunitinib	BSC	£37,217
Source: Assessment report, table 158, page 275		

- Using local investigator review had a minor impact on the ICER in both P-NETs and GI+Lung NETs
  - Most significant change was in the P-NETs population for suninitib vs placebo
- Changing to ITT data led to ICER's 3 times higher than the base case

Scenario analyses – results

Alternative utility values

Using utility values from Swinburn et al 2016

- **P-NETs: increasing values in stable disease/values same in progressed**
- **GI and Lung/GI midgut:**
  - **Everolimus: increase values in stable disease/reduction in progressed**
  - **BSC only: reduce values in stable disease/increase in progressed**
  - **Lutetium: utility values increased in both states**

	Treatment	Treatment or comparator	ICER
Pancreas	Everolimus	BSC	£41,246
	Sunitinib	BSC	£19,411
GI (midgut)	Everolimus	BSC	£352,801
	177Lu-DOTATATE	BSC	£57,745
GI and lung	Everolimus	BSC	£49,949

Source: Assessment report, table 159, page 275

- In P-NETs, everolimus and sunitinib ICERs are reduced by 10% and 6% as there is greater quality of life in stable disease compared with BSC.
- Everolimus ICER in GI and GI/Lung increased by 12% and 7% respectively
- Lutetium ICER decreased by 7%

Scenario analyses – results
Alternative survival models

Alternative set of OS and PFS curves							
Tumour location	**Treatment**	**PFS**	**OS**	**Comp**	**PFS**	**OS**	**ICER**
Pancreas	Everolimus	Loglogistic	Lognormal	BSC	Lognormal	Exponential	£28,098
	Sunitinib	Exponential	Exponential	BSC	Lognormal	Exponential	£20,726
GI and lung	Everolimus	Lognormal	Loglogistic	BSC	Lognormal	Loglogistic	BSC dominant
Source: Assessment report, table 160, page 275							

- There was minimal impact on the ICER for sunitinib in P-NETs
- However, the ICER for everolimus in P-NETs declined by 33%
- Everolimus in GI/NETs became less effective than BSC alone in terms of discounted QALYs (despite its larger life expectancy, 7.11 vs. 6.84 years)
  - This is because of different timing in which quality of life benefits take place
  - Relative benefit with everolimus tends to occur in the latter period

Scenario analyses – results
Analysis with PFS only

Analysis limited to PFS only (due to the inherent problems with the OS data due to crossover)			
Tumour location	**Treatment**	**Comparator**	**ICER**
Pancreas	Everolimus	BSC	£57,493
	Sunitinib	BSC	£35,448
GI (midgut)	Everolimus	BSC	£88,801
	177Lu-DOTATATE	BSC	£30,115
GI and lung	Everolimus	BSC	£73,086
Source: Assessment report, table 161, page 276			

- P-NETs: increase of sunitinib ICER by 75%
- P-NETs: increase in everolimus ICER by 26%
- GI+Lung: increase in everolimus ICER from £44,000 to £73,000
- GI (midgut only): higher ICER here than in GI+Lung suggesting this subgroup is not as cost effective
- GI (midgut only): 177Lu-DOTATATE ICER is less than half of everolimus, suggesting PRRT has good long term outcomes

Scenario analyses – results
Background mortality adjustments

Background mortality adjustments to OS and PFS curves			
Tumour location	**Treatment**	**Comparator**	**ICER**
Pancreas	Everolimus	BSC	£44,032
	Sunitinib	BSC	£21,594
GI (midgut only)	Everolimus	BSC	£78,330
	177Lu-DOTATATE (no mortality adjustment)	BSC	£43,348
GI and lung	Everolimus	BSC	£46,687
Source: Assessment report, table 162, page 277			

- Limited effect on results in P-NETs and GI+Lung NETs
- GI (midgut only): ICER for everolimus goes from £200,000 in the base case to £78,330 with background mortality adjustment
- Adjustment was made to 177LU-DOTATATE as: in the base case one was not applied due to immature data
- Applying this reduces the ICER from £62,158 to £43,348

Scenario analyses – results

Costs of subsequent treatment and disease monitoring intensity

Accounting for first cycle costs of subsequent treatments			
Tumour location	**Treatment**	**Comparator**	**ICER**
Pancreas	Everolimus	BSC	£45,288
	Sunitinib	BSC	£20,624
GI (midgut only)	Everolimus	BSC	£208,095
	177Lu-DOTATATE (no mortality adjustment)	BSC	£61,619
GI and lung	Everolimus	BSC	£47,205
Source: Assessment report, table 163, page 277			

Disease monitoring intensity (increase in oncology visits)			
Tumour location	**Treatment**	**Comparator**	**ICER**
GI (midgut only)	Everolimus	BSC	£205,437
	177Lu-DOTATATE (no mortality adjustment)	BSC	£64,513
GI and lung	Everolimus	BSC	£46,249
Source: Assessment report, table 164, page 277			

Scenario analyses – results
Discount rate

Applying no discount rate (instead of the 3.5% originally used in the base case)			
Tumour location	**Treatment**	**Comparator**	**ICER**
Pancreas	Everolimus	BSC	£38,021
	Sunitinib	BSC	£17,605
GI (midgut only)	Everolimus	BSC	£131,512
	177Lu-DOTATATE (no mortality adjustment)	BSC	£49,907
GI and lung	Everolimus	BSC	£34,367
Source: Assessment report, table 165, page 277			

- The higher the discount rate the higher the incremental cost per QALY gained with targeted treatments vs. BSC alone
  - This means that their incremental costs tend to accrue before QALY benefits occur

Probabilistic sensitivity analyses

P-NETs
0% and **0.8%** probability that everolimus is cost effective at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY respectively
43.7% and **90.5%** probability that sunitinib is cost effective at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY respectively
GI+Lung NETs
1.% and **20.2%** probability that everolimus is cost effective at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY respectively
***GI (midgut only) NETs**
0% and **5.1%** probability that everolimus is cost effective at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY respectively
Source: Assessment report, section 7.2.4

Deterministic (one-way) Sensitivity analyses summary

Location/treatment	Key drivers of cost effectiveness	ICER range
P-NETs – Everolimus vs BSC	• OS HR in the active arms	£25,000 - £105,000
	• Relative dose intensity	£38,000 – £50,000
	• Mean treatment duration	£39,000 - £49,000
P-NETs – Sunitinib vs BSC	• OS HR in the active arms	£16,000 - £28,000
	• Relative dose intensity	£18,000 - £23,000
	• Mean treatment duration	£18,000 - £23,000
GI+Lung NETs – Everolimus vs BSC	• OS HR in the active arms	£23,000 - £140,000
	• Relative dose intensity	£38,000 - £47,000
	• Mean treatment duration	£38,000 - £47,000
GI (midgut only) NETs – Everolimus vs BSC	• OS HR in the active arms	£43,000 – dominated value
	• Relative dose intensity	£165,000 - £235,000
	• Mean treatment duration	£170,000 - £230,000

End of life – P-NETs

Criterion	Pfizer submission	AG comments/conclusions
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• In the placebo arm, life expectancy was estimated as **13.2 months** • Clinical expert opinion: life expectancy likely to be less than **25 months**	RADIANT-3 (Placebo+BSC) – **18.3** (95% CI 17.2, 19.4) Parametric/extrapolated - **41.6 months** (95% CI 33.9, 53.6) A6181111 (Placebo+BSC) – **14.5** (95% CI 12.6, 16.3) Parametric/extrapolated - **20.5 months** (95% CI 16.4, 27.4)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Median OS was extended by **9.5 months** (crossover unadjusted) • Median OS was extended by **13.2 months** (RPSFT adjusted)	**Everolimus vs BSC** RADIANT-4 – **1.6 months** Parametric/extrapolated – **14.7 months** **Sunitinib vs BSC** A6181111 – **5.9 months** Parametric/extrapolated - **38.5 months**

- The AG concluded that EoL may only be met by sunitinib in the P-NETs population (**20.5 months** life expectancy and **5.9 months** OS gain)

End of life – GI and Lung NETs

Criterion	AG comments/conclusions
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	RADIANT-4 (Placebo+BSC) – **29.1** (95% CI 26.1, 32.1) Parametric/extrapolated – **57.9 months** (95% CI 43.5, 86.2)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	**Everolimus vs BSC** RADIANT-4 – **2.6 months** Parametric/extrapolated – **16.6 months**

- The AG concluded that everolimus in the GI or Lung NETs population based on evidence from RADIANT-4 does not meet the EoL life expectancy criteria

Innovation

- Everolimus (Novartis):
  - Clinically effective and tolerable treatment option in patients with GI/Lung NETs with few treatment options
  - There is a high unmet need for a targeted therapy in a patient population with Lung NETs
- Lu-177 DOTATATE (AAA):
  - Novel compound that will be the first to market of an emerging class of treatments known as Peptide Receptor Radionuclide Therapy (PRRT)
  - There is a significant unmet need for patients with inoperable GEP-NETs who are progressive under SSAs
  - NETTER-1 study has shown that 177Lu-DOTATATE provides a major therapeutic benefit for this patient population
  - Favourable safety profile in comparison with the chemotherapy regimens and targeted agents currently used to treat GEP-NETs
- Sunitinib (Pfizer):
  - Sunitinib is one of only three licensed treatments in the UK for well differentiated unresectable or metastatic P-NET after disease progression
  - 1st targeted therapy demonstrating significant efficacy benefits versus placebo
  - It provides meaningful improvement in life expectancy, with improved HRQoL in a group of patients who would otherwise have a poor prognosis

Equalities issues

- No equalities issues were identified during the appraisal process
- During the scoping stage consultees commented that because of the rarity of neuroendocrine tumours, people with the disease are disadvantaged compared to more common cancers in terms of access to efficacious therapies
  - It was considered that issues about access and rarity of disease are not considered equality issues under the equalities legislation
  - The appraisal committee will consider whether its recommendations could have a different impact on people protected by the equality legislation

Key clinical issues (1)

- The AG's decision problem is in line with the final scope but excluded some comparators/interventions because;
  - Interferon alpha – not routinely used in practice and no relevant studies
  - Chemotherapy – no relevant study to include in the network
  - Lutetium (P-NETs) – population not included in NETTER-1
    - anticipated MA is broad for GEPNETs
    - AAA presented MTC and economic analysis for P-NETs using data from NETTER-1, which the AG considered inappropriate

Have the appropriate comparisons been made for each tumour locations?

- What conclusions can be drawn from the ITC for P-NETs, given:
  - Exclusion of lutetium from the network
  - High-level of crossover in RADIANT-3 and A618111, RPSFT-adjusted results also presented
  - AG considered RADIANT-3 and A6181111 to be comparable, although they differed in SSA use – 40% vs 28% respectively
    - not considered by AG to affect the relative effect of the treatments
  - A6181111 included both functioning and non-functioning tumours, but the secretory profile in RADIANT-3 was not reported

Key clinical issues (2)

- What conclusions can be drawn from the ITC for GI NETs, given:
  - The assumption that 60mg octreotide is clinically similar to placebo + BSC?
  - AG ITC used the full population from NETTER-1 and a subset of RADIANT-4 (GI only)
    - AAA used the full RADIANT-4 population (GI and lungs)
  - Comparability of RADIANT-4 and NETTER-1
    - GI (fore-, mid- and hind-gut) vs midgut NETs respectively
    - Non-functioning vs mixed (functioning and non-functioning)
    - All patients in NETTER-1 were somastostatin receptor positive, but not known for RADIANT-4
  - The inclusion of RADIANT-2 by AAA
    - Excluded in the AG ITC because the population is outside the MA for everolimus

Key cost effectiveness issues (1)

What conclusions can be drawn from the cost effectiveness results for P-NETs given that:

- There is a lack of utility data for everolimus from RADIANT-3 in the P-NETs population
- As everolimus and sunitinib are assumed to have equal efficacy, the lack of data means the results of the comparison between everolimus and sunitinib are uncertain

What conclusions can be drawn from the cost effectiveness results for GI NETs given that:

- There is limited comparability between RADIANT-4 and NETTER-1 patient populations
- The differences in patient population means the results of ITC must be interpreted with caution
- OS data from both trials are immature with more than 50% of patients still alive in at least one arm - modelling is highly uncertain

- The most plausible results for P-NETs, GI and Lung NETs and GI only NETS?
- Do any of the treatments being appraised meet the end of life criteria?

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

Produced by

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Contributions of authors

Jo Varley-Campbell	Led the clinical effectiveness systematic review from August. Screened abstracts and papers, data extracted and second-checked data extraction. Wrote the results for the clinical effectiveness review, the background and critique of the company submissions. Contributed to corresponding sections within the executive summary, discussion and appendices. Contributed to the editing of the report and collation of the final report.
Ruben Mujica Mota	Led the economic evaluation and the systematic review of the cost-effectiveness literature, critiqued one of the industry model submissions, contributed to the review of the utility literature and performed the survival analysis to populate the de novo model and statistical analyses of individual patient data provided by the companies. Wrote the respective sections in the report, including the end of life criteria and the discussion of the economic evaluation sections, and contributed to writing the methods and results of the de novo model.
Irina Tikhonova	Contributed to the design and parameterisation of the PenTAG economic model; implemented the model in Excel; wrote the sections on the design and the results of the model; contributed to the cost-effectiveness systematic review by screening titles, abstracts and papers of published cost-effectiveness studies; contributed to the editing of the report.
Chris Cooper	Provided senior project guidance from August. Screened titles, abstracts and papers for inclusion in the systematic review. Data extracted and second-checked extraction. Led on contacting on-going trials and study authors. Checked and extracted studies from relevant systematic reviews. Wrote the methods sections (clinical effectiveness reviews (RCT and Non-RCT), and contributed to the writing of the clinical effectiveness section and

	corresponding sections within the executive summary and appendices. Contributed to the editing of the report. Designed and carried out literature searches for the systematic reviews of clinical and cost effectiveness, trials registries searching, utilities and identification of model parameters. Undertook separate searches to inform a NMA and advised on searches for the background. Advised on citation and supplementary searches. Critiqued company literature searches. Wrote the searching sections and appendices of the SRs of clinical and costs effectiveness and utilities. Wrote the searching for the NMA. Undertook document retrieval.
Ed Griffin	Provided critique of the submission by AAA Ltd and contributed to the development of the PenTAG independent economic assessment, including the analysis of costs and their methodological description.
Marcela Haasova	Project managed and led the clinical effectiveness review for part of the duration of the project (until August 2016), wrote the project protocol, and contributed to discussions about searches.
Jaime Peters	Carried out the indirect treatment comparison, wrote the critique of the company submission and contributed to the writing and editing of the report.
Stefano Lucherini	Reviewed the utility literature to populate the de novo economic model and wrote the respective section.
Juan Talens-Bou	Third reviewer August - project completion. Screened abstracts and papers and data extracted. Undertook update searching, searching for background and supplementary searching. Checked all data tables and calculations, contributed to the editing of the clinical effectiveness review and executive summary. Contributed to the editing of the report.
Linda Long	Contributed to the systematic review of clinical effectiveness. Assessed and wrote the summary of non-randomised controlled trials and contributed to the writing of the background.
David Sherriff	Provided clinical advice and contributed to the editing of the report.
Mark Napier	Provided clinical advice and contributed to the editing of the report.
John Ramage	Provided clinical advice and contributed to the editing of the report.
Martin Hoyle	Project manager for part of the duration of the project (August – December 2016), contributed to the design of the economic model, checked the PenTAG economic model, and contributed to the editing of the report. Director and Guarantor of the report.

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Abstract

Background

Neuroendocrine tumours (NETs) are a group of heterogeneous cancers which develop in cells in the diffuse neuroendocrine system. Patients considered here have unresectable or metastatic neuroendocrine tumours with disease progression. The interventions are everolimus, 177Lu-DOTATATE and sunitinib. The following NETs locations are considered separately: pancreatic, gastrointestinal (GI) & lung and GI (midgut only). Here, we present a systematic review of clinical effectiveness and cost-effectiveness studies, and our de novo economic analysis. We also critique submissions from the pharmaceutical companies.

Methods

We systematically reviewed the effectiveness literature on advanced, progressive NETs. We wrote a survival partition cohort-based economic evaluation in Microsoft Excel. This comprised three health states: progression-free survival, progressed disease, and death. The perspective was that of the UK NHS & Personal Social Services.

Results

Three RCTs, RADIANT-3 (pancreatic NETs: everolimus vs. BSC), A6181111 (pancreatic NETs: sunitinib vs. BSC) and RADIANT-4 (GI and lung NETs: everolimus vs. BSC), met the inclusion criteria in our clinical effectiveness systematic review. The risk of bias was low. Whilst the NETTER-1 RCT, of 177Lu-DOTATATE + Octreotide 30mg vs Octreotide 60mg was excluded from our review, we nonetheless present the results of this trial, as it informs our estimate of cost-effectiveness of 177Lu-DOTATATE.

The pancreatic NETs trials consistently found that the interventions improved PFS and OS versus BSC. Our indirect comparison in pancreatic NETs found no significant difference in PFS between everolimus and sunitinib. Estimates of OS gain were confounded due to high rates of treatment switching from BSC to sunitinib or everolimus. The companies used a statistical technique to adjust for this switching. After adjustment, our indirect comparison suggests a lower, but non-significant, hazard of death with sunitinib compared to everolimus.

In GI and lung NETs, everolimus significantly improved PFS compared to BSC, and a non-significant trend in improved OS compared to BSC.

Adverse events were more commonly reported following treatment with interventions compared to placebo.

Novartis compared the cost-effectiveness of everolimus vs. sunitinib in pancreatic NETs and everolimus vs. BSC in GI and Lung NETs. AAA Ltd compared the cost-effectiveness of 177Lu-DOTATATE plus octreotide 30mg vs. sunitinib vs. everolimus for pancreatic NETs and 177Lu-DOTATATE plus octreotide 30 mg vs. everolimus for GI NETs. Pfizer did not submit an economic evaluation of sunitinib.

In our base case for pancreatic NETs, assuming list prices, we estimate incremental cost-effectiveness ratios (ICERs) for everolimus vs. BSC of £45,493 per QALY and sunitinib vs.

BSC of £20,717 per QALY. These ICERs increase substantially without the adjustment for treatment switching. For GI and lung NETs, we estimate the ICER for everolimus vs. BSC of £44,557 per QALY. For GI (midgut), the ICERs were: everolimus vs. BSC £199,233 per QALY and in a scenario analysis, 177Lu-DOTATATE vs. BSC £62,158 per QALY. We judge that no treatment meets NICE's End of Life criteria, although we cannot rule out that sunitinib in A6181111 does.

Conclusions

Given NICE's current stated range for the cost-effectiveness threshold of £20,000 to £30,000 per QALY, based on list prices, only sunitinib might be considered good value for money in England and Wales.

Word count: 500

Scientific summary

Background

Neuroendocrine tumours (NETs) is the overarching term for the group of heterogeneous cancers which develop in cells in the diffuse neuroendocrine system. The aetiology of NETs is poorly understood. NETs develop slowly and may remain undetected over a number of years, hence in many cases the cancer may have already metastasised.

The characteristics of a NET will determine the methods of treatment and impact the prognosis. Important characteristics include the location, grade and differentiation, stage of tumour and secretory profile of the tumour.

Public Health England (PHE) published in October 2016, the first data briefing on the incidences and survival of NETs and neuroendocrine carcinomas (NECs) in England. In 2013 and 2014, 8,726 neoplasms were diagnosed, equating to 4,000 per year or approximately a rate of 8 per 100,000 persons per year (not age-standardised). Prognosis is generally better with an early diagnosis however NETs are commonly diagnosed at a later stage when the tumour has already metastasised.

Diagnosis of NETs can be difficult as they are often small tumours (some may be less than 1cm in size), they can occur almost anywhere in the body and there are a vast array of symptoms (or there may be no symptoms at all). Most individuals with NETs will experience non-specific symptoms such as pain, nausea and vomiting, and, in some cases, anaemia due to intestinal blood loss. Most gastro-enteropancreatic NETs are non-functioning and present predominantly with mass effects of the primary tumour or metastases. Symptoms are more common with functioning pancreatic NETs, where hormones are significantly elevated.

The aim of treatment, where realistically possible, should always be curative. However, in the majority of cases it is most likely to be palliative. Since metastatic disease is common for individuals with NETs, improving the quality of life is often the primary aim of treatment (as opposed to curing the disease). Individuals with NETs can maintain a good quality of life for a long period of time.

There are a vast array of treatment options for treating NETs. The initial treatments start with surgery and symptom treatment. Treatments which follow surgery and symptom control include: liver transplant, interferon alpha, chemotherapy, ablation therapies, targeted radionuclide therapy (including 177Lu-DOTATATE), transhepatic artery embolisation/chemoembolization, external-beam radiotherapy and emerging therapies (including everolimus and sunitinib).

Changes in project scope

During the course of this report, NICE consulted on amendments to the original project scope. The revised scope was agreed on the 18th August 2016 and the intervention lanreotide and the comparator octreotide were removed.

Objectives

The key objectives of this technology assessment report, in keeping with the final NICE scope are two-fold. Firstly to estimate the clinical effectiveness of three interventions (everolimus, 177Lu-DOTATATE and sunitinib) for treating unresectable or metastatic neuroendocrine tumours with disease progression. The second objective is to establish the cost effectiveness of these interventions. The comparator treatments are chemotherapy, interferon alpha and best supportive care.

Methods

The assessment comprises a systematic review of clinical and cost-effectiveness studies, a review and critique of the company submissions and a *de novo* economic analysis.

Clinical effectiveness systematic review

Evidence for the clinical effectiveness of everolimus, 177Lu-DOTATATE and sunitinib, within their marketing authorisation, for treating unresectable or metastatic neuroendocrine tumours with disease progression was assessed by conducting a systematic review. This review was undertaken following the methodological guidance published by the Centre for Reviews and Dissemination (CRD).

Identification of studies

Literature searching for clinical effectiveness studies was conducted in May 2016 and updated in September 2016.

The following bibliographic databases were searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); MEDLINE-Daily (Ovid); Epub-Ahead-of-Print (Ovid); EMBASE (Ovid); CENTRAL (The Cochrane Library, Wiley Interface) and Web of Science (including conference proceedings citation index; Thomson Reuters). These trial registries were hand-searched: Current Controlled Trials; ClinicalTrials.gov; the Food and Drug Administration (FDA) website; and the European Medicines Agency (EMA) website (including European Public Assessment Reports [EPARs]). The following web-sites were searched: the European Neuroendocrine Tumour Society (ENETS) (http://www.enets.org/) and the UK and Ireland Neuroendocrine Tumour Society (UKINETS) (http://www.ukinets.org/).

After the reviewers completed the screening process, forwards and backwards citation searching was conducted to identify further potentially includable studies. The company submissions were assessed for unpublished data.

Study selection

The population was defined as people with progressed unresectable or metastatic NETs in locations covered by existing and anticipated marketing authorisation for the interventions. The interventions of interest were everolimus (NETs of pancreatic, gastrointestinal or lung origin), 177Lu-DOTATATE (NETs of pancreatic or gastrointestinal origin) and sunitinib (pancreatic NETs). These were compared with each other or with: interferon alpha, chemotherapy regimens and/or best supportive care (BSC). Evidence for the following outcome measures were considered: overall survival (OS), progression free survival (PFS), response rates (RR), symptom control, adverse effects of treatment (AEs) and health-related quality of life (HRQoL). If the evidence allowed the following groups were considered:

location of tumour, grade/degree of differentiation, stage of tumour, secretory profile and number of previous treatment(s).

Title and abstracts were independently double-screened by two reviewers for inclusion against the predefined inclusion criteria. Disagreements were resolved by discussion. Studies meeting inclusion at title and abstract stage were ordered as full texts and double-screened by three reviewers. The methodological quality of each included study was assessed by one reviewer and checked by a second reviewer. The study quality was assessed according to recommendations by the CRD for randomised controlled trials (RCTs).

Data analysis/synthesis

Data were tabulated and narratively synthesised. Where the data allowed, indirect treatment comparisons were performed using the Bucher method.

Cost-effectiveness systematic review

Cost-effectiveness studies were reviewed according to the methods used in the systematic review of clinical effectiveness, extended to include electronic search of bibliographic databases of health economic studies. In addition to economic evaluation studies, costing studies in UK settings were included. Only full texts were included, but we considered any relevant evidence on UK studies reported in conference posters as supplementary.

Results

Clinical effectiveness systematic review

Number and quality of effectiveness studies

Of 6209 titles/abstracts screened, three trials, RADIANT-3, A6181111 and RADIANT-4, met the inclusion criteria for the clinical effectiveness systematic review. The three trials were made up from 56 citations (6 full texts, 1 errata and 49 conference abstracts). The efficacy and safety outcomes were tabulated and discussed in a narrative review.

> *A fourth trial, NETTER-1, was identified under the original scope but excluded under the revised scope. This RCT compared 177Lu-DOTATATE to octreotide 60mg. Following the changes in scope, this trial no longer met the inclusion criteria for the systematic review. However, the assessment group (AG) appreciate this trial might be of interest to the committee and following the request of NICE, have presented results and comparative analysis of it in section 4.7.*

The risk of bias within all included trials was low and remained consistent between the three studies regarding selection, performance, detection, attrition and reporting bias.

Summary of benefits and risks

Pancreatic NETs

Two trials provided evidence for the effectiveness of everolimus (RADIANT-3) and sunitinib (A6181111) in the treatment of pancreatic NETs. Both interventions were compared to placebo. BSC was also given in both the intervention and placebo arms, for both trials.

RADIANT-3 recruited a total of 410 participants in the intended to treat (ITT) population (n=207 for everolimus and n=203 for placebo). A618111 recruited a total of 171 participants (n=86 for sunitinib and n=85 for placebo). The median age range of the participants was 56-58 years (20-87 years in RADIANT-3 and 25-84 years in A6181111), and the percentage of males recruited ranged from 47-58%. In both trials, the majority of individuals had a World Health Organisation performance score (WHO PS) of zero, RADIANT-3 (66%) and A6181111 (55%).

Evidence consistently suggested a treatment effect in favour of both everolimus plus BSC and sunitinib plus BSC when compared to placebo plus BSC for the outcomes of interest.

Treatment with everolimus was associated with a 66% reduction in the risk of progression (Hazard Ratio (HR) 0.34 [95% confidence interval (CI) 0.26, 0.44], by central review). Similarly, the treatment with sunitinib was associated with a 68% reduction in the risk of progression (HR 0.32 [95% CI 0.18, 0.55], central review).

Crossover from the placebo arm to the treatment arm was 73% in RADIANT-3 and 69% in A6181111. The crossover significantly compromised the OS results. The HR for unadjusted OS from RADIANT-3 was reported to be 0.94 (95% CI 0.73, 1.20; p=0.30) and for A6181111 0.73 (95% 0.50, 1.06; p=0.094). Using the Rank Preserving Structural Failure Time (RPSFT) model the hazard ratio for overall survival from RADIANT-3 was reported to be 0.60 (95% CI 0.09, 3.95) and for A6181111 0.34 (95% 0.14, 1.28; p=0.094).

Tumour response rates were assessed locally for RADIANT-3 and assumed to be locally assessed for A6181111. Complete response was achieved by 2 individuals receiving sunitinib (A6181111), it was not achieved in any of the other arms. Both trials report higher rates for partial response and stable disease and lower rates for progressive disease in the treatment arms (everolimus and sunitinib) when compared placebo.

Overall, adverse events were more commonly reported following treatment with everolimus and sunitinib than with placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-3) were stomatitis (64%), rashes (49%), diarrhoea (34%), fatigue (31%) and infections (23%). Following treatment with sunitinib (A6181111) the five most common all grade AEs were diarrhoea (59%), nausea (45%), vomiting (34%), asthenia (34%) and fatigue (32%). HRQoL was assessed in A6181111 (sunitinib) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. There were no overall differences between study groups, except for diarrhoea (21.4 point) and insomnia (7.8 point) being higher in the sunitinib arm than the placebo arm. HRQoL was not reported in RADIANT-3.

Indirect treatment comparison for Pancreatic NETs

RADIANT-3 and A6181111 were used to compare everolimus to sunitinib in an indirect treatment comparison (ITC) using the Bucher method.

The ITC for PFS from central radiology review suggests no difference in the HR for the treatments (HR 1.06, 95%CI 0.57, 1.97). Whereas, the ITC for PFS from local review suggests everolimus is associated with a 17% decrease in disease progression or death compared to sunitinib (HR 0.83, 95%CI 0.49, 1.42). The 95%CI is wide and includes the null

hypothesis that there is no difference in PFS effectiveness between everolimus and sunitinib.

For OS, the ITC suggests that there is 2.56 times greater hazard of dying from treatment with everolimus than sunitinib, which is statistically significant. However as these analyses are based on published HRs from RADIANT-3 and A6181111, which were not adjusted for treatment switching after disease progression, these results should not be relied upon. The ITC for OS where the companies have used the RPSFT method to adjust for treatment switching suggests a lower hazard of death associated with sunitinib compared to everolimus (HR 1.76 [0.20, 15.78]). However the 95% CI is very wide and includes the null effect.

For response rates, the ITC suggests that there is an 82% increase in the odds of a partial response in individuals treated with sunitinib compared to everolimus. However, sunitinib was associated with a 52% increase in the odds of progressive disease when compared to everolimus. Everolimus was associated with a 2.3 times greater odds for disease stability than sunitinib. However, all of these indirect treatment comparisons were associated with wide 95% CIs, suggesting that there is little evidence of a difference in response rates between everolimus and sunitinib.

For all grades of AE, the ITC suggests a 19% increase in the odds of experiencing stomatitis and a 42% increase in the odds of experiencing nausea with sunitinib compared to everolimus. For rash, fatigue, diarrhoea, dysguesia, epistaxis, loss of weight, thrombocytopenia, decrease appetite, headache, vomiting and asthenia (all grades), the evidence suggests an increase in the odds of experiencing the AE with everolimus compared to sunitinib. However, except for decreased appetite, all of these indirect treatment comparisons were associated with wide 95% CIs that included the null hypothesis of no difference, suggesting that there is little evidence of a difference in AEs between everolimus and sunitinib. For all grades of decreased appetite, there was a statistically significant increase in the odds of experiencing the event with everolimus compared to sunitinib. For the grade 3/4 AEs, the ITC could only consider 7 AEs due to available data from the two trials. The evidence suggests an increased odds of experiencing grade 3/4 stomatitis, fatigue, diarrhoea, nausea and throbocytopenia with everolimus compared to sunitinib, and an increased odds of experiencing decreased appetite and asthenia with sunitinib compared to everolimus. However, all of the indirect treatment comparisons for grade 3/4 AEs were associated with wide 95% CIs, that included the null hypothesis of no difference, suggesting that there is little evidence of a difference in AEs between everolimus and sunitinib.

Gastrointestinal (GI) and Lung NETs

One trial (RADIANT-4) provided evidence for the effectiveness of treatments in GI and lung NETs of everolimus plus BSC. The intervention was compared to placebo and both arms, received BSC. This trial included a total of 302 participants in the ITT population (n=205 for everolimus and n=97 for placebo). The median age was 65 years for everolimus and 60 years for placebo (range 22-86 years) and 47% were male. The majority of individuals had WHO PS score of zero (73-75%).

Evidence consistently suggested a treatment effect in favour of the use of everolimus plus BSC compared to placebo plus BSC for the outcomes of interest. Treatment with everolimus was associated with a 52% reduction in the risk of disease progression (HR 0.48 [95% CI 0.28, 0.54]). For OS, treatment with everolimus plus BSC was associated initially with 36% improvement for individuals with lung and GI NETs compared to placebo (HR 0.64 [0.40, 1.05]). However, follow-up data from the company submission reports a 27% improvement in OS following treatment with everolimus (HR 0.73 [95% CI 0.48, 1.11]). Tumour response rates were assessed by central radiology review. No arm achieved complete response. Individuals receiving everolimus had a favourable response for partial disease, stable disease, progressive disease and tumour shrinkage in comparison to those in the placebo arm. Overall, adverse events were more commonly reported following treatment with everolimus compared to placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-4) were stomatitis (63%), diarrhoea (31%), fatigue (31%), infections (29%) and rash (27%). HRQoL was reported in the company submission from Novartis for RADIANT-4. The Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire was used. [redacted].

GI NETs

Following a data request from the AG to Novartis, results from RADIANT-4 were provided for individuals recruited with just GI NETs (n=118 for everolimus vs n=57 for placebo).

Median PFS for GI NETs from RADIANT-4 was 13.1 months for treatment with everolimus and 5.4 months for placebo (HR 0.56, [95% CI 0.37, 0.84]). Median OS estimated from a Kaplan-Meier at the 25th percentile was [redacted] in the everolimus arm compared to [redacted] in the placebo arm. [redacted] Individuals receiving everolimus [redacted] response for stable disease, progressive disease and tumour shrinkage in comparison to those in the placebo arm. Overall, adverse events were more commonly reported following treatment than receiving placebo for individuals with GI NETs. The five most common all grade adverse events following treatment with everolimus were stomatitis (71.8%), infections (59%), diarrhoea (44.4%), peripheral oedema (40.2%) and fatigue (36.8%).

Lung NETs

Following a data request from the AG to Novartis, results from RADIANT-4 were provided for individuals recruited with just lung NETs (n=62 for everolimus vs n=27 for placebo).

There were [redacted] assigned to everolimus compared to [redacted] for the placebo arm. Everolimus was associated with a [redacted] in the risk of disease progression compared to placebo. There were [redacted] assigned to everolimus arm compared to [redacted] for the placebo arm. Survival was [redacted] following everolimus treatment compared with placebo. Rates of stable disease and progressive disease [redacted] with everolimus. Overall, adverse events were more commonly reported following treatment with everolimus than placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-4) [redacted]

Normally, we would not report in detail the results of the NETTER-1 RCT, because it concerns a comparator which is not in the NICE Scope. However, we do this here on request from NICE, as it is the pivotal trial that will underpin the anticipated marketing authorisation for lutetium and informs our economic analysis for lutetium.

The NETTER-1 RCT in an unpublished RCT comparing 177Lu-DOTATATE and Octreotide 30mg (n=116) to Octreotide 60mg (n=113). There are currently four published abstracts relating to NETTER-1. Data provided on NETTER-1 is either from AAA's company submission, or from data given to the AG following a request to AAA.

NETTER-1 is a poorly designed study, as there is no control arm. Any differences observed between the arms for effectiveness will be uncertain as to whether they are a result of the addition of 177Lu-DOTATATE or the doubling of the dose of octreotide LAR. The rationale for not having a control arm to this study was that patients enrolled in the trial would have already experienced progressive disease following 20 or 30 mg of octreotide LAR and it would not have been ethical to maintain them on the same dose. Since no alternative efficacious treatment was available a higher dose of 60mg of octreotide LAR was approved.

NETTER-1 Outcomes

[redacted]

Indirect treatment comparison –GI NETs

RADIANT-4 and NETTER-1 were used to compare everolimus to 177Lu-DOTATATE in an indirect treatment comparison (ITC) using the Bucher method. The following strong assumptions and cautionary notes are given for this comparison:

1. The comparator arm in RADIANT-4 (placebo + BSC) was assumed to be equivalent to the comparator arm in NETTER-1 (octreotide 60mg).
2. NETTER-1 recruited individuals with midgut NETs whilst RADIANT-4 recruited fore-, mid- and hind-gut. Therefore, the distribution of tumour locations differ substantially between the trials.
3. For the grade 3+4 AE comparison, the company for NETTER-1 provided data on AEs grade 3 to 5 whereas RADIANT-4 provided data on AEs grade 3+4.
4. None of the data used for this network is in the public domain. NETTER-1 is currently unpublished and RADIANT-4 does not report outcomes for the subgroup of participants with GI NETs only (instead RADIANT-4 reports outcomes for the combined group of GI + lung NETs). All data was received following requests to the companies.

For PFS, the indirect treatment comparison suggested that 177Lu-DOTATATE + octreotide 30mg is associated with a statistically significant [redacted] in disease progression or death compared to everolimus + BSC [redacted]

The results of the ITC for OS suggest a [redacted] in the hazard for death with 177Lu-DOTATATE + octreotide 30mg compared to everolimus + BSC, however this results is associated with a wide 95%CI [redacted]

From the available data on response rates, the ITC results suggest that objective response and stable disease [redacted] with everolimus + BSC than 177Lu-DOTATATE + octreotide 30mg: objective response [redacted] stable disease [redacted] However, the evidence suggests [redacted] of progressive disease between 177Lu-DOTATATE + octreotide 30mg and everolimus + BSC [redacted]

For all grades, data on 9 AEs could be compared from RADIANT-4 and NETTER-1. The findings suggest that 177Lu-DOTATATE is generally associated with [redacted] of experiencing AEs when compared to everolimus+BSC. This finding is statistically significant for the AEs of headache and nausea, but not for abdominal pain, anaemia, decreased appetite and diarrhoea. The [redacted] of experiencing fatigue associated with 177Lu-DOTATATE compared to everolimus+BSC is close to statistical significance: [redacted] For peripheral oedema, there is a statistically significant [redacted] of experiencing the AE with everolimus+BSC than with 177Lu-DOTATATE: [redacted]Data on grade 3/4 AEs were only available for the indirect treatment comparison for five AEs: abdominal pain, decreased appetite, diarrhoea, fatigue and nausea. For the grade 3/4 AEs, 177Lu-DOTATATE is associated with a [redacted] of experiencing the AE compared to everolimus+BSC, but the calculated 95% CIs are wide and all include the null hypothesis of no difference between the two treatments.

Cost-effectiveness systematic review

Four studies were identified, all were in patients with advanced pancreatic NETs. Two studies, one conducted in Poland and the other in Mexico, were model-based cost-utility analyses of sunitinib plus BSC vs. BSC alone based on the A6181111 trial data. Another study was a model-based cost-utility analysis of everolimus vs. sunitinib conducted in the US, which used effectiveness data from a matched-adjusted indirect comparison of the RADIANT-3 and A6181111 trials. The fourth study was a model-based cost-utility analysis of sunitinib plus BSC vs. BSC only that was submitted as evidence to the Scottish Medicine Consortium and for which only a conference poster was found. All of these studies used the same semi-Markov model structure of three health states, stable disease, progressive disease and death, and used parameter values derived from partitioning of parametric OS curves between those states using parametric PFS curves.

All of these studies were sponsored by manufactures of the respective treatments under evaluation. The study of everolimus vs sunitinib found that the ICER for everolimus vs sunitinib was equivalent to £28,816 at US prices of 2010.

Among the studies that compared sunitinib plus BSC vs. BSC alone, the UK study found that sunitinib plus BSC had a £22,587 discounted cost per QALY gained relative to BSC only. This result allowed for an adjustment for cross-over to active treatment in the placebo plus BSC arm of A6181111.

The studies identified had severe limitations primarily due to the fact that they were based on only phase III trials with no active treatment comparators. In the case of the US study of the everolimus vs sunitinib indirect comparison, the evaluation lacked a BSC alone comparator, and may have been based on data that have since been superseded by new results reported by the trial investigators. Further, the data on resource utilisation were limited, which in the best case was derived from retrospective surveys of clinicians about their experience treating a few patients. The generalisability of these findings to the NHS remains in question, in particular since the only identified report of a study in a UK setting was a conference poster with insufficient information to assess its quality.

Critique of Industry submissions

Two companies submitted economic evaluations to NICE. Novartis compared the cost-effectiveness of everolimus plus BSC vs. sunitinib plus BSC in pancreatic NETs over a 20 year time horizon. It also submitted an economic evaluation of everolimus plus BSC vs. BSC alone in GI and Lung NETs over a 30 year time horizon.

Advanced Accelerator Applications SA (AAA) submitted an economic evaluation of 177Lu-DOTATATE plus octreotide 30mg vs. sunitinib plus BSC vs. everolimus plus BSC in patients with progressive pancreatic NETs over a 20-year time horizon. It also submitted an economic evaluation of 177Lu-DOTATATE plus octreotide 30 mg vs. everolimus plus BSC for GI NETs over a 20-year horizon.

All these evaluations employed a three health state partitioned survival Markov model, in which patients started from a stable disease and could either remain alive and in stable disease, remain alive but with progressive disease, or die. This model implied that after starting treatment in stable disease, patients could progress to disease progression and eventually die, or die while in stable disease. However since the model did not explicitly model transitions into stable disease it was not possible, without further assumptions, to determine what proportion of patients initially treated would die before and after progression.

Novartis evaluation of pancreatic NETs

In their pancreatic NETs model, Novartis assumed equal effectiveness of everolimus and sunitinib in terms of PFS and OS, based on the results of the indirect comparison of the two treatments in the RADIANT-3 and A6181111 trials. The treatment effects of everolimus relative to sunitinib on PFS estimated by the company were: HR 0.83 (95%CI, 0.49-1.41) based on local review, and 1.07 (95% CI: 0.58-1.99) by central review. The HR of everolimus vs. sunitinib for OS adjusted for cross-over from placebo to active treatment in both trials was 0.717 (95% CI 0.16-11.72). (85% and 69% of patients in the placebo arms of RADIANT-3 and A6181111, crossed-over respectively). The company stated that the cross-over adjusted OS treatment effect (HR) estimate used for sunitinib in their indirect comparison, was obtained from results submitted by Pfizer to the Scottish Medical Consortium, and it may have been derived using different methods to those applied by Novartis to derive the corresponding estimate for everolimus.

As a consequence of the assumption that PFS and OS outcomes were equal in the base case, the difference in QALYs was due to differences in HRQoL effects of the treatments. Since in the progressive disease phase, the health state utility values were assumed to be the same regardless of treatment, all QALY differences were due to differences in utilities in

the stable disease phase. These utilities were based on valuations by members of the general public of vignettes constructed from clinical experts' opinion of stable disease health states with and without adverse events characteristic of patients with NETs. We consider this low quality evidence. The stable disease utility values for sunitinib and everolimus were then obtained as a weighted average of the values of those vignettes where the weights were the relative frequencies of Grade 3/4 adverse events observed in the RADIANT-3 and A6181111 trials. Although the average disutility of adverse events experienced with everolimus was higher than that with sunitinib, the company estimated that the incidence rate of any of the AEs considered was four-fold higher with sunitinib than with everolimus. This ultimately led to a base case QALY gain of everolimus versus sunitinib of 0.021 per patient.

Novartis estimated that everolimus also reduced healthcare costs relative to sunitinib by £1,635 per patient at list prices. Most of the difference was due to difference in the costs of managing AEs, and the rest, £200 was due to lower costs of active treatment (drug acquisition and administration).Furthermore, Novartis assume incorrectly that the cost of the sunitinib drug acquisition was incurred for the same number of mean treatment cycles as everolimus, on the basis that their ITC found no difference in PFS duration between the two treatments. Instead, we used the treatment durations for both treatments from the two RCTs. Together this resulted in Novartis finding everolimus to be dominant over sunitinib.

The Novartis submission mostly fulfils the requirements of the NICE Reference case. However, importantly BSC was omitted as a comparator, despite being a comparator in the original RCTs from which the effectiveness of the targeted treatments was derived. Another deviation from the NICE Reference case was that utility values were obtained from descriptions of health states by experts as opposed to actual health related quality of life outcomes measured in patients. Another exception is its use of list prices for octreotide treatment instead of prices at discounts available to hospitals in England.

Novartis misrepresented the wide confidence intervals in their estimates of relative effectiveness as evidence of no effect. An appropriate means of synthesising the data would have been to produce probabilistic sensitivity analysis using the point estimates of OS and PFS HRs with their associated standard errors; Novartis only presented PSA restricted by the assumption of equal effectiveness for the two treatment options. A second important limitation is the data sources on effectiveness, AEs and treatment duration outcomes of sunitinib in the A6181111 trial used in their economic evaluation by Novartis. We found updated data (including AE data in Pfizer's submission to NICE) on those outcomes which are more favourable to sunitinib, including the incidence of Grade 3/4 considered by Novartis (HR of 1.3 as opposed to Novartis's 4.7), a lower treatment duration with sunitinib, and a higher estimate of OS effectiveness for sunitinib vs. placebo (HR of 0.34 (95%CI 0.14 – 1.28) vs. Novartis's 0.43 (95% CI 0.17 – 1.20)). We used this data in our economic model. Finally a strong limitation of the indirect comparison of effectiveness, safety and concomitant SSA medication use of the two treatments is that the patient characteristics are quite heterogeneous between the two RCTs. Sensitivity analyses using available effectiveness estimates that adjust for imbalance in baseline characteristics between the two treatment arms would have partly addressed this issue but were not conducted by Novartis.

Novartis evaluation of GI/Lung

In GI/Lung NETs, Novartis compared Everolimus plus BSC with BSC alone, using data from the RADIANT-4 trial. It estimated an incremental cost-effectiveness ratio (ICER) of £43,642 per QALY gained at list prices, and an ICER of [redacted] per QALY gained at everolimus PAS discount of [redacted]. The company found that the results were most sensitive to the choice of parametric OS curves used to extrapolate outcomes up to 30-years after the start of treatment. The company also found that their ICER diminished as the time horizon was extended from the end of the trial to 30-years post-treatment horizon, so that everolimus is less likely to be cost-effective at shorter time horizons or, equivalently, at higher discount rates.

The economic evaluation met the requirements of the NICE reference case except in its use of list prices for octreotide treatment instead of prices at discounts available to hospitals in England. The analysis included costs of drug administration and acquisition, AEs, healthcare resources use and post-progression therapy. The utility values were obtained from FACT-G health-related quality of life outcomes of patients measured in the RADIANT-4 trial, and mapped to EQ-5D scores using a published algorithm. The company used the trial data to populate the model with detailed estimates of the incidence of AEs, frequency of use of subsequent treatments after disease progression, and concomitant symptomatic medication and BSC use. Health care use, including physician visits, procedure and tests, and hospitalisations were derived from a resource use survey of UK clinicians tailored specifically to the non-functional GI patient management experience.

The strength of the evaluation was its use of effectiveness and safety individual patient data from the RADIANT-4 trial. Among its weaknesses was the immature state of the OS data, since approximately [redacted] of patients were still alive at the end of follow-up in RADIANT-4. Another limitation is the lack of actual data on resource utilisation, since the survey was only partly based on a retrospective review of actual resource use by GI patients but limited to the stable disease; progressive disease (PD) resource use data represented hypothetical experiences of patients seen by the surveyed clinicians. A minor limitation is that some patients (6%) in the placebo arm in RADIANT-4 crossed over to receive everolimus after disease progression; the company did not adjust the OS estimates to account for cross-over but instead included the drug acquisition and administration costs of subsequent treatments in the analysis. Cost-effectiveness estimates were sensitive to the choice of parametric survival curves.

AAA evaluation of pancreatic NETs and GI NETs

In pancreatic NETs AAA compared 177Lu-DOTATATE with everolimus and sunitinib, but not with BSC, which we consider a major omission. They used relative health effects synthesised from their MTC of NETTER-1 (177Lu-DOTATATE versus high dose octreotide), RADIANT-3 (everolimus versus placebo), and A6181111 (sunitinib versus placebo). In GI NETs AAA compared 177Lu-DOTATATE with everolimus, but not BSC, which we again consider a major omission. They used relative health effects synthesised from their MTC of NETTER-1, RADIANT-2 (everolimus versus placebo in patients with carcinoid syndrome and functioning NETs), and RADIANT-4 (everolimus versus placebo in patients with non-functioning NETs in GI and lung primary sites). The company provided a further comparison of 177Lu-DOTATATE versus octreotide in both pancreatic NETs and GI NETs, but since octreotide is not a comparator of the MTA it was excluded from our review.

In their base case, AAA found that for people with pancreatic NETs 177Lu-DOTATATE is a cost effective option versus both everolimus (ICER of £9,847 per QALY gained at list prices) and sunitinib (177Lu-DOTATATE is dominant: both more effective and less costly at list prices). Similarly, for people with GI NETs they found 177Lu-DOTATATE to be cost effective versus everolimus (ICER of £19,816 per QALY gained at list prices). However, in our assessment we have found that reliance on strong assumptions in the MTCs, and costing oversights, introduce significant uncertainty and potential bias around these ICERs.

One modelling limitation common to both pNET and GI NET evaluations arises from the MTC networking used to estimate relative treatment effects for PFS and OS. In connecting the MTC networks it was necessary for the company to assume that octreotide 60mg is equivalent to placebo, octreotide 30mg, and placebo plus BSC; we also assumed this for our economic evaluation in GI midgut. Also, the company did not adjust for the extent of treatment switching in the pNETs RCTs, which limits the interpretation of results for OS. Furthermore, the population of RADIANT-2 had functioning neuroendocrine tumours, people who are not licensed to receive everolimus in the UK, so this trial should have been excluded from the MTA as out of scope. In a serious limitation of the pNET evaluation the company used data from the NETTER-1 trial to inform the MTC network even though no participants within NETTER-1 had pancreatic NETs. The 177Lu-DOTATATE treatment effects synthesised from the MTCs produced estimates with wide 95% confidence intervals. In pancreatic NETs the HR relative to everolimus in PFS was [redacted], and relative to sunitinib it was [redacted]. For OS the HRs were [redacted] and [redacted], respectively. Beyond survival analyses, the utility estimates for patients with pancreatic NETs and GI NETs were selected from two uncontrolled sources, for which the rationale and justification was not clear in the company's description of methods. In the pancreatic NETs evaluation the estimates for stable and progressive disease were not plausibly different (0.80 c.f. 0.79).

The company's submission it fulfils the general requirements of the NICE reference case, except for the omission of a BSC comparator, as this was a scoped treatment. Further serious limitations were however identified in the cost analyses of the evaluations. Most notably, AAA did not use the mean durations of treatment from the RCTs in their costing of everolimus and sunitinib, instead they costed for the entire period of pre-progression. Since this oversight is not relevant to 177Lu-DOTATATE, which has a fixed treatment schedule, the acquisition costs of everolimus and sunitinib are overestimated and so the evaluation of cost-effectiveness favours 177Lu-DOTATATE. Also, a dose intensity of less than 100% was applied in the case of 177Lu-DOTATATE to reflect in-trial observation, but not for everolimus or sunitinib. These two costing flaws are important because in both evaluations, the company found the ICERs were sensitive to 177Lu-DOTATATE acquisition costs. We would therefore have liked to see the ICERs tested for sensitivity to everolimus or sunitinib acquisition cost. Finally, we believe the company have underestimated the administration cost of 177Lu-DOTATATE. As a radio-labelled somatostatin analogue our guidance from expert clinicians in nuclear medicine is that greater resourcing would be expected than is costed by the company, and current routine practice in England is for admission overnight rather than day case.

PenTAG de novo economic model and evaluation

We undertook a de novo cost-effectiveness analysis of the following decision problems:

pancreatic NETs

- Everolimus +BSC
- Sunitinib + BSC
- BSC alone

GI and Lung

- Everolimus + BSC
- BSC alone

GI (midgut)

- Everolimus + BSC
- 177Lu-DOTATATE + Octreotide 30mg (included as intervention in scenario analyses)
- BSC alone

We assumed patients started treatment aged 60, and assumed a 40-year time horizon. Costs and QALYs were discounted at 3.5% p.a. This is in keeping with the NICE scope with the exception of the omission of interferon alpha, which we omitted on the advice of our clinical experts that it is rarely used.

These analyses were undertaken using the same three-health state model structure used in the economic evaluation literature in NETs, also used by the companies submitting evidence to NICE (Novartis and AAA). The model assumed partitioned-survival using summary data on PFS, OS, and time on treatment outcomes in RADIANT-3 and A6181111 (for pancreatic NETs), RADIANT-4 (for the GI and Lung population, and GI (midgut) population) and NETTER-1 (for the scenario analysis of GI midgut including 177Lu-DOTATATE). We used OS data that were adjusted by the rank-preserving failure time model whenever available.

We extrapolated observed PFS and OS in the RCTs by estimating parametric distributions of recreated individual patient time to event PFS and OS data from those trials. We assessed the internal validity of the parametric curve fits to the observed data and considered the external validity of the extrapolations by comparing the long term survival projections with registry data cited by Novartis in their submission to NICE and in consultation with our clinical advisors. For the indirect comparison in pNETs, we adjusted PFS and OS of sunitinib by the relative difference in restricted mean time to event for the respective outcome between placebo in RADIANT-3 and placebo in A6181111. A similar approach was followed for the scenario analysis of GI (midgut) that included a 177Lu-DOTATATE intervention arm.

We measured the costs of drug administration and acquisition, AEs, healthcare resources use and post-progression therapy costs. In the base case analysis, list prices were used for initial targeted treatments, and discounted prices available to English hospitals were applied to symptomatic and subsequent (after progression) treatment with octreotide. For the GI and Lung and GI (midgut) analyses, the same quantities of BSC, Grade 3/4 adverse event incidence, and subsequent treatment use (derived from data in RADIANT-4) and other health care resources (based on a survey of experts adapted to non-functional GI) were used as in the model analysis of the same location by Novartis. For the analysis in pancreatic NETs, we used the same healthcare resource use estimates as Novartis for

pNETs, which were based on individual patient data from RADIANT-3 on BSC and subsequent treatment use and adverse event incidence. Since data on subsequent treatment use for sunitinib were not available (these data were not collected in A6181111), and given that we used OS adjusted for treatment switching, we excluded such costs from the analysis of pNETs. Due to the complexity of accurately modelling subsequent treatment costs after disease progression in a partitioned survival model structure as that used by us and the company models, we also excluded subsequent treatment costs from the base case analysis of GI and Lung and GI midgut, and explored their likely importance in sensitivity analyses.

In pancreatic NETs, there were no available data on utilities derived from patient reported outcomes for health states under everolimus. Since we did have estimates for sunitinib and BSC from A6181111, we assumed that the utility of PD would be the same in all treatment arms, and that the stable disease (SD) utility of everolimus would only differ from that of sunitinib by the disutility of their different Grade 3/4 AE profiles. Given the AE data in RADIANT-4 and A6181111, we calculated that this difference was negligible and therefore assumed the same utility values for the two targeted treatments in SD. In GI and Lung and GI (midgut) NETs we used arm specific utility values for everolimus plus BSC vs. BSC alone estimated by Novartis from RADIANT-4.

In the base case analysis in pancreatic NETs, we found that sunitinib produced the most life years per patient, 6.39, followed by everolimus, 4.69, and BSC only, 3.46. The expected discounted QALYs were 3.24, 2.51 and 1.91, respectively. The respective discounted costs were £43,192, £42,646, and £15,761. Sunitinib (extendedly) dominated everolimus, i.e. while both targeted treatments produced additional QALYs over BSC alone, sunitinib did so at a lower cost per QALY gained than everolimus and with greater total QALYs and costs. At list prices, the ICER for everolimus vs. BSC was £45,493 per QALY and the ICER of sunitinib vs BSC alone was £20,717.

In the base case analysis of GI and Lung NETs, everolimus resulted in 6.21 life years and 3.74 discounted QALYs per patient, while BSC alone yielded 4.82 life years and 3.05 discounted QALYs per patient. The total per patient discounted costs to the NHS with each treatment option were £47,334 and £16,526, respectively. At list prices, the ICER was £44,557 per QALY gained with everolimus relative to BSC alone.

In the GI (midgut) population, the base case analysis resulted in 7.50 life years and 4.37 discounted QALYs for everolimus, and 7.05 life years and 4.19 discounted QALYs for BSC alone. The total costs were respectively £55,842 and £21,119. Therefore, at list prices, the ICER was £199,233 per QALY.

A range of scenario analyses were conducted. In pNETs, the more salient finding was that adjustment for the effect of cross-over on overall survival has a large effect on cost-effectiveness; when relative effectiveness estimates from ITT OS data were used, everolimus produced more costs and lower QALYs than sunitinib, and had an ICER relative to BSC of £136,455 per QALY (c.f. £45,493 base case), whereas the ICER for sunitinib vs. BSC was £37,217 per QALY gained (c.f. £20,717 base case), at current list prices.

In GI midgut, applying background mortality produced ICERs for everolimus that were higher than £40,000 per QALY (c.f. base case £199,000). Another scenario involved the indirect comparison of everolimus and BSC alone with 177Lu-DOTATATE in GI midgut. This analysis was restricted to costs and benefits accrued for the duration of PFS only. In this

analyses, 177Lu-DOTATATE (extendedly) dominated everolimus (which had an ICER of £90,181 relative to BSC at list prices), and 177Lu-DOTATATE had an ICER of £30,115 relative to BSC alone.

The structures of our model and the models of Novartis and AAA are similar: all considered the same health states (PFS, PD), and assumed survival partitioning. The main differences between our results and those submitted to NICE by the companies are explained by the following factors. In pNETs whilst we included BSC as a comparator, neither Novartis nor AAA did so. We consider this a major omission in the company analyses. This also means that we are unable to compare our estimates of cost-effectiveness of everolimus and sunitinib versus BSC with estimates from the companies. AAA perform a comparison in pNETs, but that was underpinned by the assumption that results of the only trial of 177Lu-DOTATATE, which was conducted in GI midgut NETs applied to pNETs. We consider this crucial assumption unwarranted due to lack of supporting data. Due to the lack of head-to-head RCT evidence the estimates of relative effectiveness are highly uncertain in this area. Novartis thus assumed equal effectiveness between the initial targeted treatments, which we consider an inappropriate assumption. Consequently, their estimates of health benefit were driven by utility differences associated with safety outcomes, whose impact on health related quality of life of actual patients is not documented in the available evidence. We adopted the opposite approach, that is, to populate our analyses using the available estimates of relative effectiveness, accounting for their associated uncertainty in probabilistic analysis, and assume no differences in quality of life, since the differences in safety outcomes were not sufficient to amount to detectable utility differences. In addition, Novartis adopted estimates of targeted sunitinib treatment duration that were in excess of what has been documented in the effectiveness trial of sunitinib, which we consider a major weakness. By contrast, we sourced treatment durations from the relevant RCTs.

In GI and Lung NETs the main difference with Novartis was our use of treatment specific utility values in stable disease as opposed to their use of the same utility values in stable disease in both treatment arms (everolimus plus BSC and BSC alone); Novartis considered treatment specific utilities in scenario analyses. Given the paucity of resource use data we have adopted most of the company's base cade values. The main differences in our analyses for GI (midgut) from those of AAA was in the company's assumption that everolimus would be received continuously until disease progression, which ignores treatment discontinuation while on stable disease that we accounted for, and their indirect comparison of outcomes for 177Lu-DOTATATE in NETTER-1 subjects, who had GI midgut NETs, with outcomes for everolimus in the overall RADIANT-4 population, which included Lung and non-midgut GI NETs. Our scenario analysis for GI midgut NETs used PFS data for the midgut only NETs subgroup of RADIANT-4.

End of life criteria

Based on the data from the three sources of effectiveness data (RADIANT-3, A6181111, and RADIANt-4), only sunitinib plus BSC in the pancreatic NETs population of A6181111 may meet the end of life criteria.

Conclusions

Our results suggest that there is a high degree of uncertainty in the effectiveness and cost-effectiveness in advanced, progressive pancreatic NETs and GI and Lung NETs. This uncertainty has its origins in the lack of data that naturally accompanies a rare condition. The

evidence suggests that targeted initial treatments do provide benefits in PFS but the effects on OS are uncertain, partly because the few RCTs available in this area do not adequately document how patients are managed after disease progression, because of the immaturity of some of the OS data, and because of substantial patient switching on disease progression in some trials. The Rank-preserved Structural Failure time method was used to adjust for substantial treatment switching in the two RCTs for pancreatic NETs. After this adjustment, the estimated cost-effectiveness of everolimus and sunitinib improves substantially. Given that all adjustment methods make strong assumptions concerning treatment effects, this introduces substantial and important uncertainly in estimated cost-effectiveness. Also patients involved in the different RCTs are likely to be heterogeneous, particularly in pNETs, which is associated with worse prognosis than other NETs.

Another area of uncertainty is the relative effects on health related quality of life of targeted treatments. Although some of the RCTs underpinning this technology assessment review have measured these outcomes, outcomes tend to cover only the phase while patients are on treatment and it is therefore not known how health related quality of life evolves over time, or towards the end of life. It is evidence from the available data on incidence of AEs that even while patients are on active targeted treatment the available quality of life data are inadequate to differentiate between those treatments.

Some of the uncertainty in the data will be addressed as trials such as NETTER-1 and RADIANT-4 mature, allowing for more information on overall survival.

Nevertheless, in pNETs, at current list prices, the ICERs relative to BSC alone are likely to be about £20,000 per QALY for sunitinib and about £45,000 per QALY for everolimus. Everolimus is expected to have a similar ICER in GI and Lung, but is unlikely to be cost-effective in GI midgut NETs. The effectiveness evidence on 177Lu-DOTATATE is still immature to make conclusive statements about cost-effectiveness, but our exploratory analyses suggest that it produces significantly better PFS outcomes than everolimus or BSC, and purely on these outcomes, its ICER vs. BSC is approximately £35,000 per QALY.

We sought to address some of the uncertainties in the evidence base by requesting data from the sponsors of the main RCTs. Unfortunately we received such data for only one of the trials, and such data only covered the data cut-off in the main effectiveness paper dating 4 years ago. Further valuable research would use individual patient data from RADIANT-4 to explore 1) the effect of adjustment for cross-over from placebo to active treatment on OS effectiveness and cost-effectiveness; 2) the robustness of results of indirect comparisons with NETTER-1 using a range of methods ranging from simple Bucher-type to more elaborate matching methods such as those reviewed and investigated in this assessment. An updated MAIC analysis for pNETs using RADIANT-3 would help to assess the robustness of the available effectiveness and cost-effectiveness evidence, particularly in the light of the recently updated OS data produced by the effectiveness RCTs.

Comparison of AG results to Company results (Excluding PASs)

Everolimus, sunitinib, and BSC in P NETs (Novartis, AAA and ourselves)

The AG and Novartis models showed close agreement in the total cost of both everolimus and sunitinib strategies, but we believe Novartis underestimate life-years for sunitinib given that they did not use updated data from A816111 in their MTC, which are more favourable to

sunitinib, including a higher estimate of OS effectiveness for sunitinib versus placebo. In contrast, the AAA model produced different cost, life-years and QALY results to ourselves. The AAA model in P NETs was seriously flawed due to their adoption of baseline PFS and OS risk from a cohort of patients with GI (midgut) NETs patients using 177Lu-DOTATATE in a non-randomised study. AAA also failed to adjust for treatment cross-over, treatment duration, and relative dose intensity in RADIANT-3 and A6181111.

Everolimus and BSC in GI and Lung NETs (Novartis and ourselves)

Overall there was satisfactory consistency in total costs and QALYs between the strategy results produced by the AG and Novartis models.

Everolimus, 177Lu-DOTATATE and BSC in GI (midgut) NETs – scenario analysis (AAA and ourselves)

The AG and AAA estimates of survival and cost for people who were treated with everolimus were significantly different, although there was some consistency in the costing of the 177Lu-DOTATATE strategy. AAA's estimates of OS for everolimus and 177-Lu-DOTATATE were significantly less than our own. For 177Lu-DOTATATE the difference in years of undiscounted life expectancy (4.79 in AAA versus 6.66 in AG) is due to the different methods of OS extrapolation, as AAA used a proportional hazards treatment effect on a baseline Weibull distribution function, which showed an increasing trend in death risk, whereas AG used an exponential distribution, which is characterised by a constant risk of death, supplemented by background mortality risk. AAA did not provide any statistical evidence in support of its assumed proportional hazards model for 177Lu-DOTATATE in NETTER-1; AG fitted separate parametric curves to 177Lu-DOTATATE in NETTER-1 and found that the exponential was the model with the best goodness-of-fit statistics. The differences in survival time was most pronounced in the case of PPS following everolimus, where AAA included lung and other non-midgut NET patients from RADIANT-4 in their calculation, and baseline risk of progression and death for both everolimus and 177Lu-DOATATE was that of people treated with octreotide 60 mg; AG instead used the RADIANT-4 data as the reference patient population, to which patients treated with 177Lu-DOTATATE were matched by a Bucher-type indirect comparison adjustment method. In their costing, AAA did not include hospital consultations, assumed every patient was treated with octreotide from progression until death, and opted not to include end-of-life costs, but in summation these limitations were counter-balancing. However, the absence of adjustment for mean treatment duration and relative dose intensity observed in RADIANT-4 does unfairly inflate the cost estimate of everolimus.

Plain English Summary

Neuroendocrine tumours (NETs) usually occur in the intestine, but they are also found in the pancreas, lung and the rest of the body. Here we consider patients with advanced NETs who have previously been treated and who are not suitable for surgery. We review the evidence for the effectiveness and cost-effectiveness of three drugs used for treating NETs.

We systematically reviewed the effectiveness literature and wrote a mathematical model to estimate the cost-effectiveness of the following treatments for use in the NHS in England and Wales: sunitinib and everolimus for pancreatic NETs, everolimus for gastrointestinal and lung NETs and everolimus and 177Lu-DOTATATE for midgut NETs.

We critically reviewed three relevant clinical trials. All suggested that the new treatments slow disease progression and reduce the risk of death. However, they also increase the chance of side effects. It was difficult to compare the effectiveness of sunitinib and everolimus for pancreatic NETs, because in both relevant trials, many patients assigned the control treatment subsequently received sunitinib or everolimus after their disease relapsed. After adjustments were made to correct for this, we found no evidence for a difference in effectiveness between sunitinib and everolimus for treating pancreatic NETs.

Two pharmaceutical companies also wrote mathematical models to estimate the cost-effectiveness of their drugs: Novartis for everolimus and AAA Ltd for 177Lu-DOTATATE.

Given currently accepted thresholds for cost-effectiveness, our analysis suggests that, based on publicly available drugs prices, only sunitinib for pancreatic NETs might be considered good value for money in England and Wales.

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Abbreviations

AAA	Advanced accelerator applications
ACTH	Adrenocoricotrophic hormone
AEs	Adverse effects of treatment
AG	Assessment group
BSC	Best supportive care
CDF	Cancer Drugs Fund
CI	Confidence intervals
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrIs	Credibility intervals
CSR	Clinical study report
CT	Computed tomography
DIC	Deviance information criteria
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumor Society
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full analysis set
GEP	Gastroenteropancreatic
GI	Gastrointestinal
GRP	Gastrin-releasing peptide
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRC	Independent reading centre
ITC	Indirect treatment comparison
ITT	Intended to treat
LAR	Long acting release
MCMC	Markov chain Monte Carlo
MDT	Multidisciplinary team
MEN1	Multiple endocrine neoplasia type 1
MRI scans	Magnetic resonance imaging
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
mTOR	Mammalian target of rapamycin
NE	Not evaluable
NECs	Neuroendocrine carcinomas
NEN	Neuroendocrine neoplasm
NETs	Neuroendocrine tumours
NOS	Not otherwise specified
OD	Odds ratios
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Schemes
PD	Progressive disease
PET	Positron emission tomography and computed tomography
PFS	Progression free survival
PHE	Public Health England
pNETS	Pancreatic neuroendocrine tumours
PR	Partial response

PRRT	Peptide receptor radionuclide therapy
PS	Performance score
QALY	Quality Adjusted Life Year
QLQ-30	Quality-of-life questionnaire vs3.0
RCT	Randomised controlled trial
RPSFT	Rank Preserving Structural Failure Time
RR	Response rates
SD	Stable disease
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SSA	Somatostatin analogues
TEAE	Treatment-emergent adverse event
TNM	Tumor-node-metastasis
UICC	Union for international cancer control
UKINETS	UK and Ireland Neuroendocrine Tumour Society
VEGF	Vascular endothelial growth factor
VHL	von Hippel-Lindau syndrome
VIP	Vasoactive intestinal peptide
WHO	World Health Organisation

1 Background

1.1 Description of the health problem

Neuroendocrine tumours (NETs) is the overarching term for the group of heterogeneous cancers which develop in cells in the diffuse neuroendocrine system. The diffuse endocrine system is made up of neuroendocrine cells found in the respiratory and digestive tracts. Since these cancers share common clinical features, they are considered under the same group of neoplasms.[1] Most commonly, NETs are found in the lungs, pancreas or gastrointestinal system. NETs also encompass carcinoids any may be referred to as neuroendocrine carcinoids (NECs) which leads to substantial confusion over their name.[2]

1.1.1 Aetiology, pathology and prognosis

The aetiology of NETs is poorly understood.[1] Predominantly, NETs are sporadic in nature (i.e. arise from *de novo* changes), however there is a small genetic risk associated with familial endocrine cancer syndromes. Neuroendocrine cells are present throughout the gut and are the largest group of hormone-producing cells in the body.[2] NETs develop slowly and may remain undetected over a number of years. Therefore, it is common for NETs to be diagnosed when they have already metastasised (that is, spread to other organs or tissues in the body).

1.1.1.1 Characteristics of neuroendocrine tumours

The characteristics of a NET will determine the methods of treatment and impact the prognosis. Important characteristics include the location, grade and differentiation, stage of tumour and secretory profile of the tumour. There are however, inconsistencies in the reproducibility of diagnoses between pathologists and institutions – suggested to be caused by the use of a variety of different classification systems, and a lack of adherence to them.[2]

1.1.1.1.1 Location

Most NETs have been generally classified as foregut (including those in the lungs), midgut or hindgut, since it was thought that they were derived from embryonic neural crest cells. However this theory is not now accepted and now classification should be on site of origin of the tumour, i.e. lung, stomach, small bowel, large bowel (colon). The term carcinoid is outdated but colloquially refers to NET of the small bowel which secrete 5Hydroxtryptamine and carcinoid is still in common usage for NET of the lung. NET is the preferred term for all the tumours. NET tumours maybe grouped together as gastroenteropancreatic neuroendocrine tumours (GEP NETs). Typically, the locations are as follows:[1]

- Foregut tumours: develop in the bronchi, stomach, gallbladder duodenum, and pancreas
- Midgut tumours: develop in the jejunum, ileum, appendix and right colon
- Hindgut tumours: develop in the left colon and rectum

Prognosis can be dependent on where the tumour is located. An analysis of 13,715 carcinoid tumours over a 5-decade period in the USA reported that the best 5-year survival rates were found in patients with rectal (88.3%), bronchopulmonary (73.5%), and appendiceal (71.0%) NET.[3] Lowest 5-year survival rates were found in patients with pancreatic NETs (pNETs) (37.5%).[3]

Pancreatic NETs

NETs from the pancreas may also be called endocrine tumours of the pancreas and include insulinomas (which produce the hormone insulin), gastrinomas (which produce the hormone gastrin), glucagonomas (which produce the hormone glucagon), VIPomas (which produce the hormone vasoactive intestinal peptide) and somatostatinoma (which produce the hormone somatostatin). However, the majority of pNETs are non-functioning and do not produce measurable hormone that give symptoms.

Other NETs

Other, rarer locations for NETs include the thyroid gland (medullary thyroid tumours), skin (Merkel cell cancer), pituitary gland, parathyroid gland and the adrenal gland.

This assessment report focuses on the tumours of the pancreas, gastrointestinal (GI) tract and lung since these are locations for which the interventions of interest are licensed.

1.1.1.1.2 Tumour grade/degree of differentiation

The grade of a NET can be defined as grade 1, 2 or 3. The grade relates to an estimation of how fast the cells are dividing to form new cells and is based on the histological assessment and the mitotic count of the tumour. The grade of a tumour is also related to its differentiation. Differentiation relates to how well/little the tumour looks like the normal tissue/tissue of origin. Well-differentiated and low grade cancer cells look more like normal cells and tend to grow and spread more slowly than poorly differentiated cells. High-grade tumours have cells that look very abnormal and are likely to grow and spread rapidly.

In 2010, the WHO introduced a new system for grading cancer tumours (Table 1).[4] This grading system is also endorsed by the European Neuroendocrine Tumor Society (ENETS) grading schemes.[5, 6]

Table 1: Grade of a neuroendocrine tumour (NET)

Grade	Differentiation	Ki-67 Index[a]	Mitotic count/ 10 HPF[b]
NET Grade 1 (low grade)	Well-differentiated tumour with a low number of cells actively dividing	≤2%	<2 [c]
NET Grade 2 (intermediate grade)	Well-differentiated tumour, but with a higher number of cells actively dividing	3-20%	2-20[c]
Neuroendocrine carcinoma, Grade 3 (NEC; high grade)	Poorly differentiated, malignant carcinoma (most aggressive form of NET)	>20%	>20

Key: HPF, High power fields; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour;
Notes: a, Ki-67 index: % of tumour cells in a 2000 cell sample from the areas of highest nuclear labelling; b, 10 HPF = 2 mm^2 based on each HPF being 0.2 mm^2 with at least 40 fields evaluated in areas at highest mitotic density; c, Note that the exception to the 2% MIB1 threshold is the pancreas. A large study showed that when a 5% rather than 2% Ki-67 labelling index cut-off was applied, Ki-67 was an independent predictor of prognosis.

1.1.1.1.3 Stage of tumour

Determination of the size of a tumour and whether it has spread beyond its original site is known as the stage of the tumour. Tumour staging is performed according to a system of site-specific criteria. There are two main systems for staging NETs; the Union for international cancer control (UICC) TNM (7th edition; Table 2),[7] and the ENETS staging

system(Table 3).[5, 6] The Royal College of Pathologists recommended both the WHO and the ENETS systems for assessing the staging of a NET.[8] In current practice, both staging systems are used together with the grading system above. The difference between TNM and ENETS is not great and would not affect outcomes relating to this report.

Table 2: TNM staging criteria of NETs of the digestive tract and pancreas according to UICC TNM 7th edition

	T-Stage			
Site	T1	T2	T3	T4
Stomach	Invasion of (sub)mucosa and size ≤1cm	Invasion of muscularis propria or size >1cm	Invasion of subserosa	Perforation of serosa or invasion of adjacent structures
Duodenum, Ampulla, Upper jejunum	Invasion of (sub)mucosa and size ≤1cm	Invasion of muscularis propria or size >1cm	Invasion of pancreas or retroperitoneum	Invasion of peritoneum or other organs
Lower Jejunum, Ileum	Invasion of (sub)mucosa and size ≤1cm	Invasion of muscularis propria or size >1cm	Invasion of subserosa	Invasion of peritoneium or other organs
Colon/ Rectum	Invasion of (sub)mucosa T1a: size <1cm T1b: size 1-2cm	Invasion of muscularis propria or >2cm	Invasion of subserosa/ pericolic/ perirectal fat	Invasion of peritoneum or other organs/ structures
Appendix	Size ≤2cm T1a: <1cm T1b: >1cm to <2cm	Size ≥2 to ≤4 cm or extension to caecum	Size >4 cm or extension to ileum	Perforation of peritoneum or invasion of other organs
Pancreas	Limited to pancreas and size <2cm	Limited to pancreas and size >2cm	Outside pancreas but no invasion of coeliac axis/SMA any size	Invasion of coeliac axis/SMA

Key: SMA, superior mesenteric artery

Table 3: TNM staging criteria for NETs of the stomach, appendix and pancreas according to the ENETs system

	T-Stage			
Site	T1	T2	T3	T4
Stomach	Invasion of (sub)mucosa and size <1 cm	Invasion of muscularis propria or subserosa or size >1 cm	Penetration of serosa	Invasion of adjacent structures
Appendix	Size <1 cm and invasion of submucosa or muscularis propria	Size <2 cm and invasion of submucosa, muscularis propria and/or <0.3 cm into subserosa/mesoappendix	Size >2 cm and/or >0.3 cm into subserosa/ mesoappendix	Invasion of peritoneum or other organs
Pancreas	Limited to pancreas and size <2 cm	Limited to pancreas and size 2–4 cm	Limited to pancreas and size >4 cm or invasion of duodenum or bile duct	Invasion of coeliac axis / SMA, stomach, spleen, colon, or adrenal gland

Key: SMA, superior mesenteric artery

1.1.1.1.4 Secretory profile

A tumour that is releasing above typical levels of hormones is known as a functioning tumour. The increase in hormone release will often cause symptoms which may themselves need treating in addition to treating the cancer. Table 4 reports the typical hormones released based on the primary tumour sites. Tumours that are not releasing hormones, and therefore have no hormone-related clinical features, are known as non-functioning tumours.

Table 4: Typical hormones released based on primary tumour site

Primary Tumour Site	Hormone released
Pancreas	Insulin, glucagon, pancreatic polypeptide, somatostatin, gastrin, vasoactive intestinal peptide (VIP), adrenocorticotrophic hormone (ACTH), prolactin.
Stomach and duodenum	Gastrin, serotonin, somatostatin, gastrin-releasing peptide (GRP).
Ileum and caecum	Serotonin, tachykinins, substance P.
Colon and rectum	Serotonin, somatostatin, peptide YY.
Appendix	Serotonin, somatostatin, enteroglucagon

Source: Appendix 5 Ramage 2012 online supplementary material

1.1.2 Epidemiology

1.1.2.1 Incidence and/or prevalence

In October 2016 Public Health England (PHE) published, the first data briefing on the incidence and survival of NETs and neuroendocrine carcinomas (NECs) in England. In 2013 and 2014, 8,726 neoplasms were diagnosed, equating to 4,000 per year or approximately a rate of 8 per 100,000 persons per year (not age-standardised). Although the annual incidence of NETs is low, due to the long survival of individuals with NETs, the prevalence is much greater, and has been calculated as 35/100,000.[9]

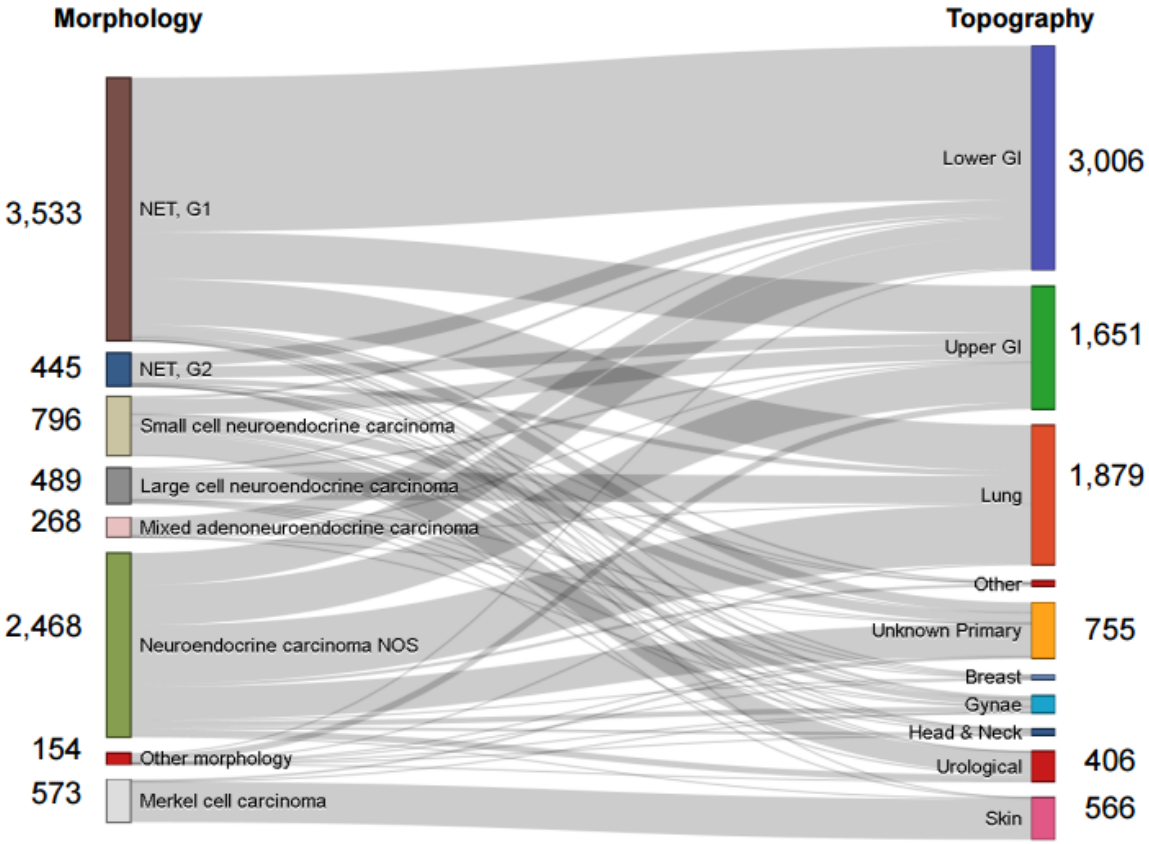
Incidence trends for NETs were compared between a Norwegian registry and an American registry[10]. From the time period 1993-1997 to 2000-2004, there was an incidence rate increase of 72% for NETs in Norway (2.35 to 4.06 per 100,000 people).Over the same time periods in America, the increase was 37% (4.22 to 5.79 per 100,000 people) for the Caucasian population and 40% (5.48 to 7.67 per 100,000 people) for the black population. In a Canadian population, between 1994 and 2009, the incidence rates of all location NETs increased by 138% (2.46 to 5.86 per 100,000 people).[11]

More specifically for the subgroup GI NETs, Ellis et al. (2010)[12] reviewed incidence rates in the UK between 1971 and 2006. Between this time period, 10,324 cases of GI NETs were identified from the national population-based cancer registry. They report an overall increase per 100,000 people from 0.27 in men and 0.35 in women (1971 - 1978) to 1.32 for men and 1.33 for women (2000 - 2006). This is equivalent to an increase in incidence rates for GI NETs from 1971 to 2006 of 392% for men and for women 282%.[12]

These incidence rates of the diagnosis of NETs however, do not account for the overall prevalence of NETs. Since a delay in diagnosis is typically 5 to 7 years after the appearance of the first symptoms, many cases of NETs are undiagnosed.[1]

Public Health England produced a diagram depicting the morphology (the neuroendocrine neoplasms form) and topography (the neuroendocrine neoplasms location) of the 8,726 diagnosed NETs and NECs in 2013 and 2014 (Figure 1). Low grade (grade 1) NETs and not otherwise specified NECs make up the predominant morphology of neuroendocrine neoplasms in England.

Figure 1: Morphological and topological distribution of 8,726 neuroendocrine neoplasms diagnosed in England, 2013 and 2014



Key: GI, gastro-intestinal; G1 grade 1; G2, grade 2; NET, neuroendocrine tumour; NOS, not otherwise specified

Source: Public Health England: Incidence and survival in neuroendocrine tumours and neuroendocrine carcinomas (NETs/NECs) in England, 2013-2014

The PHE briefing describes some characteristics of the cohort:

- almost an exact 50:50 male:female ratio
- no obvious variation with geographic region
- no obvious variation for ethnicity
- distribution of age similar to that of other malignant cancers combined
- higher incidence of patients from the most affluent population quintile (20.2%) compared to the most deprived quintile (18.6%; p=0.011)

1.1.2.2 Risk factors

As NETs are sporadic in nature, there are very few factors known to determine susceptibility to developing a NET.

In the USA, African-American males have a higher overall incidence rate of NETs than other demographic groups.[3] Following an epidemiological review of NETs in Japan, the authors compared the distribution of the origin of NETs between European and Americans to their Asian population. In the former countries a midgut origin represented 30-60% of new NETs,

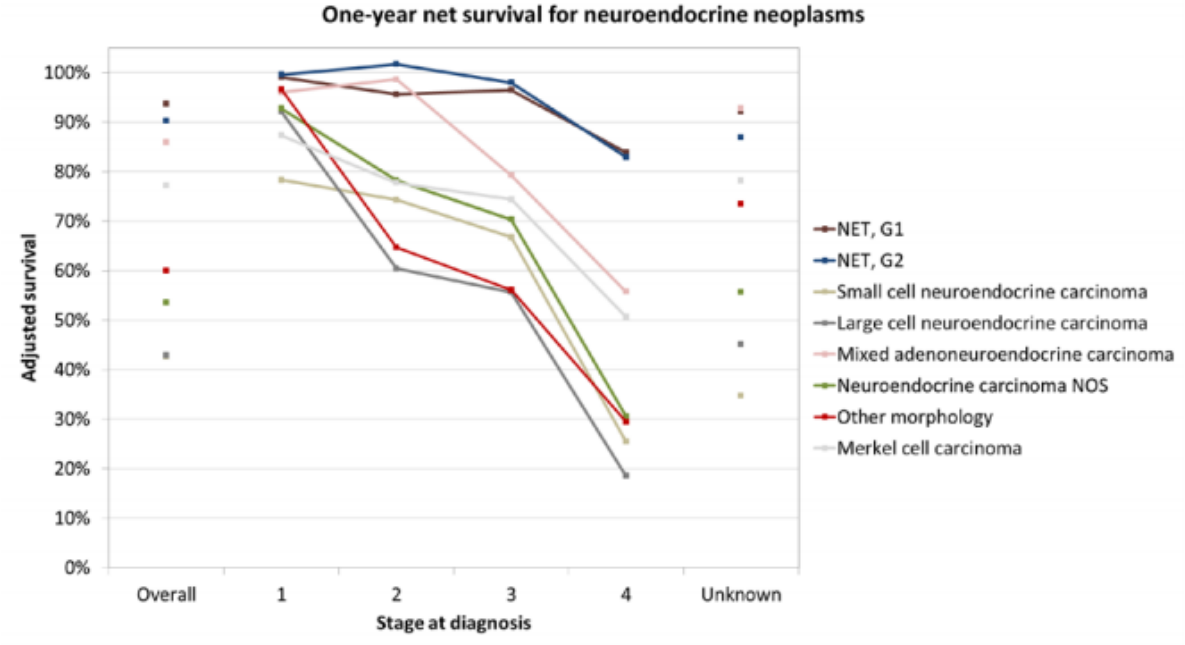
whilst in Japan and Asian Americans the midgut was the origin of less than 10%. In a parallel way, the hindgut constituted a higher proportion of new NETs in Asian populations.[13] An analysis case-control study on risk factors for NETs of the small intestine, stomach, lung, pancreas and rectum in 740 individuals with NETs and 924 healthy controls in the USA indicated an increased risk for women with a family history of cancer and diabetes mellitus.[14] In contrast, the UK PHE report found no association of ethnicity and gender with NET prevalence.[15]

There are some suggestions that individuals suffering from rare family syndromes may have a higher risk of developing NETs. These family syndromes include multiple endocrine neoplasia type 1 (MEN1), neurofibromatosis type 1 and von Hippel-Lindau syndrome (VHL).

1.1.2.3 Survival

While prognosis is generally better with an early diagnosis, the majority of NETs are diagnosed at a later stage when the tumour has already metastasised. The PHE briefing presented one-year net survival data for neuroendocrine neoplasms (Figure 2). A high one-year survival rate was observed in NETs (including NETs in advanced stages of presentation).

Figure 2: One year net survival for neuroendocrine neoplasms diagnosed in England, 2013-2014



Key: G1, grade 1; G2, grade 2; NET, neuroendocrine tumour; NOS, not otherwise specified
Source: Public Health England: Incidence and survival in neuroendocrine tumours and neuroendocrine carcinomas (NETs/NECs) in England, 2013-2014

In older data collected between 1986 and 1999 for 4,104 cases of malignant digestive endocrine tumours in England and Wales overall 5-year and 10-year survival was reported to be 45.9% and 38.4%, respectively[16]. Well-differentiated tumours had a higher 5-year survival rate (56.8%) whilst small cell tumours had the lowest (5.2%). Survival rates were higher for women and young people (15-54 years compared to 55-74 years and 75-99 years) and the overall prognosis was dependent on the features (e.g. tumour differentiation, anatomic site, histologic type) of the NET.[16]

While it is impossible to accurately compare different countries with the data available, median 5-years survival varied across Europe, Taiwan and Canada from 38% to 61%[11, 17, 18]. Whether survival has improved over time remains debated. Korse et al. (2013) reported in the Netherlands an on-going improvement in survival in well-differentiated NETs and suggested that the introduction of somatostatin analogues and their long-acting forms may explain this change in survival over time.[19] On the other hand, other research groups in the USA and France have not confirmed this trend.[20, 21]

1.1.3 Impact of health problem

1.1.3.1 Significance for patients in terms of ill-health (burden of disease)

While prognosis is better with an early diagnosis, NETs are generally diagnosed at a late stage when the tumour has already metastasised. In such case, treatment is rarely curative, although individuals can live and maintain a good quality of life for a number of years (e.g. 68 to 77% of people diagnosed with a carcinoid tumour will survive for five years or more)[22]. The primary management strategy for NETs is managing symptoms originating from the tumour. The onset of symptoms, however, may take between three and five years from the development of the tumour. Symptoms can vary widely, and some patients may have no symptoms or non-specific and vague (often leading to a delay in diagnosis).

Most individuals with NETs will experience non-specific symptoms such as pain, nausea and vomiting, and, in some cases, anaemia due to intestinal blood loss. Most gastro-enteropancreatic NETs are non-functioning and present predominantly with mass effects of the primary tumour or metastases (usually liver).[1] Symptoms are more common with functioning pNETs, where hormones are significantly elevated. Examples of symptom profiles are presented in Table 5.

Table 5: Clinical features of pancreatic NETs

Tumour	Symptoms
Insulinoma	Confusion, sweating, dizziness, weakness, unconsciousness, relief with eating
Gastrinoma	Zollinger-Ellison syndrome of severe peptic ulceration and diarrhoea, or diarrhoea alone
Glucagonoma	Necrolytic migratory erythema, weight loss, diabetes mellitus, stomatitis, diarrhoea
VIPoma	Verner-Morrison syndrome of profuse watery diarrhoea with marked hypokalaemia
Somatostatinoma	Cholelithiasis, weight loss, diarrhoea and steatorrhoea, diabetes mellitus
Non-syndromic pancreatic NET	Symptoms from pancreatic mass and/or liver metastases

Key: NET, neuroendocrine tumours
Source: Ramage et al 2012 [1]

Twenty percent of well-differentiated endocrine tumours of the jejunum or ileum (midgut NET) will have carcinoid syndrome. Carcinoid syndrome consists of (usually) dry flushing (without sweating; 70% of cases) with or without palpitations, diarrhoea (50% of cases) and intermittent abdominal pain (40% of cases).[1] The metastases in the liver release vasoactive compounds, including biogenic amines (e.g., serotonin and tachykinins), into the systemic circulation which cause the carcinoid syndrome. Direct retroperitoneal involvement with venous drainage bypassing the liver, may also cause carcinoid syndrome (i.e., it is not dependent on liver metastases).[1]

Carcinoid crisis may also occur in individuals with NETs. Symptoms include profound flushing, bronchospasm, tachycardia and widely and rapidly fluctuating blood pressure. It is usually linked to an anaesthetic induction for an operation or other invasive therapeutic procedure and is thought to be linked to the release of mediators leading to high levels of serotonin and other vasoactive peptides.[1]

1.1.4 Measurement of disease

There are a number of outcomes which can be measured in clinical trials or as part of the management of disease:

- Overall survival (OS): defined as the time from randomisation to death from any cause.
- Progression-free survival (PFS): defined as time from randomisation until disease progression or death.
- Objective response rate (ORR): defined as either a partial response (PR) or complete response (CR).
    - complete response (CR): all detectable tumour has disappeared
    - partial response (PR): roughly corresponds to at least a 50% decrease in the total tumour volume but with evidence of some residual disease still remaining
    - stable disease (SD): includes either a small amount of growth (typically less than 20 or 25%) or a small amount of shrinkage
    - progressive disease (PD): means the tumour has grown significantly or that new tumours have appeared. The appearance of new tumours is always PD regardless of the response of other tumours. Progressive disease normally means the treatment has failed.
- Health-related quality of life (HRQoL): How a person's well-being is affected by treatment.
    - HRQoL is a key measure for the treatment of NETs as this captures changes in symptom control. It is the control of the symptoms that have the most impact on the patient's day to day life.

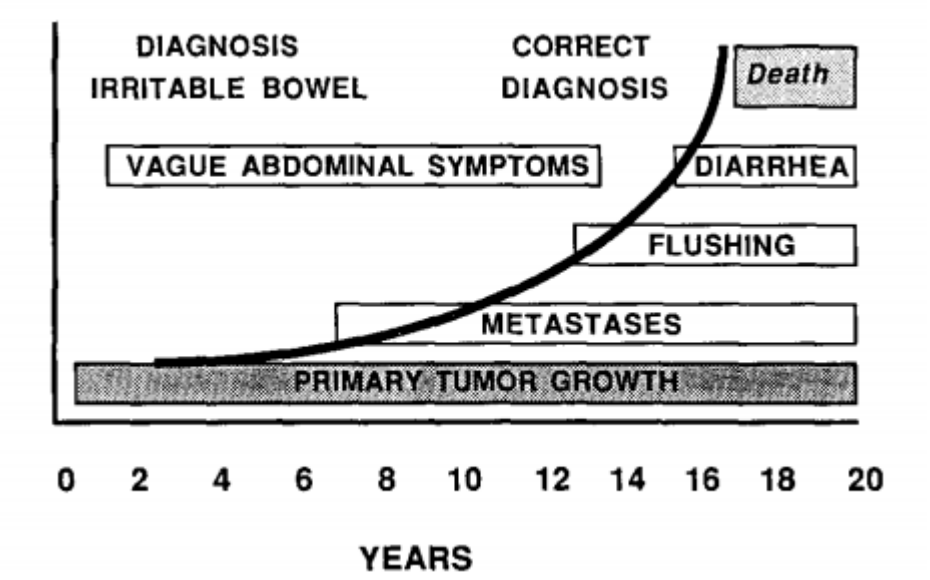
1.2 Current service provision

1.2.1 Management of disease

1.2.1.1 Diagnosis

Diagnosis of NETs can be difficult as they are often small tumours (some may be less than 1cm in size), they can occur almost anywhere in the body and present a vast array of symptoms or no symptoms at all. NETs are slow growing tumours and may be present for many years without recognisable symptoms. Therefore, diagnosis is often with quite late stage disease. Figure 3 depicts the typical manifestations of a NET.

Figure 3: Natural history of a neuroendocrine tumour



Source: Vinik et al. 1989 [23]

Typical symptoms in the early stages include vague abdominal pain and potential changes in bowel habits, which primarily are diagnosed as irritable bowel syndrome.[23] More progressive symptoms include shortness of breath, loss of appetite and weight loss.[24] Diagnosis is primarily following detailed histology. Other tests may include urine tests, blood tests, ultrasound scans, CT scans, MRI scans, radioactive scans and PET/CT scan. Diagnosis is also dependent on the clinical manifestations, peptide and amine secretions and specialised radiological and nuclear imaging of the NETs.[1] Being able to determine the secretory products of a NET is helpful with the diagnosis, to assess the efficacy of subsequent treatment and to assess changes in prognosis.[1] Similarly, imaging is used for not only detecting the primary tumour, but also screening at-risk populations, assessing the extent of the disease and assessing the response to treatment in follow-ups.[1]

1.2.1.2 Treatment

The aim of treatment, where realistically possible, should always be curative. However, in the majority of cases it is most likely to be palliative (i.e. aimed at symptom control). Since metastatic disease is common for individuals with NETs, often improving the quality of life is the primary aim of treatment (as opposed to curing the disease).[1] Individuals with NETs can maintain a good quality of life for a long period of time.[1] Quality of life is therefore assessed regularly throughout treatment.

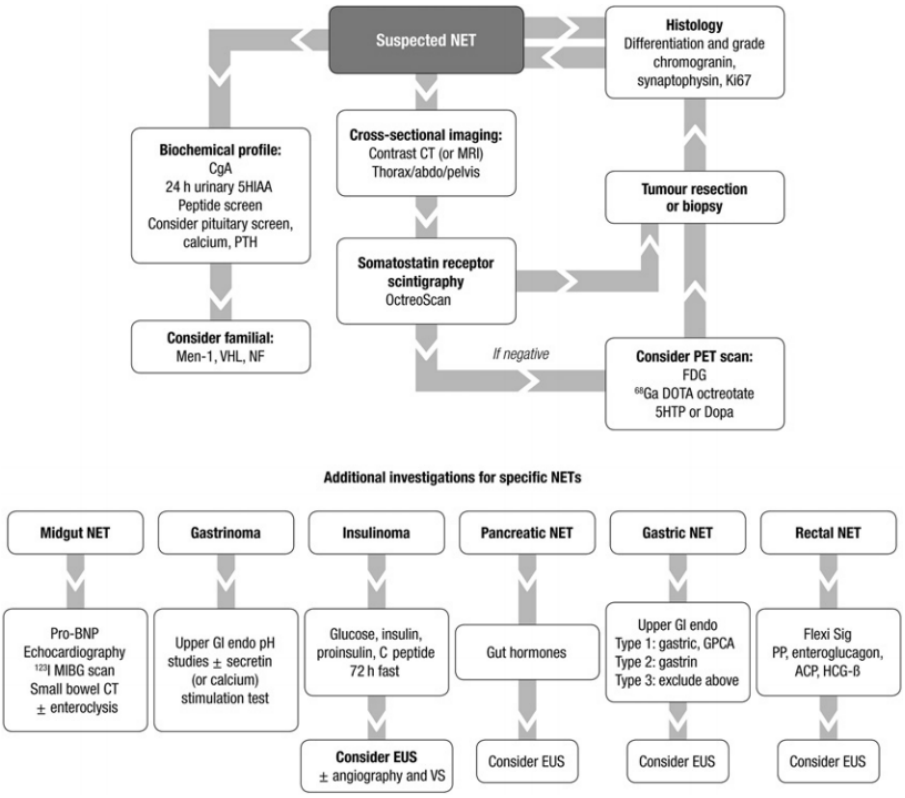
There is a vast array of treatment options for treating NETs. The initial treatments often start with surgery and symptom treatment. Surgery is the only curative treatment for NETs. Symptom treatment, particularly with hormonal hypersecretion functional NETs, can significantly impact an individual's quality of life since the symptoms themselves, as opposed to the cancer, may be life threatening (e.g., severe diarrhoea and hypokalaemia).[1] Symptom control is often with a somatostatin analogue, e.g., octreotide or lanreotide. Available treatments which follow surgery and initial symptom control include:

- Liver transplant
- Interferon alpha

- Chemotherapy
- Ablation therapies
- Targeted radionuclide therapy
    - Including one of the interventions of interest from this assessment report; 177Lu-DOTATATE
- Transhepatic artery embolisation/chemoembolisation
- External-beam radiotherapy
- Emerging therapies
    - Including two of the interventions of interest from this assessment report; everolimus and sunitinib

Describing an overarching treatment pathway for NETs is challenging, since there are many different options depending on the characteristics of the NET (e.g. location, grade, differentiation, secretory profile, etc.). Figure 4 reports an algorithm for diagnosis of a suspected NET from guidelines published in 2012 by a group who are members of the UK and Ireland Neuroendocrine Tumour Society (UKINETS).[1]

Figure 4: Algorithm for the investigation of neuroendocrine tumours (NETs).



Key: ACP, Acid Phosphatase; BNP, brain natriuretic peptide; CgA, chromogranin A; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; GI, gastrointestinal; GPCA, gastric parietal cell autoantibody; HCG, human chorionic gonadotrophin; 5HIAA, 5-hydroxyindoleacetic acid; 5HTP, 5-hydroxytryptophan; Men-1, multiple endocrine neoplasia 1; MIBG, meta iodobenzylguanidine; NF, neurofibromatosis; PET, positron emission tomography; PP, pancreatic polypeptide; PTH, parathyroid hormone; VHL, Von Hippel Lindau.

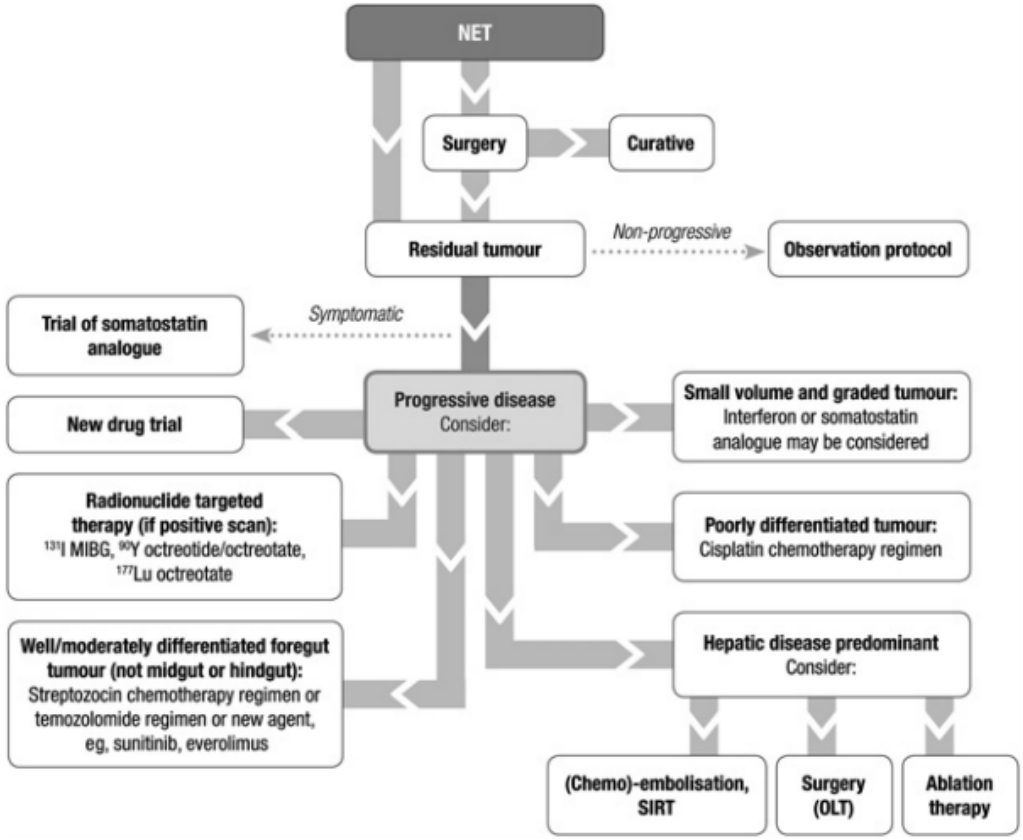
Source: Ramage et al. 2012 *Gut,*[1]

Figure 5 and Figure 6 are both treatment pathways for an individual with a diagnosed NET in the UK setting.[1, 25] Figure 5 was published by UKINETs in 2012 and Figure 6 is taken from Trust Guidelines issued from Norfolk and Norwich University Hospital (one of 29 multidisciplinary teams for treating NETs in the UK) in 2010.

Figure 7 and Figure 8 are both also treatment pathways, but for Europe and not the UK specifically. These pathways were published by ENETS as part of their consensus guidelines (http://www.enets.org/current_guidelines.html). Eight consensus guidelines were published in total and Figure 7 and Figure 8 were taken from the guidelines titled 'distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasm (NEN) and NEN of unknown primary site':[26] The title of the remaining seven ENETs guidelines published are:

- gastroduodenal neuroendocrine neoplasms,
- neuroendocrine neoplasm of the jejunum and ileum
- digestive neuroendocrine tumours
- functional and non-functional pNETs
- high grade gastro-entero-pancreatic (GEP) Neuroendocrine tumours and neuroendocrine carcinomas
- colorectal neuroendocrine neoplasms
- neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas)

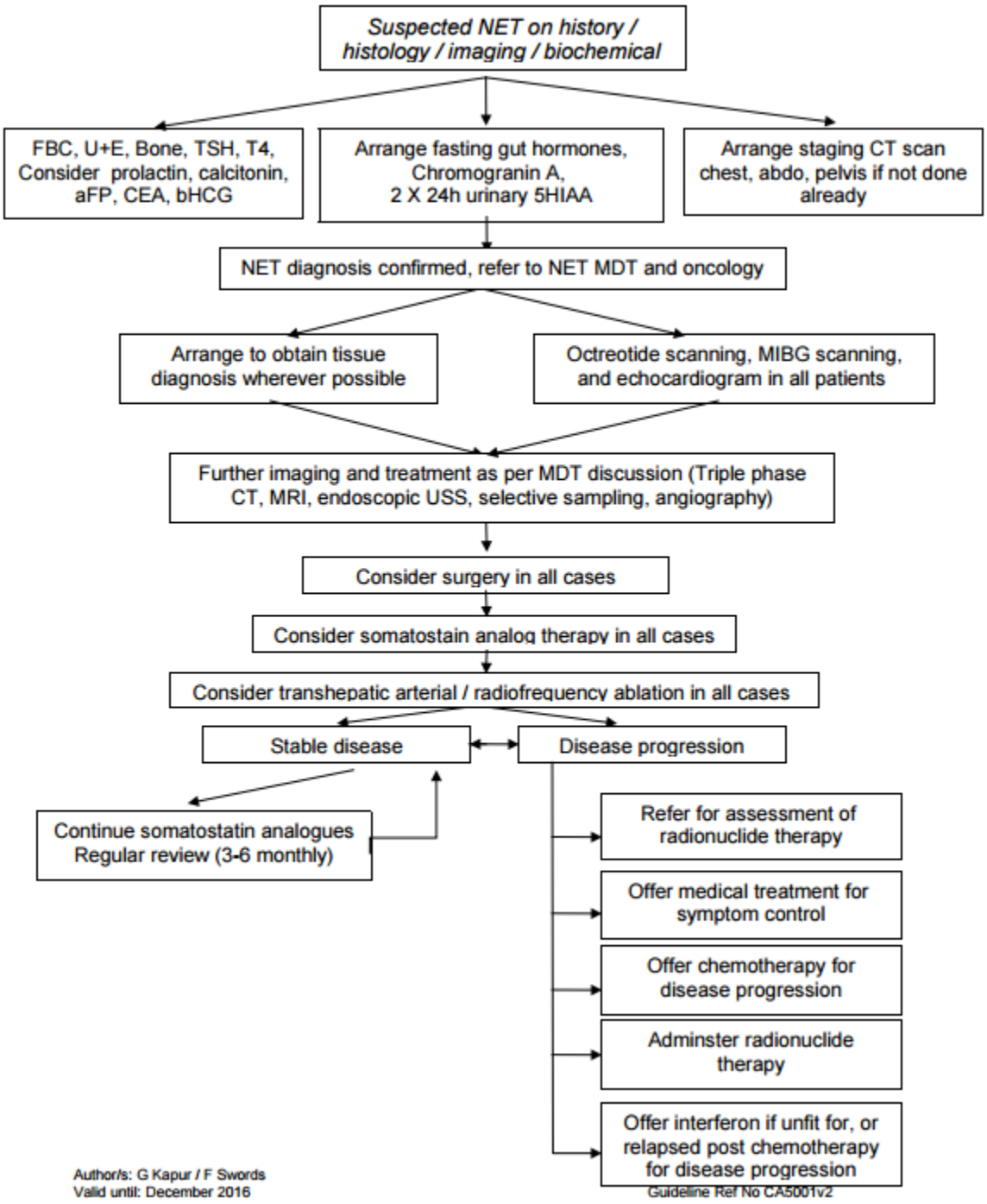
Figure 5: Algorithm for the treatment of neuroendocrine tumours (NETs).



Key: MIBG, meta_iodobenzylguanidine; OLT, orthotopic liver transplantation; SIRT, selective internal radiation therapy

Source: Ramage et al. 2012 *Gut,*[1]

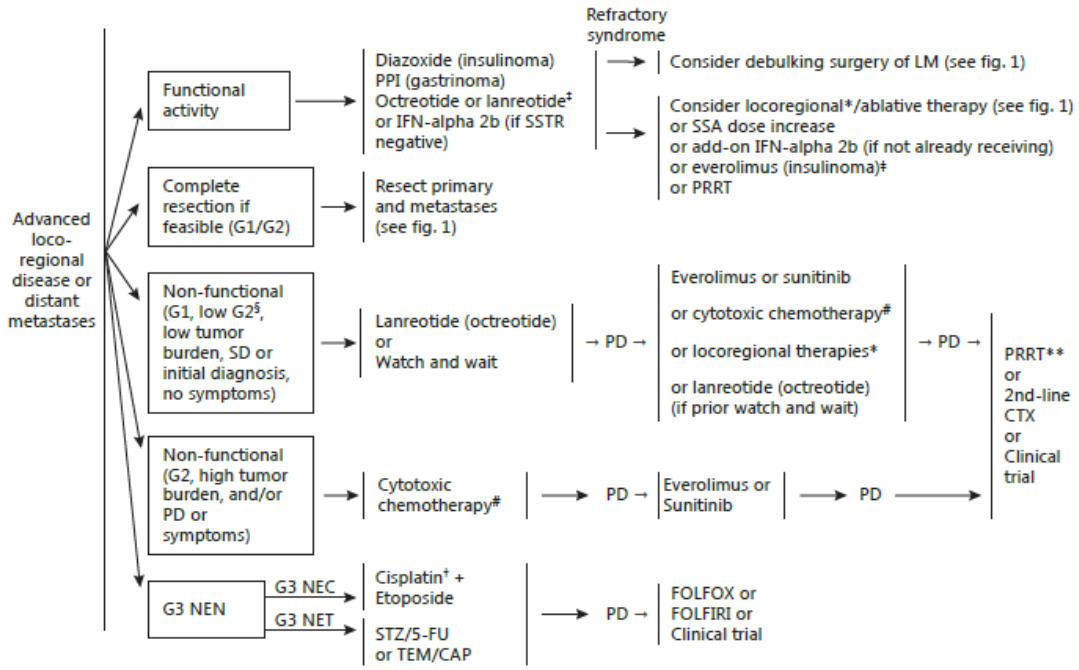
Figure 6: Trust guidelines for the management of Adult Patients with NETs issued by Norfolk and Norwich University Hospital



Key: 5HIAA, 5-hydroxyindoleacetic acid; CT, computed tomography; FBC, full blood count; MDT, multidisciplinary team; MRI, magnetic resonance imaging; NET, neuroendocrine tumour; U+E, urea and electrolyes; TSH, thyroid stimulating hormone; USS, ultrasound scan;

Source: Swords et al. 2010, Norfolk and Norwich University Hospital, NETs centre of excellence, Trust; Guidelines[25]

Figure 7: Therapeutic algorithm for the management of pancreatic NEN with advanced locoregional disease and/or distant metastases

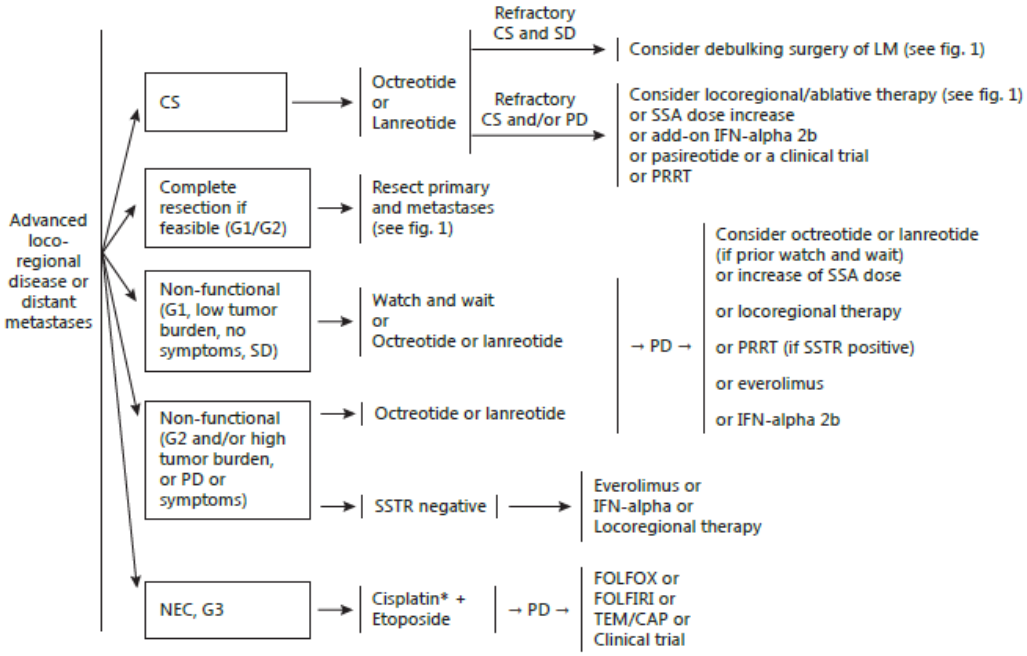


Key: 5-FU = 5-Fluorouracil; CS = carcinoid syndrome; CTX = chemotherapy; LM = liver metastasis; PD = progressive disease; SD = stable disease; TEM/CAP = temozolomide/capecitabine.

Notes: § Ki-67 <5–10%; * locoregional therapies are contraindicated after Whipple procedure; # recommended chemotherapy includes STZ/5-FU or STZ/doxorubicin; TEM/CAP is an alternative chemotherapy regimen if STZ-based chemotherapy is not available; * * if SSTR imaging is positive; ‡ patients should be closely monitored for paradoxical reaction (increasing hypoglycemia); † cisplatin may be replaced by carboplatin; G3 NET is coined for tumors with Ki-67 >20% but well- or moderately differentiated morphology. The term 'or' indicates that the use of the other options at further progression should be considered, e.g. patients with G1 or low-grade G2 NET and/ or low tumor burden who received everolimus may be treated with standard cytotoxic chemotherapy upon progression before unapproved drugs, second-line chemotherapy or a clinical trial is considered.

Source: Pavel et al. 2016, Neuroendocrinology[26]

Figure 8: Therapeutic algorithm for the management of intestinal (midgut) NEN with advanced locoregional disease and/or distant metastases.



Key: CS = Carcinoid syndrome; LM = liver metastasis; PD = progressive disease; SD = stable disease; TEM/CAP = temozolomide/capecitabine. * Cisplatin may be replaced by carboplatin
Source: Pavel et al. 2016, Neuroendocrinology[26]

1.2.2 Current service cost

The economic burden to the NHS of healthcare provision for people with NETs is not well documented. This may be partly due to the rarity and heterogeneity of the disease, but also because significant new therapeutic options have only recently come about.

Public Health England reported approximately 4,000 new cases of neuroendocrine neoplasms are diagnosed each year. From a budgetary perspective this is a small sub-group of the 300,000 new cancer diagnoses registered annually in England,[27] but with the arrival of new high-cost targeted therapeutics the cost-effectiveness of disease management is now a relevant area for scrutiny through secondary research.

The main costs involved in current service provision for people with inoperable progressive NETs can be divided into the cost of diagnosis and monitoring of disease (e.g., blood markers, CT, MRI and PET imaging), the cost of acquiring and administering active and supportive treatments (in particular long-acting repeat somatostatin analogue therapy, also chemotherapy), the costs of managing symptoms (if the tumour is functioning), the cost of managing adverse events and the cost of human resources for patient consultation, multidisciplinary team (MDT) meetings, and hospitalised care.

1.2.3 Variation in services and/or uncertainty about best practice

The provision of health services for people with NETs in England is predominantly delivered by specialist gastroenterologists or oncologists in the NHS acute sector. There are variations in clinical practice.

1.2.4 Relevant national guidelines, including National Service Frameworks

Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours were published in 2012 by a group who are members of the UKINETS[1]

Related guidelines by NICE include, 'Diagnosis and management of metastatic malignant disease of unknown primary origin (2010) NICE guideline 2104. Static guidance.'

Finally, a related NICE pathway is the, 'metastatic malignant disease of unknown primary origin overview (2010) NICE pathway.'

1.3 Description of technology under assessment

1.3.1 Summary of Interventions

The scope of this review is to ascertain the clinical and cost-effectiveness of three interventions for unresectable or metastatic neuroendocrine tumours with disease progression. These interventions are everolimus, 177Lu-DOTATATE and sunitinib.

1.3.1.1 Everolimus (Afinitor, Novartis)[28]

Everolimus is an orally active agent that is able to slow down the growth and spread of a tumour. It acts by binding to the protein FKBP-12 to form a complex, which is able to block the mammalian target of rapamycin (mTOR) protein. Division of tumour cells and growth of blood vessels require mTOR and it is through the blocking of mTOR, that everolimus is able to slow down the growth and spread of the tumour.

Everolimus has a marketing authorisation for tumours of pancreatic origin: '*Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease*'. It also has a marketing authorisation for gastrointestinal or lung origin neuroendocrine tumours; '*Afinitor is indicated for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours'.*

Everolimus is an oral drug typically given at a dose of 10 mg a day. Treatment is recommended to be continued for as long as benefits are observed or an unacceptable level of side effects occur. The dose of everolimus may be reduced or stopped in an effort to minimise side effects. Tablets should be taken at the same time of day, every day.

The most common side effects of everolimus (affecting more than 1 in 10 people) include; rash, pruritus (itching), nausea, decreased appetite, dysgeusia (taste disturbances), headache, decreased weight, peripheral oedema (swelling, especially of the ankles and feet), cough, anaemia (low red blood cell counts), fatigue (tiredness), diarrhoea, asthenia (weakness), infections, stomatitis (inflammation of the lining of the mouth), hyperglycaemia (high blood glucose levels), hypercholesterolaemia (high blood cholesterol levels), pneumonitis (inflammation of the lungs) and epistaxis (nosebleeds). Everolimus is not suitable for people who are hypersensitive to rapamycin derivatives.

Everolimus was removed from the Cancer Drug Fund on 12th March 2015; it was previously available for the treatment of progressive unresectable or metastatic well differentiated neuroendocrine tumour of the pancreas.

1.3.1.2 Lutetium-177 DOTATATE (Lutathera, Imaging Equipment)[29]

Lutetium-177 DOTATATE is a radiolabelled somatostatin analogue. It is made up from a radionuclide (177Lu) and the peptide-chelator complex [DOTA0, Tyr3-]-octreotate (DOTATATE). The (Tyr3)-octreotate binds to malignant cells that overexpress somatostatin receptors (specifically the SSTR2 receptor). Once bound, the 177Lu-DOTATATE accumulates within the NET cell delivering cytotoxic radiation that kills the tumour cells.

177Lu-DOTATATE currently does not have marketing authorisation in the UK for any indication.

Administration of 177Lu-DOTATATE is through an intravenous infusion and involves three days of hospital appointments, including an overnight stay. Typically, four cycles are administered over a total of eight to ten months.

There are two main types of side effects from 177Lu-DOTATATE, those relating to the therapy and those relating to the radiation dose in the body. Side effects related to the therapy include nausea, pain, flushing, sweating, palpitations, wheezing, diarrhoea, hair loss, fatigue. Side effects relating to the radiation dose include affecting bone marrow production and kidney function which in turn may increase infections.

177Lu-DOTATATE was removed from the Cancer Drugs Fund on the 4th November 2015; it was previously available for treatment of advanced neuro-endocrine tumours after sunitinib/chemotherapy, for pancreatic NETs and, for mid-gut carcinoid, after octreotide/somatostatin therapies.

1.3.1.3 Sunitinib (Sutent, Pfizer)[30]

Sunitinib is a protein kinase inhibitor that is able to reduce the growth and spread of cancer and cut off the blood supply that enables cancer cell growth. Sunitinib works by blocking the enzymes, known as protein kinases, found in some receptors at the surface of cancer cells. The development of new blood vessels and the growth and spread of cancer cells requires this enzyme, and it is through the blocking of this enzyme that sunitinib is able to slow the growth and spread of the tumour.

Sunitinib has a marketing authorisation for tumours of pancreatic origin: '*SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pNETs with disease progression in adults.'*

Sunitinib is an oral drug typically given at a dose of 37.5 mg a day. Treatment is recommended to be continued for as long as benefits are observed or an unacceptable level of side effects occur. The dose of sunitinib may be reduced or stopped in an effort to minimise side effects.

The most common side effects of sunitinib are fatigue (tiredness), gastrointestinal disorders (such as diarrhoea, feeling sick, inflammation of the lining of the mouth, indigestion and vomiting), respiratory (such as shortness of breath and cough) and skin disorders (such as skin discoloration, dryness of the skin and rash), hair colour changes, dysgeusia (taste disturbances), epistaxis (nosebleeds), loss of appetite, hypertension (high blood pressure), palmar-plantar erythrodysaesthesia syndrome (rash and numbness on the palms and soles), hypothyroidism (an underactive thyroid gland), insomnia (difficulty falling and staying asleep), dizziness, headache, arthralgia (joint pain), neutropenia (low levels of neutrophils, a

type of white blood cell), thrombocytopenia (low blood platelet counts), anaemia (low red blood cell counts), and leukopenia (low white blood cell counts).

Sunitinib is available on the Cancer Drugs Fund for the treatment of pancreatic neuroendocrine carcinomas where all the following criteria are met:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Biopsy proven well differentiated pancreatic neuroendocrine tumour
3. a) 1st line indication, OR b) 2nd line indication, OR, c) 3rd line indication
4. no previous vascular endothelial growth factor (VEGF) targeted therapy

1.3.2 Identification of important sub-groups

From the NICE scope, the following sub-groups were identified as important in the treatment of NETs:

- location of tumour;
- grade/degree of differentiation;
- stage of tumour;
- secretory profile; and
- number of previous treatments.

Further information on these subgroups can be found in section 1.1.1.1

1.3.3 Current usage in the NHS

It was difficult to ascertain the current usage of everolimus, sunitinib and 177Lu-DOTATATE in the NHS. AAA in their submission report that in the UK, although unlicensed, 177Lu-DOTATATE has been used to treat patients in England through the Cancer Drugs Fund (CDF) [redacted] Likewise, Pfizer report that Sunitinib is also available through the CDF and is used in the NHS in England for the treatment of patients with pNET (52 requests were made in the 12 months ending March 2015). Novartis did not report in their submission estimated use of everolimus within the NHS in England, however our clinicians suggest the rate of use for everolimus is higher than that of sunitinib.

1.3.4 Anticipated costs associated with intervention

The cost of treating a patient with everolimus or sunitinib varies from one patient to the next because the duration of treatment with these oral preparations is continuous and largely dependent on effectiveness for the individual. The mean duration of treatment with everolimus in the RADIANT-3 and RADIANT-4 trials of NET patients is about 9 months, with a range of one week to two years.[31] In practice, it is disease stability and drug tolerability that trigger the decision to purchase the next month of therapy. Everolimus and sunitinib are normally self-administered so the cost of drug delivery is limited to the time needed by hospital pharmacy staff to dispense them. In contrast the drug acquisition cost of 177Lu-

DOTATATE is less variable between patients because its delivery is fixed to a maximum of four treatment cycles. Also, in comparison to the oral preparations of everolimus and sunitinib the delivery of 177Lu-DOTATATE is more resource intensive. 177Lu-DOTATATE is a radio-labelled intravenous preparation, so administration involves careful handling, specialist staff, and post-administration observation, which for most patients means an over-night hospital stay. Beyond acquisition and administration the remaining treatment-related costs arise from disease monitoring and the medical management of adverse events, which will of course differ across treatments but are less substantial components of overall cost.

We expect that all the these cost components vary between individuals and hence they are subject to modelling, but the acquisition costs of treatments are presented in Table 6 for simple comparative purposes.[32]

Table 6: Cost of interventions at list price, without patient access scheme arrangements

Comparator	Unit size	Acquisition cost[a]	Treatment period
Everolimus	5mg tablet	£2,250.0028	30-days
(10mg typical daily dose)	10mg tablet	£2,673.0028	30-days
Sunitinib	12.5mg capsule	£784.7028	28-days
(37.5mg typical daily dose)	25mg capsule	£1,569.4028	28-days
	50mg capsule	£3,138.8028	28-days
177Lu-DOTATATE	7.4 GBq single cycle (of four)	[redacted]	[redacted]

Notes: a: excludes patient access scheme where agreed; b: unit cost supplied by AAA Ltd.

2 Changes to project scope

During the course of this review, NICE consulted on amendments to the original project scope. The revised scope was agreed on the 18th August 2016 and the following changes between the original and revised scope are noted (Table 7; differences are highlighted in bold and red):

Table 7: Old and New Scope

	Old scope	New Scope
Intervention(s)	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • **Lanreotide (neuroendocrine tumours of mid-gut, pancreatic or unknown origin)** • Lutetium-177 DOTATATE (neuroendocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • Lutetium-177 DOTATATE (neuroendocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)
Population(s)	People with progressed unresectable or metastatic neuroendocrine tumours According to the specific locations covered by **the marketing** authorisation of the interventions	People with progressed unresectable or metastatic neuroendocrine tumours According to the specific locations covered by **existing and anticipated** marketing authorisation of the interventions
Comparators	• the technologies listed above will be compared with each other where appropriate. • **octreotide (long-acting release formulation)** • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, fluorouracil (5-FU), doxorubicin, temozolomide, capecitabine) • best supportive care	• The technologies listed above will be compared with each other where appropriate. • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life
Other considerations	If the evidence allows the following subgroups will be considered: • location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s) Guidance will only be issued in accordance with the marketing authorisation.	If the evidence allows the following subgroups will be considered: • location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s) Guidance will only be issued in accordance with the marketing authorisation.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

	Costs will be considered from an NHS and Personal Social Services perspective. **The use of lutetium-177 DOTATATE is conditional on the presence of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours. The economic modelling should include the costs associated with diagnostic testing for somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours in people who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the 'Guide to the Methods of Technology Appraisals'**	Costs will be considered from an NHS and Personal Social Services perspective.

2.1 What is the impact of the changes in scope?

The population and outcomes under review are unchanged from the original scope.

The following intervention was removed:

- Lanreotide (neuroendocrine tumours of mid-gut, pancreatic or unknown origin)

The following comparator was removed:

- Octreotide (long-acting release formulation)

2.2 What is the effect of this decision?

The following RCT is now excluded from the systematic review as it does not meet the inclusion criteria of the revised scope.

- NETTER-1 – Lutetium-177 DOTATATE (177Lu-DOTATATE) plus Octreotide 30mg compared to Octreotide 60mg

The significant impact of this decision is on the available evidence for 177Lu-DOTATATE. The removal of octreotide as a comparator to the NICE scope means that the NETTER-1 trial no longer meets the inclusion criteria of the new scope.

This means that we do not now have any includable RCT evidence for the clinical effectiveness of 177Lu-DOTATATE.

2.3 How have we dealt with this issue?

Our systematic review of clinical effectiveness adheres to the revised scope issued by NICE on the 18th August 2016. We have produced a revised protocol to reflect these changes. The original and revised scope is included in Appendix 10.

For 177Lu-DOTATATE, and in respect to the exclusion of the NETTER-1 trial, we have searched for non-randomised studies. 6854 studies were identified of which 32 met our inclusion criteria. These are all single arm studies. This is explored in greater detail in section 4.4.

The AG appreciate that as the only RCT of 177Lu-DOTATATE identified, the NETTER-1 trial may be of interest to the committee and so have presented the main outcomes in section 4.7, with results of an indirect treatment comparison with everolimus from RADIANT-4.

Our de novo economic model and analyses do include the NETTER-1 study data in a scenario analysis. Specifically, 177Lu-DOTATATE is indirectly compared with the initial treatments received by the GI subgroup in RADIANT-4, i.e. everolimus and placebo (best supportive care alone) in a scenario analysis.

3 Definition of the decision problem

3.1 Decision problem

3.1.1 Population

The population specified in the final scope issued by NICE is people with progressed unresectable or metastatic neuroendocrine tumours. In addition, the population must be in accordance to the specific locations covered by the existing and anticipated marketing authorisations of the interventions.

Subgroups of interest based on the NICE scope include;

- location of the tumour,
- grade/degree of differentiation of the tumour,
- stage of the tumour,
- secretory profile of the tumour,
- number of previous treatments.

3.1.2 Interventions

- **Everolimus – for NETs of gastrointestinal, pancreatic or lung origin (Afinitor, Novartis)** is an oral inhibitor of the mTOR protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. It has a marketing authorisation in the UK for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.[33] For gastrointestinal or lung origin it has a marketing authorisation in the UK for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours in adults with progressive disease.[34] It has been studied in two clinical trials (one with individuals with functioning tumours and one with individuals with non-functioning tumours) compared with placebo in adults with advanced unresectable or metastatic neuroendocrine tumours of gastrointestinal or lung origin.[33]
- **Lutetium-177 DOTATATE – for NETs of gastrointestinal or pancreatic origin (Lutathera, Imaging Equipment)** is a radio-labelled analogue of somatostatin designed to deliver radiation to the cells. It is a type of therapy known as a targeted radionuclide therapy or peptide receptor radionuclide therapy (PRRT). It kills tumour cells by binding to a specific type of somatostatin receptor, called sst2 receptors, which are overexpressed by the malignant cells. It does not currently have marketing authorisation in the UK for any indication. It has been studied in a clinical trial in people with inoperable, locally advanced or metastatic somatostatin receptor positive mid-gut neuroendocrine tumours (Ki67 index ≤ 20%) with or without disease progression compared with octreotide long acting release (LAR). 177Lu-DOTATATE is administered by intravenous infusion.[33]
- **Sunitinib – for NETs of pancreatic origin (Sutent, Pfizer)** is a protein kinase inhibitor that works by preventing tumour proliferation and inhibiting blood vessel growth, leading to cancer cell death. It has a marketing authorisation for treating

unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Sunitinib is administered orally.[33]

3.1.3 Comparators

The final scope issued by NICE specified that the interventions should be compared with each other, and with:

- Interferon alpha
- Chemotherapy regimes (including but not restricted to combinations of streptozocin, 5-Fu, doxorubicin, temozolomide and capecitabine)
- Best supportive care

The AG noted following consultation with our clinicians that interferon alpha was not commonly used within UK clinical practice.

3.1.4 Outcomes

The outcomes of interest based on the NICE scope include:

- Overall survival
- Progression-free survival
- Response rates (including complete response, partial response, stable disease, progressive disease, tumour shrinkage, objective response rate)
- Symptom control
- Adverse effects of treatment
- Health-related quality of life

3.1.5 Key issues

The primary factors which may influence the clinical effectiveness of treatment for individuals with NETs are predominately covered within the population subgroups in section 3.1.1.

In addition to the number of prior treatments covered as a subgroup of section 3.1.1, the use of concomitant treatment (primarily somatostatin analogue (SSAs) use) whilst partaking in the clinical trials may also be a key issue. This is because the administration of SSAs as a concomitant treatment is not uniform in the treatment of NETs, as some individuals will receive SSA therapy and some will not.

Treatment switching from placebo to the active treatment is also another key issue for consideration in respect of how the switching may confound the outcomes reported for the placebo arm.

3.2 Overall aims and objectives of assessment

The aim of this report is to review the clinical effectiveness and cost effectiveness of everolimus, 177Lu-DOTATATE and sunitinib for treating unresectable or metastatic NETs with disease progression in a multiple technology appraisal (MTA). This includes a systematic review of clinical effectiveness studies to assess the medical benefit and risks associated with these treatments and a comparison across the treatments against available alternative standard treatments. The report will also assess whether these drugs are likely to

be considered good value for money for the NHS through a model based economic evaluation.

4 Assessment of clinical effectiveness

4.1 Methods for reviewing effectiveness

Evidence for the clinical effectiveness of everolimus, 177Lu-DOTATATE and sunitinib within their marketing authorisation for treating unresectable or metastatic neuroendocrine tumours with disease progression was assessed by conducting a systematic review of published and unpublished research evidence. This review was undertaken following the methodological guidance published by the Centre for Reviews and Dissemination (CRD).[35]

4.1.1 Changes to the protocol

As discussed in section 2(Changes to project scope), NICE issued a revised scope for this project on the 18th August 2016. The revised scope necessitated a change to our published protocol [36] as lanreotide was removed as an intervention and octreotide was subsequently removed as a comparator. A revised protocol was drafted (see Appendix 8). There were no other changes to the published protocol.

4.1.2 Identification of studies

The literature search aimed to systematically identify studies relating to the clinical effectiveness of everolimus, 177Lu-DOTATATE and sunitinib in the treatment of unresectable or metastatic neuroendocrine tumours with disease progression. The search strategy was developed in MEDLINE (Ovid) and then adapted for use in the other resources searched.

The bibliographic literature search was undertaken in May 2016 and the search was further updated in September 2016.

Searching of bibliographic and on-going trials databases

The following bibliographic databases were searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); MEDLINE-Daily (Ovid); Epub-Ahead-of-Print (Ovid); EMBASE (Ovid); CENTRAL (The Cochrane Library, Wiley Interface) and Web of Science (including conference proceedings citation index; Thomson Reuters).

The search syntax took the following form: (search terms for neuroendocrine tumours) AND (search terms for the interventions under review). These searches were not limited by study design, language or by date.

The following trial registries were hand-searched: Current Controlled Trials; ClinicalTrials.gov; the Food and Drug Administration (FDA) website; and the European Medicines Agency (EMA) (including European Public Assessment Reports [EPARs]).

The full search strategies are recorded in Appendix 1.

Web-searching

The following web-sites were searched:

- The European Neuroendocrine Tumour Society (http://www.enets.org/); and
- The UK and Ireland Neuroendocrine Tumour Society (http://www.ukinets.org/)

De-duplication

All references were exported into Endnote X7 (Thomson Reuters), where automatic and manual de-duplication was performed.

Screening

Title and abstracts were independently double-screened by two reviewers. Studies meeting inclusion at title and abstract stage were ordered as full texts and independently double-screened by three reviewers.

Citation searching, appraisal of company submissions and identification of systematic reviews of RCTs

All studies meeting full-text inclusion criteria were citation chased. Forwards citation searching was conducted in Web of Science (Thomson Reuters) and backwards citation searching was conducted manually, through the appraisal of the bibliographies of included studies. Citation searching is reported in Appendix 1.

Included RCTs from systematic reviews identified were checked against the table of included studies for this review. Studies included in the clinical effectiveness sections of company submissions were also checked against the table of studies included in this review.

4.1.3 Inclusion and exclusion criteria

Inclusion and exclusion criteria for the selection of clinical effectiveness studies was defined according to the decision problem outlined in the original NICE scope (no longer publically available).

Studies identified prior to the publication of the revised scope were re-checked for inclusion against this revised scope[33].

The inclusion and exclusion criteria for the original and revised scope are summarised in Table 8. Studies were also required to be in the English language.

The systematic review of clinical effectiveness focused only on RCTs. Where no RCTs were identified for an intervention of interest, a systematic review of non-randomised evidence was conducted (see section 4.3).

In addition to identifying RCTs, systematic reviews of RCTs (although not formally included in the systematic review) were used as potential sources of additional references of efficacy evidence.

Studies published as abstracts or conference presentations were included if sufficient details were presented to allow both an appraisal of the methodology and an assessment of the results to be undertaken.

Table 8: Old and New Scope

Criteria	Old scope	New scope
Intervention(s)	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • **Lanreotide (neuroendocrine tumours of mid-gut, pancreatic or unknown origin)** • 177Lu-DOTATATE (neuroendocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • 177Lu-DOTATATE (neuroendocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)
Population(s)	People with progressed unresectable or metastatic neuroendocrine tumours According to the specific locations covered by existing and anticipated marketing authorisation of the interventions	People with progressed unresectable or metastatic neuroendocrine tumours According to the specific locations covered by existing and anticipated marketing authorisation of the interventions
Comparators	The technologies listed above will be compared with each other where appropriate. • **octreotide (long-acting release formulation)** • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care	The technologies listed above will be compared with each other where appropriate. • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life
Other considerations	If the evidence allows the following subgroups will be considered: • location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s) Guidance will only be issued in accordance with the marketing authorisation.	If the evidence allows the following subgroups will be considered: • location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s) Guidance will only be issued in accordance with the marketing authorisation.

Source: NICE Scope [33] Old scope held on file, no longer in public domain

4.1.4 Data extraction and management

Studies included at full-text were shared between three reviewers for the purposes of data extraction. A standardised data specification form was used and data extracted were double-checked by a second reviewer. Where multiple publications of the same study were identified, data were extracted and reported as if a single study.

Information sourced for extraction and tabulation included: study design and methodology, baseline characteristics of participants, and the following outcomes; progression free survival (PFS), overall survival (OS), response rate (RR), adverse events (AE), and health related quality of life (HRQoL).

Where information on key data were incomplete, we attempted to contact the study author(s). In addition, the companies were approached via NICE to provide missing data and supplementary individual patient data.

4.1.5 Assessment of risk of bias

The methodological quality of each included study was assessed by one reviewer and checked by a second reviewer, using criteria based on those proposed by the NHS CRD for RCTs.[35] An additional question (question 10, Table 9) was added to assess the applicability of the study to the NHS in England.

Table 9: Quality assessment

Treatment allocation	1. Was the assignment to the treatment groups really random? 2. Was treatment allocation concealed?
Similarity of groups	3. Were the groups similar at baseline in terms of prognostic factors?
Implementation of masking	4. Were the care providers blinded to the treatment allocation? 5. Were the outcome assessors blinded to the treatment allocation? 6. Were the participants blinded to the treatment allocation?
Completeness of trial	7. Were all a priori outcomes reported? 8. Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes? 9. Did the analyses include an ITT analysis?
Generalisability	10. Are there any specific limitations which might limit the applicability of this study's findings to the current NHS in England?

Key: ITT, intention-to-treat; NHS, National Health Service
Notes: Criteria were based on CRD guidance.[35]

4.1.6 Methods of data analysis/synthesis

Data were tabulated and narratively synthesised. If sufficient evidence were available and study designs homogenous, meta-analysis would be performed. In addition, where the data allowed, an indirect treatment comparison would be performed.

Study design and baseline characteristics for all included studies are presented followed by the outcome results. Outcomes from the studies are reported by tumour location, first for pNETs, and then for GI and lung NETs combined, since this was how the included study was published. Additional data were subsequently made available so that the clinical effectiveness for GI NETs and lung NETs could be assessed as isolated tumour locations.

4.1.6.1 Indirect Treatment Comparisons

Where data were available the Bucher method[37] was used for an indirect treatment comparison (ITC) for the outcomes PFS, OS, RR and AEs. Further details can be found in section 4.2.5.2

4.2 Results

The results of the study identification in accordance with the updated NICE scope are first discussed in this section, which is followed by the quality of the evidence and overview tables of the included trials and their population baseline characteristics. Outcomes (where available; PFS, OS, RR, HRQoL and AEs) are then reported by tumour location. If available, outcomes are then reported by subgroup. Subgroups considered were based on the NICE scope under other considerations (see NICE scope; Table 8).

Where non-randomised evidence was sought, details are presented after the RCT evidence. These data are tabulated and narratively discussed in brief.

4.2.1 Quantity and quality of research available (RCT evidence)

4.2.1.1 Studies identified

Titles and abstracts were screened from 6,209 unique references identified by the searches, from which 273 full-text papers were retrieved for detailed consideration. Two hundred and seventeen full-texts were excluded (a table of these excluded references, along with exclusion decisions can be found in Appendix 4).

Update searches were conducted in September 2016. A total of 645 references were identified and 25 were selected for full-text retrieval. Of these six citations were formally included in the review.

Six systematic reviews[38-43] and three trials were included in the review: RADIANT-3,[31] RADIANT-4,[44] and A6181111.[45] Following scrutiny of the included studies from the six systematic reviews, no further evidence was identified. The three included trials were made up from 56 citations, see Table 10.[31, 45] A table of all the included citations is given in Appendix 3.

Table 10: Identified citations

Trial	Full-texts	Conference abstracts	Other	Main Reference Paper
RADIANT-3	4	22	NA	Yao et al. 2011[31]
A6181111	1	19	1 errata	Raymond et al 2011[45]
RADIANT-4	1	8	NA	Yao et al. 2016[44]

Of note, two citations related to a study by Yao et al. (2014)[46]. This study met our inclusion criteria, however it was excluded as the paper was retracted by the authors because *'the authors discovered statistical errors which need further validation'*. The study compared everolimus (n=44) to placebo (n=35) in Chinese patients with pNETs.

No randomised studies were identified that met the inclusion criteria of the systematic review for clinical evidence for the following interventions and comparators of interest:

- 177Lu-DOTATATE to any of the included comparators
- Everolimus to the comparators interferon alpha or chemotherapy

- Sunitinib to the comparators interferon alpha or chemotherapy

The AG ran an additional search (see Appendix 2 for search strategy) with the aim of identifying any RCTs that compared chemotherapy to best supportive care (BSC) or placebo. Identified studies would help inform discussions around the clinical effectiveness of the interventions in comparison to chemotherapy through an indirect treatment comparison. Following the screening of 850 citations, no studies were identified. The AG, on the advice from our clinicians did not search for RCTs comparing interferon alpha to BSC or placebo, since interferon alpha is not commonly used in UK clinical practice.

In summary, three trials were identified that met the inclusion criteria, RADIANT-3,[31] RADIANT-4,[44] and A6181111.[45]

NETTER-1

NETTER-1 was identified through four published abstracts as an includable trial from the systematic review in accordance with the original NICE scope. NETTER-1 was not included in this systematic review as it did not meet the revised inclusion criteria of the updated scope issued by NICE on the 18th August 2016.

NETTER-1 is an RCT which compares 177Lu-DOTATATE plus octreotide LAR 30mg to octreotide LAR 60mg. Whether octreotide LAR could be deemed a concomitant treatment, as the doses were different in each treatment arm, were explored.

The AG sought consultation from our clinicians, who were unable to confirm whether the different dosing in octreotide LAR would result in different clinical effectiveness results.

The AG undertook further analysis and searched for RCT dosing studies (see Appendix 2 for searching strategy) to ascertain whether octreotide LAR 30mg had the same clinical effectiveness as octreotide LAR 60mg in the NETs population. Following screening of 180 citations, no studies were identified.

As the AG could not verify with any certainty that octreotide LAR 30mgs had the same clinical effectiveness as octreotide LAR 60mg and octreotide LAR was not a comparator within scope, this study was excluded from the review.

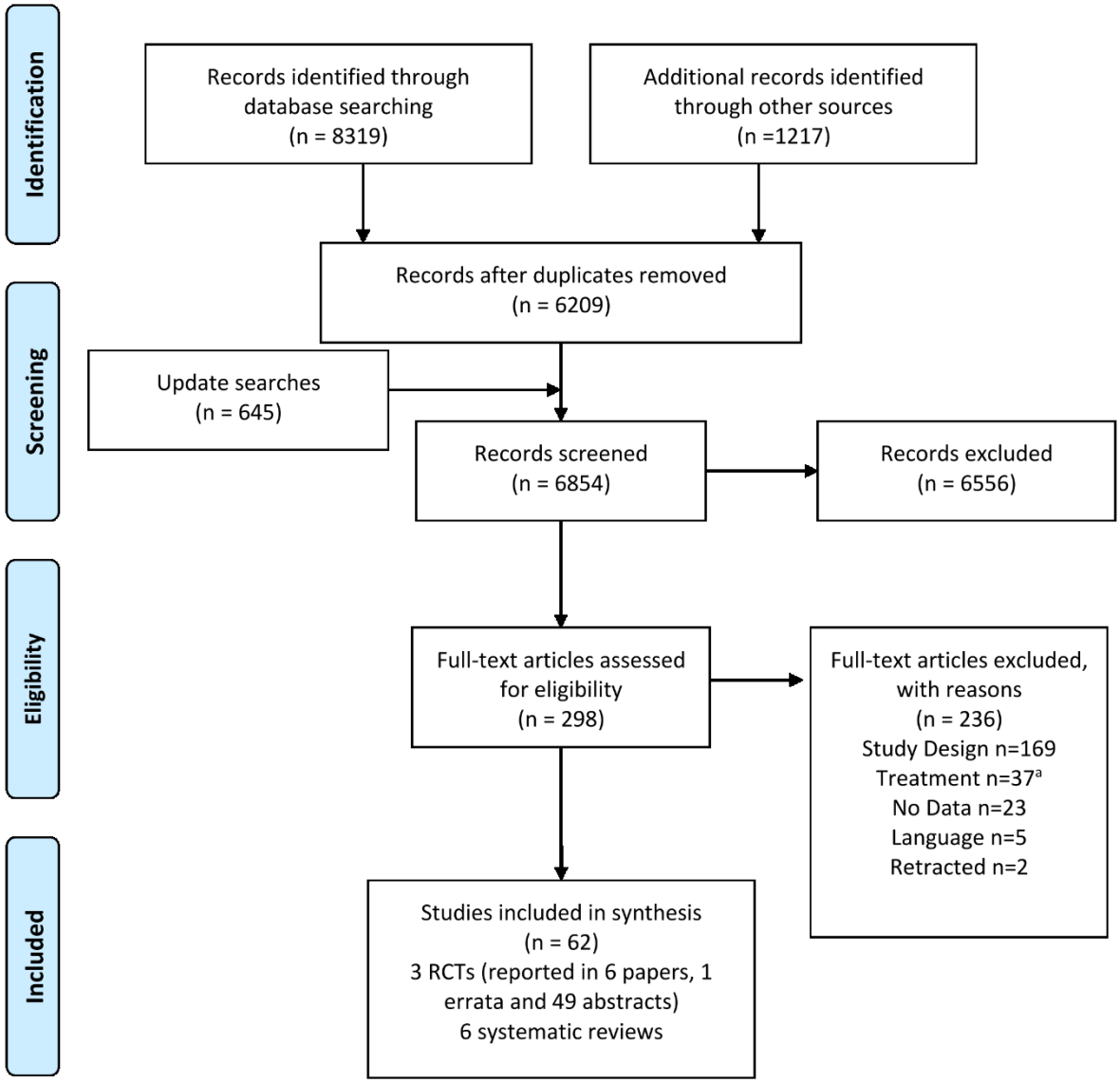
Taken from the company submission, AAA report the rational for treating the comparator arm with a high dose of octreotide (60mg) was as follows:

'A higher dose was required by the regulatory authorities at the time of the parallel scientific advice meeting with the FDA and EMA considering that the patients enrolled in the trial had have progressive disease following 20 or 30 mg octreotide LAR, and it was not ethical to maintain them on the same dose regimen. Consequently, 60 mg octreotide LAR at 4-week intervals dose was agreed for the control arm in the absence of an alternative efficacious treatment approved for this type of tumour'(AAA company submission, page 44).

The AG appreciate that as the only RCT of 177Lu-DOTATATE identified, this trial may be of interest to the committee and so have presented the main outcomes in 4.7 with results of an ITC with everolimus from RADIANT-4.

The study selection process is outlined in Figure 9.

Figure 9: PRISMA flow diagram



4.2.2 Quality Appraisal

The three identified RCTs were appraised. Where necessary for clarification purposes, published protocols available as online supplementary material from each of the main citations for the three studies were referred to. For each trial, data from all publications for that trial contributed to the quality appraisal.

Overall, the risk of bias was found to be the same between the three trials in respect of selection, performance, detection, attrition and reporting bias. It was assessed that these trials demonstrated a low risk of bias.

Table 11: Quality Appraisal

Item	RADIANT-3	A6181111	RADIANT-4
1. Was the assignment to the treatment groups really random?	Low Risk	Low Risk	Low Risk
2. Was treatment allocation concealed?	Low Risk	Low Risk	Low Risk
3. Were the groups similar at baseline in terms of prognostic factors?	Unclear risk[a]	Unclear risk[b]	Unclear risk[c]
4. Were the care providers blinded to the treatment allocation?	Low Risk	Low Risk	Low Risk
5. Were the outcome assessors blinded to the treatment allocation?	Low Risk	Low Risk	Low Risk
6. Were the participants blinded to the treatment allocation?	Low Risk	Low Risk	Low Risk
7. Were all a priori outcomes reported?	Low Risk	Low Risk	Low Risk
8. Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes?	Low Risk[e]	Low Risk[e]	Low Risk
9. Did the analyses include an ITT analysis?	Low Risk	Low Risk	Low Risk
10. Are there any specific limitations which might limit the applicability of this study's findings to the current NHS in England?	Unclear risk[d]	Unclear risk[e]	Unclear risk

Notes: a, baseline characteristics of time from initial diagnosis and number of disease sites; b, baseline characteristics of ECOG performance status, Ki067 index, median time since diagnosis, no. of sites of disease; c, baseline characteristics for gender and prior surgery treatment; d, around 38% of the participants are European; e, around 67% of the participants are European

4.2.2.1 Treatment allocation

RADIANT-3, A6181111 and RADIANT-4 all used a centralised internet or telephone registration system for determining treatment allocation. RADIANT-3 and RADIANT-4 based their stratification on prognostic factors (tumour location, RADIANT-4; WHO performance status RADIANT-3 and RADIANT-4, previous chemotherapy use, RADIANT-3; previous SSA use, RADIANT-4). The study A6181111 stratified by country/region only.

It was assessed that there was a low risk of bias in all three trials for selection bias / treatment allocation.

4.2.2.2 Similarity of groups

Baseline characteristics were predominantly similar between the two arms for each for RADIANT-3, A6181111 and RADIANT-4. There were, however, the following differences between arms from the trials:

- **RADIANT-3:** participants in the everolimus arm tended to have shorter time from initial diagnosis at baseline compared to the placebo arm (31% vs 21% were <6 months to <2 years and 26% vs 40% were 2 years to ≤5 years respectively. The proportion of individuals with 2 disease sites were higher in the everolimus arm compared to placebo (41% vs 32%).
- **A6181111:** there were a higher proportion of participants with Eastern Cooperative Oncology Group (ECOG) performance status 0 in the sunitinib arm compared to placebo (62% vs 48%) whilst performance status 1 was lower in the sunitinib arm compared to placebo (38% vs 51%).
- **RADIANT-4:** there were a higher proportion of women in the everolimus arm compared to the placebo arm (57% vs 45%). There were also less individuals treated

with surgery prior to entering the study in the everolimus arm compared to placebo arm (59% vs 72%).

Differences between arms for the ECOG performance status in the A6181111 are most likely to affect clinical effectiveness results with those receiving sunitinib having proportionally a better performance status than those receiving placebo. Otherwise, it was considered by the clinicians that these baseline differences between participants in the treatment arms are unlikely to remarkably impact the clinical effectiveness outcomes reported from the trials.

4.2.2.3 Implementation of masking

RADIANT-3, A6181111 and RADIANT-4 were all double-blind and, as such, the participants, investigators, site personnel and trial teams were blinded to the allocated treatment. In addition, central reviews of tumour progression were carried out in both RADIANT-3 and RADIANT-4, these outcome assessors were also blinded to treatment allocation. Information from the protocols indicated identical appearance, packing, labelling and scheduling of administration of both everolimus and placebo in both RADIANT-3 and RADIANT-4. A6181111 did not provide information on the appearance of their placebo medication.

It was assessed that there was a low risk of bias in respect of blinding of outcome assessors, participants and care providers.

4.2.2.4 Completeness of trial data

All *a priori* outcomes reported in the protocols were reported in RADIANT-3, A6181111 and RADIANT-4. Intention-to-treat analysis was carried out in each of the trials. Explanations for changes in participant numbers for reported AEs were poorly reported by all three trials. Both RADIANT-3 and A6181111 had fewer participants for their AEs outcomes compared to the number of participants recruited, whereas RADIANT-4, had an additional participant in the placebo arm that was not accounted for (n=97 randomised and n=98 reported in AEs).

It was assessed that there was a low risk of bias for the completeness of trial data from all three trials.

4.2.2.5 Generalisability

The population evaluated by RADIANT-3, A6181111 and RADIANT-4 were all in line with the licensed indication for each treatment and with the final scope issued by NICE. All of the studies were multicentre including centres in both the UK and Europe. Thirty-eight percent of the population from RADIANT-3 were European whilst 67% of the population from A6181111 were European. RADIANT-4 did not report what proportion of their population were European.

To assess generalisability of the trials to the UK setting, the AG sought data on the prevalence of NETs in the UK. There is limited information available on the current prevalence of NETs in the UK. PHE published on the 4th October 2016 the first documentation of incidences and survival in NETs, based on a cohort of 8,726 neoplasms diagnosed in England in 2013-2014.

PHE describe the occurrence of NETs in the UK to have a 50:50 male to female ratio with no obvious variation with geographic region or ethnicity. The three trials report an average split for the male:female with the percentage of males recruited ranging from 43-58%.

PHE deemed the age at which NETs are most prevalent to be similar to that of all other malignant cancers. The age range for participants in the three trials seems to be younger (median age ranging between 56 and 65 years) than the typical population with NETs in the UK.

Based on the very limited data available on what the UK demographic for people with NET constitutes, it was assessed that all three trials had an unclear risk for the applicability of their results in the UK.

4.2.3 Study design and participant characteristics – pancreatic NETs

This review includes the two trials which evaluate treatments in pNETs (RADIANT-3 – everolimus and A6181111 – sunitinib). Characteristics of the study design are summarised in Table 12. In both trials, participants were randomised 1:1, their intervention was compared to placebo and BSC was given in both the intervention and placebo arms. Both RADIANT-3 and A6181111 measured the following outcomes: PFS, OS, RR (to include complete response, partial response, stable disease, progressive disease and objective response rate) and adverse events. A6181111, also reported HRQoL.

The primary endpoint was the same (PFS) for both trials. Median treatment duration was 4.6 months in A6181111 and [redacted] in RADIANT-3 for the treatment arm and [redacted] for the placebo/BSC arm. Median follow-up reported was 17 months for RADIANT-3 and 34.1 months for A6181111.

A summary of information relating to drug administration is given in Table 13. Mean relative dose intensity of the active treatment was slightly lower in the everolimus studies (0.86 in RADIANT-3) compared to the sunitinib study (0.91 in A6181111). The use of somatostatin analogues were permitted in both treatment arms in both trials. Treatment switching after disease progression (from placebo to active treatment) was allowed in both trials.

The A6181111 trial was discontinued early following the recommendation from the safety monitoring committee, *'because of the greater number of deaths and serious adverse events in placebo group and the difference in progression-free survival favouring sunitinib'*. Statistical power of the study was reduced because of the early termination. Only 171 individuals were randomised rather than the target of 340.

In order to achieve sufficient statistical power, RADIANT-3 estimated 392 individuals would need to be randomised to detect a clinically meaningful improvement in PFS. This target was reached as 410 patients were recruited and randomised to the study.

Table 12: Study Characteristics - pNETs

Study ID	ITT (N)	Intervention	Tumour Locations Included	Inclusion Criteria	Randomisation stratification factor	Primary Endpoint	Secondary Endpoint	Median treatment duration, median (range)	Median follow-up months
RADIANT- 3	207	Everolimus + BSC	Pancreas	Low or intermediate grade, advanced (unresectable or metastatic), disease progression within past 12 months	Stratified according to status with respect to prior chemotherapy (receipt vs. no receipt) and according to WHO PS (0 vs. 1 or 2) at baseline	PFS	OS, ORR, duration of response, safety	8.79 months (0.25-27.47	17 months
NCT 00510068	203	Placebo + BSC						3.74 months (0.01-37.79)	
A6181111	86	Sunitinib + BSC	Pancreas	Pathologically confirmed, well-differentiated, advanced and or metastatic, disease progression within past 12 months	NR	PFS	OS, ORR, time to response, duration of response, safety, patient reported outcomes	4.6 months (0.4-17.5)	34.1 months
NCT 00428597	85	Placebo + BSC						3.7 months (0.03-20.2)	

Key: BSC, best supportive care; NR, not reported, WHO, World Health Organisation; ORR, objective response rate; OS, overall survival; PFS, progression free survival; HRQoL, Health related quality of life; PS, performance status,

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3); Raymond et al., New Eng J Med, 2011 (A6181111);

Table 13: Drug administration - pNETs

Study ID	Tumour Location	ITT (N)	Interventions evaluated (dose)	Mean relative dose intensity[a]	Dose reductions/ interruptions n/N (%)	Treatment switching n/N (%)	Somatostatin analogue use during study
RADIANT- 3	Pancreas	207	10 mg oral everolimus once daily; best supportive care ([redacted])[d]	0.86	(59)	NA	Approximately 40% of individuals Everolimus arm: 37.7%[e]
		203	Matching placebo; best supportive care (includes SSA)[d]	0.97	(28)	148/203 (73)	Placebo arm : 39.9%[f]
A6181111	Pancreas	86	37.5 mg/d oral sunitinib once daily[c]; best supportive care	0.91	(30)	NA	n= 23 (n=22 were already on SSA; n=1 started following study enrolment)
		85	Matching placebo; best supportive care	1.01	(12)	59/85 (69)[b]	n= 25 (n=20 were already on SSA; n=5 started following study enrolment)

Key: SSA, somatostatin analogue; n, number; ITT; intention to treat; NA, not applicable; NR, not reported;

Notes: a, ratio of administered to planned doses; b, n=38 patients at disease progression before study termination and n=21 after study closure; c, treatment interruptions and a dose reduction to 25 mg per day were permitted to manage adverse events. Patients who did not achieve an objective tumour response could have a dose increase to 50 mg per day providing they did not have treatment-related non-haematoologic AEs >grade 1 or haematologic AEs > grade 2; d, [redacted] e, percentage given as 39.7 in Yao et al. 2016; f, percentage given as 41.4 in Yao et al. 2016

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3) and company submission; Raymond et al., New Eng J Med, 2011 (A6181111) and company submission

4.2.3.1 Population characteristics - pNETs

Baseline demographic and disease characteristics for RADIANT-3 and A6181111 are reported in Table 14.

RADIANT-3 and A6181111 recruited similar aged participants (median age ranged from 56-58 years). There was a slightly higher proportion of men recruited to RADIANT-3 (53% to everolimus arm and 58% to placebo arm) compared to A6181111 (49% sunitinib arm and 47% placebo arm). Both studies recruited pNETs individuals only.

The functionality of the tumour was not reported in RADIANT-3; whilst A6181111 recruited a mixture of functioning (>30%) and non-functioning (~50%) individuals (the functionality of the remaining ~20% was not clarified).

A6181111 recruited individuals with well-or moderately defined tumours whilst RADIANT-3 recruited around 80% of individuals with well-defined tumours and the remainder had moderately defined tumours.

RADIANT-3 measured performance status (PS) using the WHO PS score system whilst A6181111 measured PS using the ECOG PS. Our clinicians suggested that there is little difference between PS measured by WHO or ECOG. The majority of individuals had a PS score of zero in RADIANT-3 (66-67%), with the majority of the remaining individuals having a PS score of one (30-32%) and the remainder scoring a PS of two (3%). A6181111 had a lower proportion of individuals scoring a PS of zero (62% in the sunitinib arm and 48% in the placebo arm) and a higher proportion of individuals scoring a PS of one (38% in the sunitinib arm and 51% in the placebo arm) than RADIANT-3. One individual was recruited with a PS of two in the placebo arm, this was a protocol deviation for A6181111.

Proportions of individuals who had received previous treatments were variable between RADIANT-3 and A6181111, see Table 14 for further information. Of particular note, somatostatin analogue use prior to treatment was around 50% in RADIANT-3 and between 35-38% in A6181111.

Table 14: Baseline Characteristics

Study ID	Intervention	Tumour Location	N	Age, yrs (median (range))	Male n/N (%)	Tumour Functioning n/N (%)		Tumour Differentiation n/N (%)			WHO PS n/N (%)	Previous Treatments n/N (%)
						Yes	No	Well.	Mod.	Unknown		
RADIANT-3	Everolimus + BSC	Pancreas	207	58 (23-87)	110/207 (53)	NR	NR	170/207 (82)	35/207 (17)	2/207 (1)	0: 139/207 (67) 1: 62/207 (30) 2:6/207 (3)	Radiotherapy: 47/207 (23) Chemotherapy: 104/207 (50) Somatostatin Analogues: 101/207 (49)
	Placebo + BSC		203	57 (20-82)	117/203 (58)	NR	NR	171/203 (84)	30/203 (15)	2/203 (1)	0: 133/203 (66) 1: 64/203 (32) 2:6/203 (3)	Radiotherapy: 40/203 (20) Chemotherapy: 102/203 (50) Somatostatin Analogues: 102/203 (50)
A6181111	Sunitinib + BSC	Pancreas	86	56 (25-84)	42/86 (49)	25/86 (29)	42/86 (49)	86/86 (100)[b]		(0)	ECOG PS: 0: 53/86 (62) 1: 33/86 (38) 2:0/86 (0)	Surgery: 76/86 (88) Radiation Therapy: 9/86 (10) Chemoembolization: 7/86 (8) Radiofrequency ablation3/86 (3) Percutaneous Ethanol Injection 1/86 (1) Somatostatin Analogues: 30/86 (35)
	Placebo + BSC		85	57 (26-78)	40/85 (47)	21/85 (25)	44/85 (52)	85/85 (100)[b]		(0)	ECOG PS: 0: 41/85 (48) 1: 43/85 (51) 2: 1/85 (1)[a]	Surgery: 77/85 (91) Radiation Therapy: 12/85 (14) Chemoembolization: 14/85 (16) Radiofrequency ablation: 6/85 (7) Percutaneous Ethanol Injection 2/85 (2) Somatostatin Analogues: 32/85 (38)

Key: BSC, Best Supportive Care, N, Number; WHO, World Health Organisation; PS, performance status; mod, moderately

Notes: a, enrolment of this individual was a protocol violation; b, assumed from inclusion criteria requiring individuals to present with well-differentiated NETs and poorly differentiated NETs being an exclusion criteria

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3) and Table 4.2 (page 37) from Novartis submission; Raymond et al., New Eng J Med, 2011 (A6181111);

4.2.4 Study design and participant characteristics – GI and Lung NETs

This review includes RADIANT-4 which evaluates everolimus in individuals with GI and lung NETs. Characteristics of the study design are summarised in Table 15. Participants were randomised 2:1 for everolimus to placebo. BSC was given in both the intervention (everolimus) and the placebo arm. RADIANT-4 measured the following outcomes: PFS, OS, RR (to include complete response, partial response, stable disease, progressive disease and objective response rate) and adverse events. The primary endpoint was PFS. Median treatment duration was 9.3 months in the everolimus arm and 4.5 months in the placebo arm. Median follow-up was 21 months.

A summary of information relating to drug administration is given in Table 16. The use of somatostatin analogues were permitted in both treatment arms. Treatment switching (from placebo to active treatment) was not allowed in RADIANT-4.

RADIANT-4 estimated 285 individuals would be needed for randomisation with a ratio of 2:1. This requirement was met as 302 individuals were randomised.

Table 15: Study Characteristics – GI and Lung NETs

Study ID	ITT (N)	Intervention	Tumour Locations Included	Inclusion Criteria	Randomisation stratification factor	Primary Endpoint	Secondary Endpoint	Median treatment duration, median (range)	Median follow-up months
RADIANT- 4 ***NCT 01524783***	205 97	Everolimus + BSC Placebo + BSC	Lung + GI (Ileum Rectum Unknown Origin Jejunum Stomach Dudoenum Colon Other Caecum Appendix)	Pathologically confirmed, advanced (unresectable or metastatic), non-functional, well differentiated (grade 1 or 2), disease progression within past 6 months	Stratified by previous somatostatin analogue treatment, tumour origin and WHO PS (0 vs 1)	PFS	OS, ORR, disease control rate, HRQoL, WHO PS, safety, pharmacokinetics, changes in chromogranin A and neuron-specific enolase levels	9.3 months (0.1-27.7)[a] 4.5 months (0.9-30.0)[b]	21 months

Key: BSC, best supportive care; NR, not reported, WHO, World Health Organisation; ORR, objective response rate; OS, overall survival; PFS, progression free survival; HRQoL, Health related quality of life; PS, performance status,
Notes: a, converted into months by AG, reported as 40.4 weeks (0.7-120.4); b, converted into months by AG, reported as 19.6 weeks (4.0-130.3)
Source: Yao et al., Lancet, 2016 (RADIANT-4)

Table 16: Drug administration - GI and Lung NETs

Study ID	Tumour Location	ITT (N)	Interventions evaluated (dose)	Mean relative dose intensity[a]	Dose reductions/ interruptions n/N (%)	Treatment switching n/N (%)	Somatostatin analogue use during study
RADIANT- 4	Lung + GI	205	10 mg oral everolimus once daily; best supportive care	0.90[c]	135/202 (67)	NA	NR[b]
		97	Matching placebo; best supportive care	1.00 [d]	29/98 (30)	Not permitted	

Key: GI; gastrointestinal; SSA, somatostatin analogue; n, number; ITT; intention to treat; NA, not applicable; NR, not reported
Notes: a, ratio of administered to planned doses; b, somatostatin analogues were allowed only for control of emergent carcinoid symptoms; c, reported as 0.794 in the company submission; d, reported as 0.962 in the company submission
Source: Yao et al., Lancet, 2016 (RADIANT-4)

4.2.4.1 Population characteristics - GI and Lung NETs

Baseline demographic and disease characteristics for RADIANT-4 are reported in Table 17.

The median age ranged from 60-65 years in RADIANT-4. There was a slightly lower proportion of men recruited to the everolimus arm (43%) compared to the placebo arm (55%). Only individuals with non-functioning, well defined tumours were recruited to RADIANT-4.
Performance status was measured using the WHO PS score system. The majority of individuals had a PS score of zero (73-75%) and the remaining scoring one (27-25%). Proportions of individuals who had received previous treatments were variable between arms, see Table 17 for further information.

Table 17: Baseline Characteristics

Study ID	Intervention	Tumour Location	N	Age, yrs (median (range))	Male n/N (%)	Tumour Functioning n/N (%)		Tumour Differentiation n/N (%)			WHO PS n/N (%)	Previous Treatments n/N (%)
						Yes	No	Well.	Mod.	Unknown		
RADIANT-4	Everolimus + BSC	Lung, GI	205	65 (22-86)	89/205 (43%)	0/205 (0%)	205/205 (100%)	205/205 (100%)[a]		(0)	[redacted]	Surgery: 121/205 (59) Chemotherapy: 54/205 (26) Radiotherapy: 44/205 (22) Locoregional+ablative therapy: 23/205 (11) Somatostatin Analogues: 109/205 (53)
	Placebo + BSC		97	60 (24-83)	53/97 (55%)	0/97 (0%)	97/97 (100%)	97/97 (100%)[a]		(0)	0:73/97 (75) 1:24/97 (25)	Surgery: 70/97 (72) Chemotherapy: 23/97 (24) Radiotherapy: 19/97 (20) Locoregional+ablative therapy: 10/97 (10) Somatostatin Analogues: 54/97 (56)

Key: BSC, Best Supportive Care, N, Number; WHO, World Health Organisation; PS, performance status; mod, moderately
Notes: a, assumed from inclusion criteria requiring individuals to present with well-differentiated NETs and poorly differentiated NETs being an exclusion criteria
Source: Yao et al., New Eng J Med, 2011 (RADIANT-3) and Table 4.2 (page 37) from Novartis submission; Raymond et al., New Eng J Med, 2011 (A6181111); Yao et al., Lancet, 2016 (RADIANT-4)

4.2.5 Assessment of effectiveness RCT evidence

The following outcomes have been assessed:

- Progression free survival (PFS)
- Overall survival (OS)
- Response rate (RR)
  - Complete response, partial response, stable disease, progressive disease, objective response rate, tumour shrinkage
- Adverse events (AE)
- Health Related Quality of Life (HRQoL)

4.2.5.1 Outcomes for RCT evidence for Pancreatic NETs

4.2.5.1.1 Progression Free Survival

RADIANT-3 and A6181111 report PFS as their primary outcome. Disease progression was defined by both trials as, '*the time from randomisation to the first evidence of progression or death from any cause'*.[31, 45] Both trials used the response evaluation criteria in solid tumours (RECIST) version 1.0 criteria[47] to define disease progression. RADIANT-3 reported PFS from central radiology review and also local investigator review, whilst A6181111 only reported PFS from local investigator review in their published paper[45]. PFS from the assessment of an independent review was available from the company submission.

RADIANT-3 reported median PFS assessed by central review as 11.4 months (95% confidence interval (CI) 10.8, 14.8) for the everolimus plus BSC arm and 5.4 (95% CI 4.3, 5.6) for the placebo plus BSC arm. Everolimus was associated with a 66% reduction in the risk of disease progression or death for people with pNETs compared to placebo (hazard ratio (HR) 0.34 [95% CI 0.26, 0.44]; Table 18).

In the submission from Pfizer, PFS from the assessment of an independent review was reported for sunitinib plus BSC as 12.6 months (95% CI 11.1, 20.6) and for placebo plus BSC as 5.8 months (95% CI 3.8, 7.2). Sunitinib was associated with a 68% reduction in the risk of disease progression or death for people with pNETs compared to placebo (HR 0.32 [95% CI 0.18, 0.55]; Table 18).

Table 18: Progression Free Survival by central radiology review – Pancreatic NETs

Study ID	Tumour Location	Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
RADIANT-3	Pancreas	*Everolimus + BSC* (95/207) 11.4 (10.8, 14.8)	*Placebo + BSC* (142/203) 5.4 (4.3, 5.6)	0.34 (0.26, 0.44) P<0.001
A6181111	Pancreas	*Sunitinib + BSC* 12.6 (11.1, 20.6)	*Placebo + BSC* 5.8 (3.8, 7.2)	0.32 (0.18, 0.55) P<0.001

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3); Page 43 from Pfizer submission (A6181111)

Locally assessed PFS for RADIANT-3 was 11.0 months (95% CI 8.4, 13.9) in the everolimus plus BSC arm compared to 4.6 months (95% CI 3.1, 5.4) in the placebo plus BSC arm. Everolimus was associated with a reduction (65%) in the risk of disease progression or death for people with pNETs compared to placebo (HR 0.35 [95%CI 0.27, 0.45]; Table 19). The A6181111 trial reported locally assessed PFS to be 11.4 months (95% CI 7.4, 19.8) in

the sunitinib plus BSC arm and 5.5 months (95% CI 3.6, 7.4) in the placebo plus BSC arm. Sunitinib was associated with a 58% reduction in the risk of disease progression or death for people with pNETs compared to placebo (HR 0.42 [95%CI 0.26, 0.66]; Table 19). Both trials reported a shorter time for PFS in both arms for locally assessed PFS in comparison to central/independent review.

Table 19: Progression Free Survival by local investigator review – Pancreatic NETs

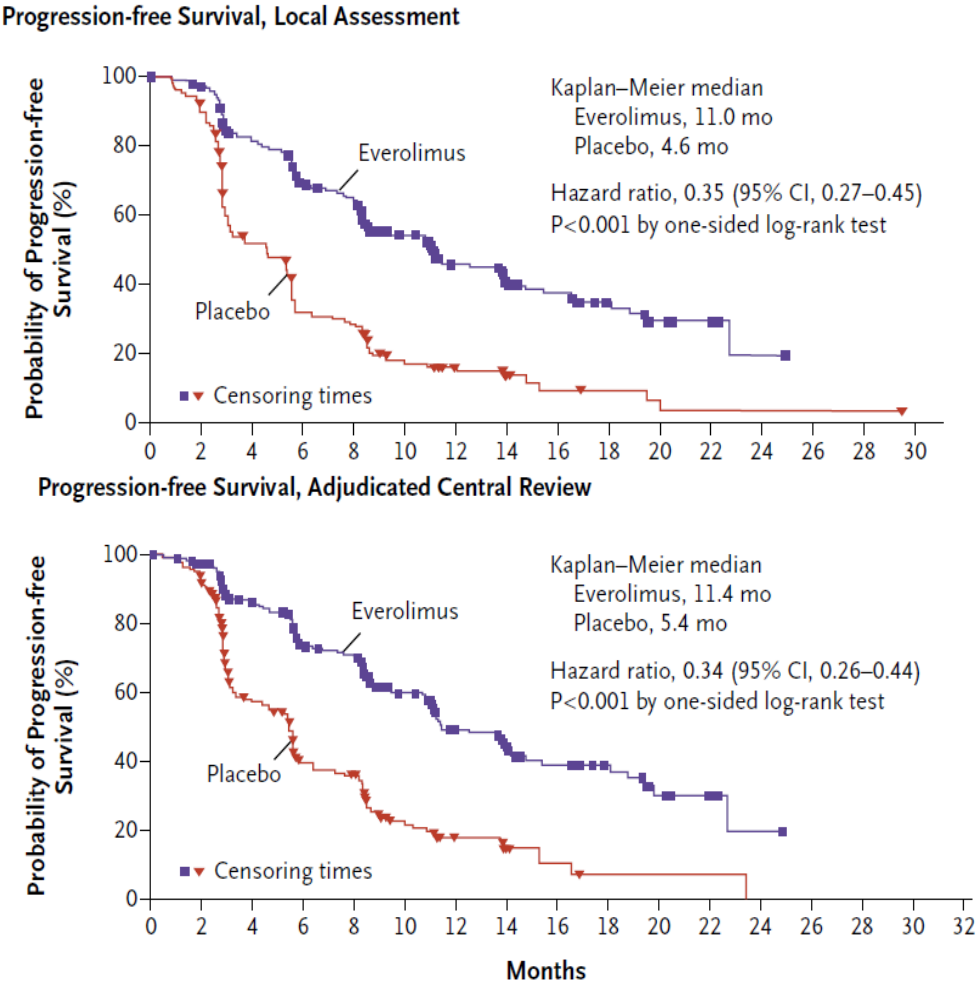
Study ID	Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
RADIANT-3	*Everolimus + BSC* (109/207) 11.0 (8.4, 13.9)	*Placebo + BSC* (165/203) 4.6 (3.1, 5.4)	0.35 (0.27, 0.45) P<0.001
A6181111	*Sunitinib + BSC* (30/86) 11.4 (7.4, 19.8)	*Placebo + BSC* (51/85) 5.5 (3.6, 7.4)	0.42 (0.26, 0.66) P<0.001

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3); Raymond et al., New Eng J Med, 2011 (A6181111)

Kaplan-Meier curves for progression free survival

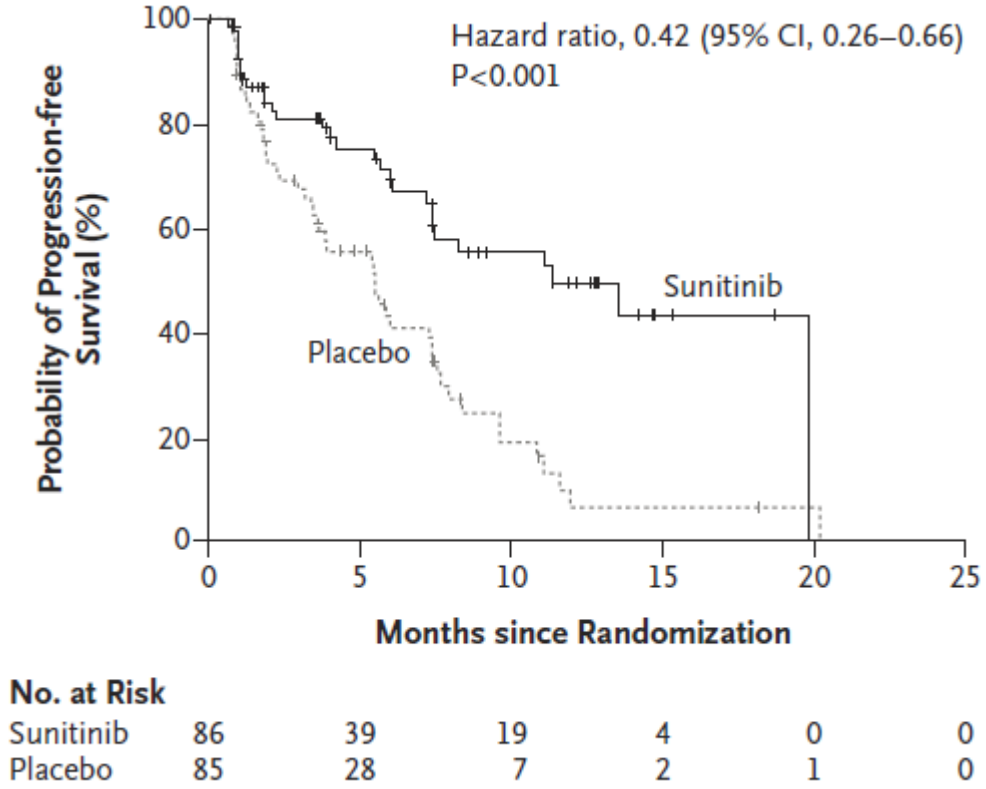
Kaplan-Meier curves are presented for both trials. RADIANT-3 presented plots for both local and central review (Figure 10) whilst A6181111 presented a plot for local review (Figure 11).

Figure 10: Kaplan-Meier plot for Progression Free Survival, (local and central review) for RADIANT-3



Source: Figure 4.3 (page 39) Novartis submission

Figure 11: Kaplan-Meier plot of Progression Free Survival for A6181111,



Note: ITT population
Source: Figure 4 (page 45) Pfizer submission

4.2.5.1.2 Overall Survival

Both of the pNET studies (RADIANT-3 and A6181111) reported some data related to OS.

RADIANT-3 report that their OS data was immature, '*median overall survival was not reached at the time of this analysis… final analysis of overall survival will be performed once approximately 250 deaths have occurred.'* [31] In addition, of the 203 people initially assigned to receive placebo in RADIANT-3, 172 people (85%) received open-label everolimus and 148 people (73%) crossed over from placebo to everolimus following disease progression. By individual's crossing over from placebo to everolimus, the detection of a treatment-related survival benefit is confounded with (intention to treat) ITT analysis. RADIANT-3 report HR for OS to be 1.05 (95% CI 0.71, 1.55; Table 20).

As it had not been reached, median OS was not reported by A6181111. Instead, A6181111 reported survival probability at month 6. Survival was predicted to be higher in the sunitinib arm 92.6 % (95% CI 86.3, 98.9) compared to the placebo arm, 85.2% (95% CI 77.1, 93.3). Survival was improved by 59% following sunitinib treatment compared with placebo (HR 0.41 [95% CI 0.19, 0.89], Table 20).

Table 20: Overall Survival – Pancreatic NETs

Study ID	Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
RADIANT-3	*Everolimus + BSC* (n=207) Not reached	*Placebo + BSC* (n=203) Not reached	1.05 (0.71,1.55)[b] P=0.59
A6181111	*Sunitinib + BSC* (n=86) (77/86) 92.6 (86.3 -98.9)[a]	*Placebo + BSC* (n=85) (64/85) 85.2 (77.1-93.3)[a]	0.41 (0.19, 0.89)[c] P=0.02

Notes: a, survival probability (%) at month 6; b, median overall survival was not reached at the time of analysis; c, most individuals were in follow-up at the data cut off point, HR for death
Source: Yao et al., New Eng J Med, 2011 (RADIANT-3); Raymond et al., New Eng J Med, 2011 (A6181111)

Both companies (Novartis for everolimus (RADIANT-3) and Pfizer for sunitinib (A6181111)) presented updated OS data in their submission.

Additional OS data were available from Yao et al. 2016. The initial analysis presented in the initial published paper[31] was analysed on the 28th February 2010. In their submission, Novartis present interim OS analysis from the 23rd February 2011 and final OS analysis from the 5th March 2015. The final OS data is also available in the published paper by Yao et al. 2016. At the interim time point, median OS was still not reached in the everolimus plus BSC arm but it was 36.63 months for the placebo plus BSC arm (HR 0.89, [95% CI 0.64, 1.23]). At the final OS time point, median OS for everolimus plus BSC it was 44.0 (95% CI 35.6, 51.8) months and for placebo plus BSC was 37.68 months (95% CI 29.1, 45.8), indicating an overall improvement in median OS of 6.3 months (HR 0.94 [95% CI 0.73, 1.20], p=0.30; Table 21). Novartis in their submission comment that, '*the results may be confounded due to the high level of crossover from placebo to everolimus and the receipt of subsequent anti-neoplastic therapies' (Novartis company submission, page 43).* Novartis accounted for the crossover from placebo to everolimus using the Rank Preserving Structural Failure Time (RPSFT) model. The RPSFT results are shown in Table 22, and suggests a 40% reduction in OS with everolimus compared to placebo (HR 0.60, 95%CI 0.09, 3.95).

Additional overall survival data was also available from Pfizer in their submission (page 45-9). Pfizer performed final OS analysis in the A6181111 trial after 5 years of follow-up post study closure. From the ITT population, median OS in the sunitinib plus BSC arm was 38.6 months (range, 25.6 – 56.4 months; n=55 deaths) and in the placebo plus BSC arm 29.1 months (range, 16.4-36.8 months; n=58 deaths). An improvement of 9.5 months (HR = 0.73 [95% CI 0.50, 1.06], p=0.094; Table 21). After accounting for crossover using the RPSFT method, median OS in the placebo group (if the 69% of patients who crossed over to sunitinib had remained on placebo) was estimated at 13.2 months (range, 11.3-16.5 months) (HR = 0.34 [95% CI 0.14*, 1.28], p=0.094). *or 0.15, reported as both within company submission

Table 21: Final Overall Survival – Pancreatic NETs

Study ID	Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
RADIANT-3	*Everolimus + BSC* (n=207) (81/207)[a] 44.0 (35.6, 51.8)	*Placebo + BSC* (n=203) (73/203)[a] 37.7 (29.1, 45.8)	0.94 (0.73-1.20) P=0.30
A6181111	*Sunitinib + BSC* (n=86) (31/86)[a] 38.6 months (range: 25.6 – 56.4)	*Placebo + BSC* (n=85) (27/85)[a] 29.1 months (range: 16.4-36.8)	0.73 (0.50, 1.06) p=0.094

Notes: a, calculated from total number of participants minus number of deaths;
Source: Pfizer submission (page 45-49) and Yao et al., J of Clin Oncol, 2016 (RADIANT-3)

Table 22: Survival rates following everolimus, placebo and RPSFT-corrected placebo treatment in RADIANT-3

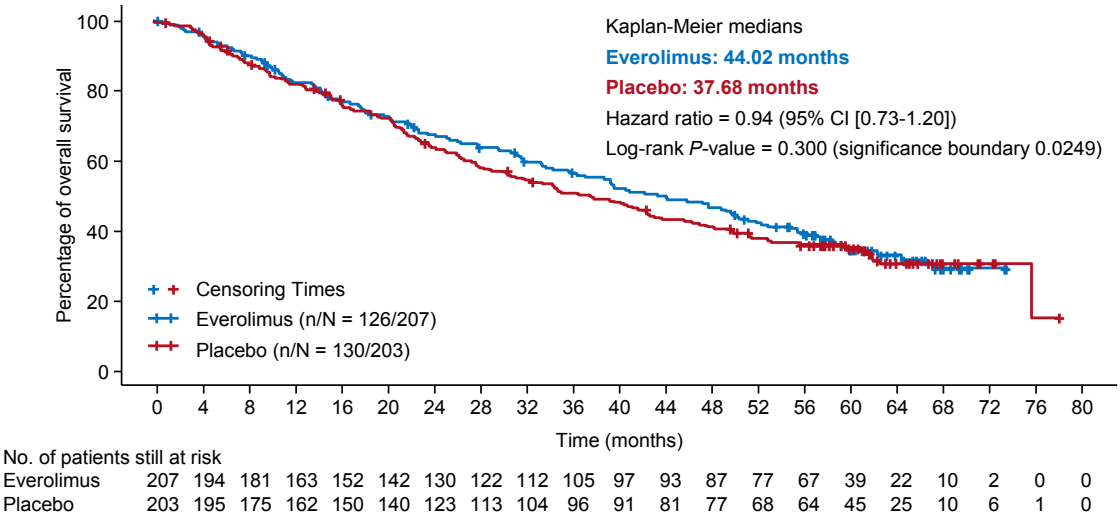
Survival rate (95% CI)	Everolimus + BSC	Placebo + BSC	RPSFT-corrected placebo	HR between everolimus versus corrected placebo
6 months	93.1 (88.6, 95.9)	91.6 (86.8, 94.7)	88.9 (83.6, 92.5)	-
12 months	82.6 (76.6, 87.2)	82.0 (75.9, 86.7)	74.9 (68.1,80.4)	-
18 months	75.0 (68.3, 80.4)	74.3 (67.6, 79.8)	64.6 (57.4,71.0)	-
24 months	67.7 (60.7, 73.8)	64.0 (56.8, 70.2)	≤55.6 (NA, NA)	0.60 (0.09, 3.95)
36 months	56.7 (49.4, 63.3)	50.9 (43.6, 57.7)	NA (NA, NA)	-
48 months	46.9 (39.7, 53.8)	41.3 (34.3, 48.1)	NA (NA, NA)	-
60 months	34.7(27.7, 41.7)	35.5 (28.7, 42.4)	NA (NA, NA)	-

Key: BSC: best supportive care, CI: confidence interval, HR: hazard ratio, NA: not assessable, RPSFT: rank-preserving structural failure time.
Source: Novartis Submission, Table 4.6 (page 45) and Yao et al., J of Clin Oncol, 2016 (RADIANT-3)

Kaplan-Meier curves for overall survival

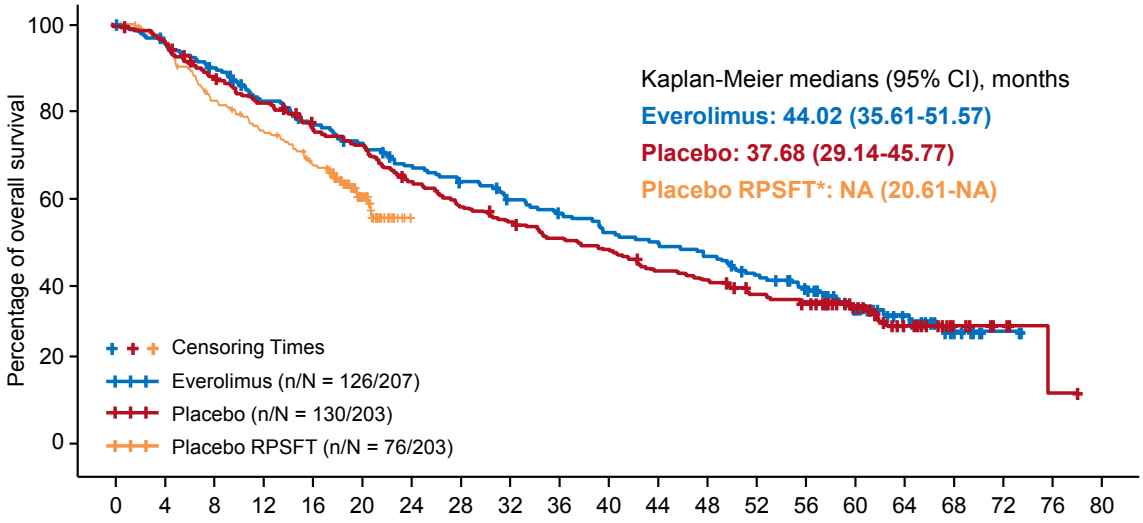
Kaplan-Meier curves were presented by both trials for OS. RADIANT-3 presented plots for OS (Figure 12) and RPSFT adjusted OS (Figure 13) as did A6181111 (see Figure 14 for OS and Figure 15 for RPSFT OS).

Figure 12: Kaplan-Meier plot for overall survival from RADIANT-3 (everolimus vs placebo)



Source: Figure 4.6 (page 44) Novartis submission

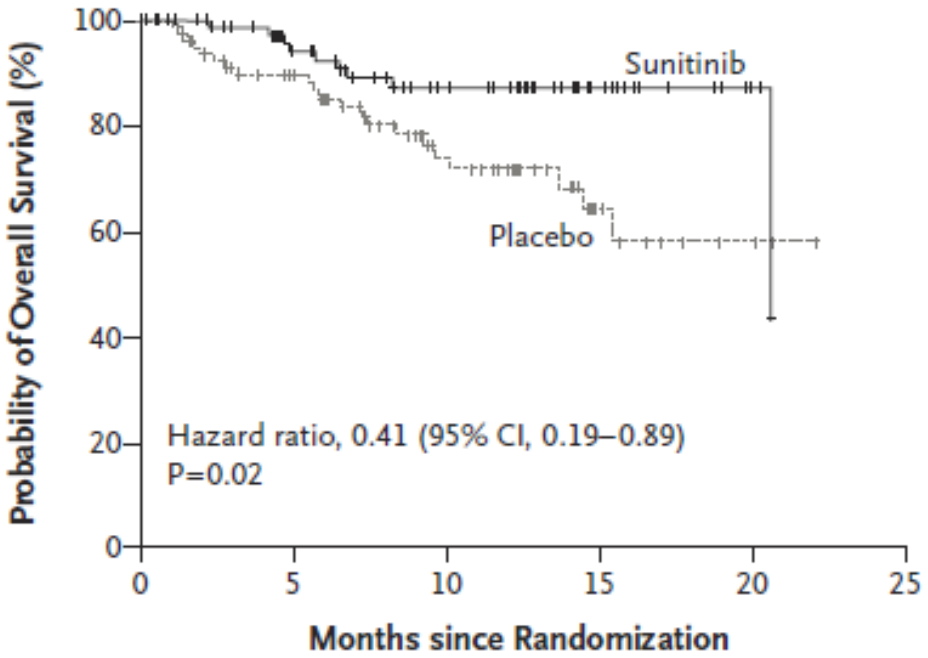
Figure 13: Kaplan-Meier plot of the final OS analysis from RADIANT-3 adjusting using RPSFT (everolimus vs placebo)



No. of patients still at risk																				
Everolimus	207	194	181	163	152	142	130	122	112	105	97	93	87	77	67	39	22	10	2	0	0
Placebo	203	195	175	162	150	140	123	113	104	96	91	81	77	68	64	45	25	10	6	1	0
Placebo RPSFT	203	189	159	143	125	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Source: Figure 4.7 (page 45) Novartis submission

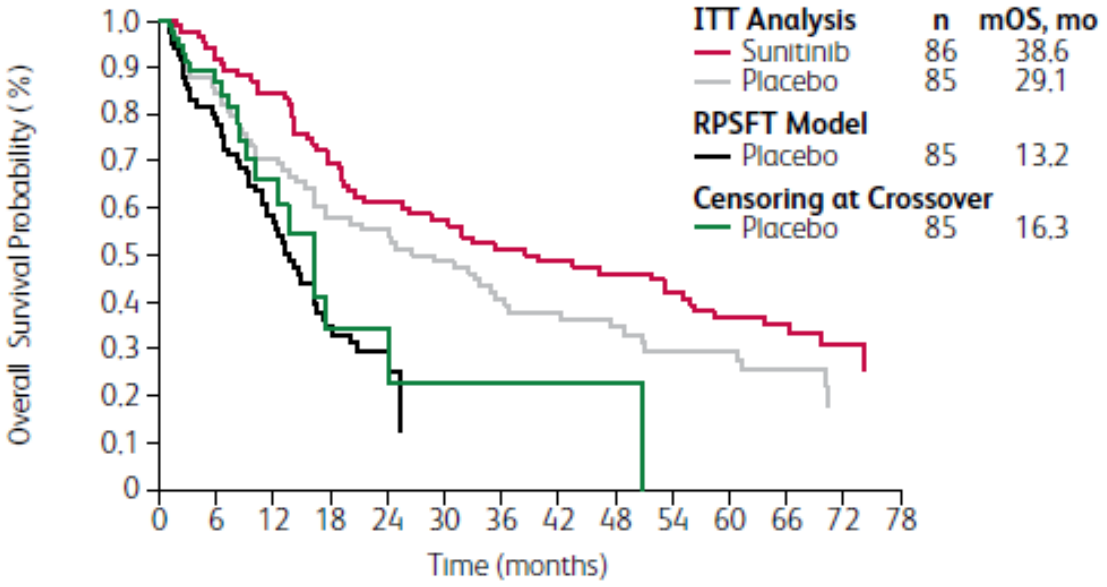
Figure 14: Overall survival, blinded phase, ITT population, from A6181111 (sunitinib vs placebo)



No. at Risk						
Sunitinib	86	60	38	16	3	0
Placebo	85	61	33	12	3	0

Source: Figure 5 (page 46) Pfizer submission

Figure 15: Kaplan-Meier estimate of overall survival with and without adjustment for crossover, final analysis, ITT population from A6181111 (sunitinib vs placebo)



Source: Figure 6 (page 48-49) from Pfizer submission

4.2.5.1.3 Response Rate

Both studies used RECIST v1.0 to assess tumour response. Response rate was assessed by local investigators in RADIANT-3 and it was unclear whether response rate was assessed locally or centrally in A6181111, however since PFS was only assessed locally in Raymond et al.[45], it might be assumed response rate was also assessed locally in A6181111. A618111 performed their clinical assessments at screening, during week 5 and 9 and every 8 weeks thereafter, whenever progression was suspected and at the end of treatment or withdrawal from the study. Whereas, RADIANT-3 performed assessments at baseline and every 12 weeks thereafter.

Complete response, partial response, stable disease and progressive disease, were reported by both studies (Table 23). RADIANT-3 also report tumour shrinkage, whilst A6181111 also report the proportion of individuals who could not be evaluated and objective response rate (Table 23). Complete response was only achieved by 2 individuals in the A6181111 study following treatment with sunitinib and BSC. Complete response was not achieved by anyone receiving placebo (both trials), nor following treatment with everolimus (RADIANT-3). Numbers of individuals achieving partial response or stable disease were higher in the treatment arms (everolimus and sunitinib) compared to the placebo arms in both trials. Likewise, there were higher proportions of individuals with progressive disease in the placebo arm compared to the treatment arm.

Novartis report in their submission that [redacted]

[redacted]**Table 23: Response Rate – Pancreatic NETs**

Study ID	Type of response	Experimental Arm n/N (%)	Control Arm n/N (%)
RADIANT-3 (local investigators)		*Everolimus + BSC*	*Placebo + BSC*
	Complete response	0/207 (0)	0/203 (0)
	Partial response	10/207 (5)	4/203 (2)
	Stable disease	[redacted](73)	[redacted](51)
	Progressive disease	[redacted] (14)	[redacted] (42)
	Tumour shrinkage	123/191[c] (64)	39/189 [c] (21)
	Objective response rate[a]	10/207 (5)	4/203 (2)
A6181111		*Sunitinib + BSC*	*Placebo + BSC*
	Complete response	2/86 (2)	0/85
	Partial response	6/86 (7)	0/85
	Stable disease	54/86 (63)	51/85 (60)
	Progressive disease	12/86 (14)	23/85 (27)
	Could not be evaluated	12/86 (14)	11/85 (13)
	Objective response rate	8/86 (9.3)[b]	0/85 (0)[b]

Notes: a, between group difference (HR 9.3; [95% CI 3.2, 15.4] p=0.007); b, Complete response combined with partial response; c, data on 30 patients with lesions that could be evaluated in the everolimus group and 42 in the placebo group were no included in the analysis for the following reasons: 14 in the everolimus group and 28 in the placebo group showed a change in the available target lesion that contradicted the overall response of progressive disease; 1 patent in the everolimus group showed a change in the available target lesion, but the overall response was unknown; and the change in the target lesion could not be assessed in 15 patients in the everolimus group and 14 in the placebo group.

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3); Company submission, Novartis; Raymond et al., New Eng J Med, 2011 (A6181111)

Novartis, in their company submission, also report central investigator response rates and adjudicated central investigator response rates from RADIANT-3. Response rates as per adjudicated central investigator are presented in Table 24.

Table 24: Response rates as per adjudicated central investigators - Pancreatic NETs

Study ID	Type of response	Experimental Arm n/N (%)	Control Arm n/N (%)
RADIANT-3 (central investigators)		*Everolimus + BSC*	*Placebo + BSC*
	Complete response	[redacted]	[redacted]
	Partial response	[redacted]	[redacted]
	Stable disease	[redacted]	[redacted]
	Progressive disease	[redacted]	[redacted]
	Tumour shrinkage	NR	NR
	Objective response rate	[redacted]	[redacted]

Notes: [redacted]

4.2.5.1.4 Adverse Events

Both RADIANT-3 and A6181111 assessed their adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v3.0.

Treatment related adverse events (all grade and grade 3 and 4 combined) are reported for both trials (Table 25). RADIANT-3 report the AEs where occurrences were in at least 10% of the safety population whereas A6181111 report the AEs which occurred in more than 15% of the safety population. Adverse events were more commonly reported following treatment with everolimus and sunitinib in comparison to placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-3) were stomatitis (64%),

rashes (49%), diarrhoea (34%), fatigue (31%) and infections (23%). Following treatment with sunitinib (A6181111) the five most common all grade AEs were diarrhoea (59%), nausea (45%), vomiting (34%), asthenia (34%) and fatigue (32%).

Table 25: Adverse Events, all grade and grade 3+4 only – Pancreatic NETs

	All GRADE				GRADE 3+4			
Study ID	**RADIANT-3[a]**		**A6181111[c]**		**RADIANT-3**		**A6181111**	
Intervention	**Everolimus + BSC n/N (%)**	**Placebo + BSC n/N (%)**	**Sunitinib n/N (%)**	**Placebo + BSC n/N (%)**	**Everolimus + BSC n/N (%)**	**Placebo + BSC n/N (%)**	**Sunitinib n/N (%)**	**Placebo + BSC n/N (%)**
On treatment deaths	12	4	5	9				
Treatment discontinuation due to study drugs	13	2	NR	NR				
Abdominal Pain	NR	NR	23/83 (28)	26/82 (32)	NR	NR	4/83 (5)	8/82 (10)
Anaemia	35/204 (17)	6/203 (3)	NR	NR	12/204 (6)	0/203 (0)	NR	NR
Asthenia	26/204 (13)	17/203 (8)	28/83 (34)	22/82 (27)	2/204 (1)	2/203 (1)	4/83 (5)	3/82 (4)
Back pain	NR	NR	10/83 (12)	14/82 (17)	NR	NR	0/83 (0)	4/82 (5)
Constipation	NR	NR	12/83 (14)	16/82 (20)	NR	NR	0/83 (0)	1/82 (1)
Cough	22/204 (11)	4/203 (2)	NR	NR	0/204 (0)	0/203 (0)	NR	NR
Decreased appetite	40/204 (20)	14/203 (7)	18/83 (22)	17/82 (21)	0/204 (0)	2/203 (1)	2/83 (2)	1/82 (1)
Decreased Weight	32/204 (16)	9/203 (4)	13/83 (16)	9/82 (11)	0/204 (0)	0/203 (0)	1/83 (1)	0/82 (0)
Diarrhoea	69/204 (34)	20/203 (10)	49/83 (59)	32/82 (39)	7/204 (3)	0/203 (0)	4/83 (5)	2/82 (2)
Dry Skin	21/204 (10)	9/203 (4)	NR	NR	0/204 (0)	0/203 (0)	NR	NR
Dysgeusia	35/204 (17)	8/203 (4)	17/83 (20)	4/82 (5)	0/204 (0)	0/203 (0)	0/83 (0)	0/82 (0)
Epistaxis	35/204 (17)	0/203 (0)	17/83 (20)	4/82 (5)	0/204 (0)	0/203 (0)	1/83 (1)	0/82 (0)
Fatigue	64/204 (31)	29/203 (14)	27/83 (32)	22/82 (27)	5/204 (2)	1/203 (<1)	4/83 (5)	7/82 (8)
Hair colour change	NR	NR	24/83 (29)	1/82 (1)	NR	NR	1/83 (1)	0/82 (0)
Headache	39/204 (19)	13/203 (6)	15/83 (18)	11/82 (13)	0/204 (0)	0/203 (0)	0/83 (0)	1/82 (1)
Hyperglycaemia	27/204 (13)	9/203 (4)	NR	NR	11/204 (5)	4/203 (2)	NR	NR
Hypertension	NR	NR	22/83 (26)	4/82 (5)	NR	NR	8/83 (10)	1/82 (1)
Infections	46/204 (23)	12/203 (6)	NR	NR	5/204 (2)	1/203 (<1)	NR	NR
Insomnia	NR	NR	15/83 (18)	10/82 (12)	NR	NR	0/83 (0)	0/82 (0)
Mucosal inflammation	NR	NR	13/83 (16)	6/82 (7)	NR	NR	1/83 (1)	0/82 (0)
Nail disorder	24/204 (12)	2/203 (1)	NR	NR	1/204 (<1)	0/203 (0)	NR	NR
Nausea	41/204 (20)	37/203 (18)	37/83 (45)	24/82 (29)	5/204(2)	0/203 (0)	1/83 (1)	1/82 (1)

Neutropenia	NR	NR	24/83 (29)	3/82 (4)	NR	NR	10/83 (12)	0/82 (0)
Palmar-plantar erythrodysesthesia	NR	NR	19/83 (23)	2/82 (2)	NR	NR	5/83 (6)	0/82 (0)
Peripheral Oedema	41/204 (20)	7/203 (3)	NR	NR	1/204 (<1)	0/203 (0)	NR	NR
Pneumonitis	35/204 (17)	0	NR	NR	5/204 (2)	0/203 (0)	NR	NR
Pruritus	30/204 (15)	18/203 (9)	NR	NR	0/204 (0)	0/203 (0)	NR	NR
Pyrexia	22/204 (11)	0/203 (0)	NR	NR	0/204 (0)	0/203 (0)	NR	NR
Rash	99/204 (49)	21/203 (10)	15//83 (18)	4/82 (5)	1/204 (<1)	0/203 (0)	0//83 (0)	0/82 (0)
Stomatitis	131/204 (64)	34/203 (17)	18//83 (22)	2/82 (2)	14/204 (7)	0/203 (0)	3//83 (4)	0/82 (0)
Thrombocytopenia	27/204 (13)	1/203 (<1)	14/83 (17)	4/82 (5)	8/204 (4)	0/203 (0)	3/83 (4)	0/82 (0)
Vomiting	31 /204 (15)	13/203 (6)	28/83 (34)	25/82 (30)	0/204 (0)	0/203 (0)	0/83 (0)	2/82 (2)

Notes: a, most common AE with a frequency of at least 10; b, non-infectious pneumonitis; c, most common AE with a frequency of at least 15; d, Pfizer in their submission report AEs from their clinical study report (CSR; 2009), where incidence rates are lower than the incidence rates reported in Raymond et al. 2011. These AEs are reported in Appendix 5

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3); Raymond et al., New Eng J Med, 2011 (A6181111)

Treatment related AEs occurring in ≥20% of patients in RADIANT-3 at the latest cut-off (5th March) were presented in the company submission from Novartis (Table 26). These AE rates are different (predominately higher) to the ones published in Yao et al. 2016. The AEs published in the paper by Yao et al. 2016 are coded using the Medical Dictionary for Regulatory Activities, version 16.1 and are given in Appendix 5, Table 168.

Table 26: Treatment related adverse events occurring in ≥20% of patients in RADIANT-3

	Everolimus plus BSC (n=204) n events (%)		**Placebo plus BSC (n=203) n events (%)**		**Open-label everolimus (n=225) n events (%)**	
	All grades	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**	**All grades**	**Grade 3 or 4**
Any preferred term	203 (99.5)	126 (61.8)	198 (97.5)	82 (40.4)	221 (98.2)	165 (73.3)
Abdominal pain	49 (24.0)	6 (2.9)	49 (24.1)	12 (5.9)	63 (28.0)	16 (7.1)
Anaemia	49 (24.0)	19 (9.3)	19 (9.4)	4 (2.0)	56 (24.9)	18 (8.0)
Asthenia	38 (18.6)	6 (2.9)	41 (20.2)	7 (3.4)	45 (20.0)	17 (7.6)
Cough	46 (22.5)	1 (0.5)	22 (10.8)	0	54 (24.0)	0
Decreased appetite	61 (29.9)	3 (1.5)	37 (18.2)	3 (1.5)	66 (29.3)	11 (4.9)
Diarrhoea	98 (48.0)	11 (5.4)	48 (23.6)	5 (2.5)	98 (43.6)	10 (4.4)
Dysgeusia	38 (18.6)	0	11 (5.4)	0	46 (20.4)	1 (0.4)
Epistaxis	44 (21.6)	0	3 (1.5)	0	38 (16.9)	0
Fatigue	91 (44.6)	6 (2.9)	54 (26.6)	5 (2.5)	74 (32.9)	11 (4.9)
Headache	62 (30.4)	1 (0.5)	30 (14.8)	2 (1.0)	52 (23.1)	6 (2.7)
Hyperglycaemia	41 (20.1)	18 (8.8)	22 (10.8)	8 (3.9)	61 (27.1)	23 (10.2)
Nausea	67 (32.8)	5 (2.5)	66 (32.5)	4 (2.0)	84 (37.3)	4 (1.8)
Oedema peripheral	76 (37.3)	2 (1.0)	23 (11.3)	2 (1.0)	66 (29.3)	2 (0.9)

Pyrexia	63 (30.9)	2 (1.0)	25 (12.3)	1 (0.5)	61 (27.1)	2 (0.9)
Rash	107 (52.5)	1 (0.5)	32 (15.8)	0	90 (40.0)	3 (1.3)
Stomatitis	110 (53.9)	10 (4.9)	27 (13.3)	0	105 (46.7)	5 (2.2)
Vomiting	61 (29.9)	2 (1.0)	42 (20.7)	5 (2.5)	74 (32.9)	10 (4.4)
Weight decreased	59 (28.9)	1 (0.5)	24 (11.8)	0	72 (32.0)	5 (2.2)

Source: Novartis submission, Table 4.17 (page 57)

4.2.5.1.5 Health Related Quality of Life

A6181111 used the EORTC quality-of-life questionnaire (QLQ-C30, vs3.0) to measure health related quality of life. EORTC QLQ-C30 was available in 73 of 86 (85%) of the individuals treated with sunitinib and 71 of 85 (84%) of those treated with placebo. The EORTC QLQ-C30 includes five functional scales: physical, role, emotional, cognitive and social; three symptom scales; fatigue, nausea/vomiting and pain and six single-item scales; dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. High scores are better for global and functioning scales whereas low scores are better for the symptom items/scales. The questionnaire was administered at baseline, at every cycle (4 weeks) and at the end of treatment. There were no overall differences observed between study groups for any of these measures, except diarrhoea which was higher in the sunitinib arm than the placebo (21.4 point difference P<0.001) and insomnia (7.8 point difference P=0.04).

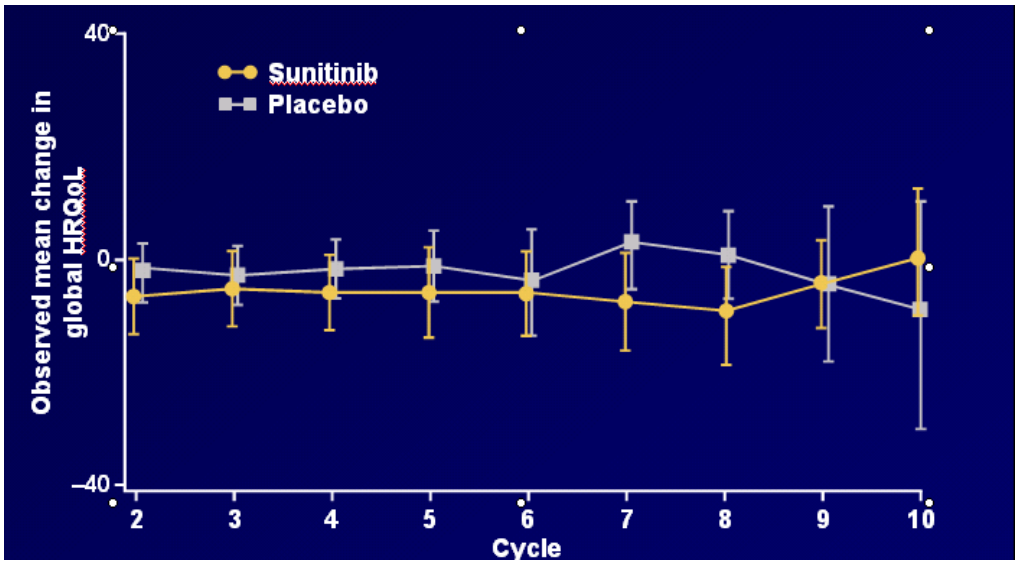
More detailed results were available for HRQoL from Pfizer's submission. Mean baseline global HRQoL scores were 67.0 (62.0, 72.0) in the sunitinib plus BSC arm compared to 64.0 (58.4, 69.6) in the placebo plus BSC arm. Overall post-baseline scores were 62.44 for sunitinib and 61.28 for placebo. Overall changes in EORTC QLQ-C30 for each item on the scale between the two arms are shown in Table 27. Changes in global HRQoL scores over time between the two arms are shown in Figure 16.

Table 27: Overall post-baseline EORTC QLQ-C30 scores (mixed-effects model), showing differences between groups

	Sunitinib	Placebo	Difference	p-value
Global HRQoL	62.44	61.28	1.15	0.6799
Functional scales				
Cognitive functioning	79.94	81.38	–1.44	0.6058
Emotional functioning	72.59	76.15	–3.56	0.3008
Physical functioning	78.92	76.13	2.79	0.3230
Role functioning	70.88	69.37	1.51	0.7113
Social functioning	74.44	76.11	–1.67	0.6487
Symptom items/scales				
Appetite loss	24.95	23.07	1.88	0.6545
Constipation	10.70	14.70	–4.00	0.1936
Diarrhoea	37.19	15.81	21.38	<0.0001
Dyspnoea	22.31	17.08	5.23	0.1339
Fatigue	40.52	38.74	1.78	0.6138
Insomnia	32.61	24.86	7.75	0.0372
Nausea and vomiting	14.29	13.15	1.15	0.6939
Pain	25.48	28.99	–3.51	0.3711
Financial difficulties	17.28	17.00	0.28	0.9367

Source: Table 10 (page 53) Pfizer submission

Figure 16: Change score and 95% CI for EORTC QLQ-C30 global HRQoL scores by cycle, PRO analysis set



Source: Figure 7 (page 52) Pfizer submission

4.2.5.1.6 Subgroup analysis

A6181111 report cox proportional-hazard analysis of PFS for the subgroups tumour functioning, number of previous systemic regimes and previous use of SSA (Table 28).

Table 28: Subgroup PFS from A6181111

Covariate	Subgroup	N	HR (95% CI)
Tumour functionality	Functioning	86	0.26 (0.13, 0.54)
	Not Functioning	46	0.75 (0.30, 1.84)
No. of previous systemic regimens	0 or 1	121	0.33 (0.19,0.59)
	≥2	50	0.61 (0.27,1.37)
Previous use of SSA	Yes	68	0.43 (0.21,0.89)
	No	103	0.41 (0.22,0.75)

Source: Raymond et al., New Eng J Med, 2011 (A6181111)

RADIANT-3 also report PFS for the subgroups based on tumour grade, previous chemotherapy use and previous long-acting SSA use (Table 29).

Table 29: Subgroup PFS from RADIANT-3

Covariate	Subgroup	N	HR (95% CI)
Tumour grade:	Well differentiated	341	0.41 (0.31, 0.53) P<0.001
	Moderately differentiated	65	0.21 (0.11, 0.42) P<0.001
Previous chemotherapy	Yes	189	0.34 (0.24,0.49) P<0.001
	No	221	0.41 (0.29,0.58) P<0.001
Previous long-acting SSA use	Yes	203	0.40 (0.28,0.57) P<0.001
	No	207	0.36 (0.25,0.51) P<0.001

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3)

Novartis (A6181111) also report covariate analysis for OS using a Cox's proportional Hazards model for previous use of SSA and previous use of chemotherapy (Table 30).

Table 30: Subgroup OS from RADIANT-3

Covariate	Subgroup	N	HR (95% CI)
Previous chemotherapy	Yes	189	
	No	221	0.78 (0.61, 1.01) P=0.056
Previous long-acting SSA use	Yes	203	
	No	207	1.15 (0.89, 1.49) P=0.288

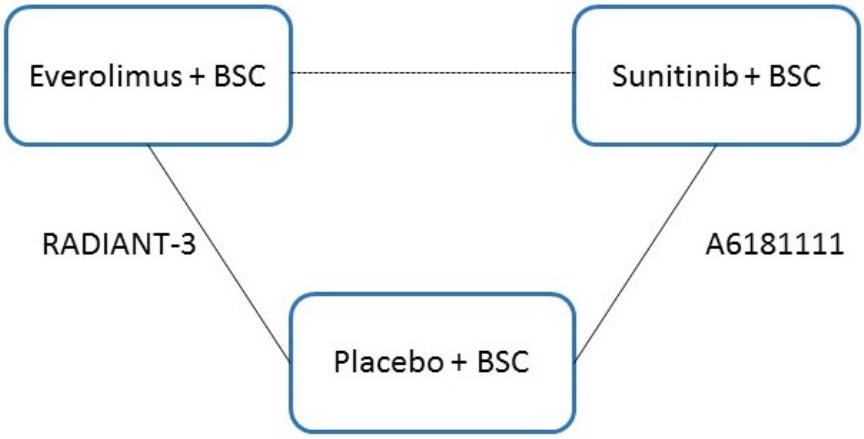
Source: Novartis submission, Table 3.8 from Appendix 3 (page 55)

Apart from previous chemotherapy in Table 30, none of these results suggest a statistically significant difference between sub-groups.

4.2.5.2 Indirect treatment comparison – Pancreatic NETs

Two RCTs were used to compare everolimus to sunitinib: RADIANT-3 (everolimus + BSC vs placebo + BSC) and A6181111 (sunitinib + BSC vs placebo + BSC), see Figure 17.

Figure 17: Diagram of the indirect treatment comparison for pancreatic NETs



The Bucher method[37] was used to indirectly compare everolimus to sunitinib in individuals with pNETs for the following outcomes: PFS, OS, RR (not including complete response, since there were zero responses in both treatment arms for RADIANT-3 and a zero response on the placebo arm of A6181111) and various AEs. Due to their only being two relevant trials for this synthesis we could not undertake any analyses for heterogeneity between the trials or inconsistency in the network.

Results for PFS and OS are reported in terms of HRs and 95% CIs. While results for RR and AEs are reported as ORs and 95% CIs. For some AEs where there were zero events in one of the arms, a continuity correction of 0.5 was added to each of the 2x2 cells to allow calculation of the ORs for AEs.

An assessment of the characteristics of the two trials (RADIANT-3 and A6181111), suggested that they were comparable to allow an indirect treatment comparison. Both trials compared the active treatment to placebo + BSC, and only included participants with advanced or metastatic disease. There was a slightly higher proportion of participants using somatostatin analogues during the study for RADIANT-3 (~40%) compared to A6181111 (~28%), however it was not thought that this would affect the relative effectiveness of the treatments.

Treatment switching from the active arm to the placebo arm was permitted in both trials after disease progression. For OS, indirect treatment comparisons have been conducted on ITT analyses and analyses adjusted for treatment switching (using the RPSFT method).

4.2.5.2.1 Progression Free Survival

Table 31 shows the evidence used from RADIANT-3 and A6181111 to inform the indirect comparison of everolimus with sunitinib for PFS assessed by local review. The analysis suggests that everolimus is associated with a 17% decrease in disease progression or death compared to sunitinib (HR 0.83, 95%CI 0.49, 1.42). The 95%CI is wide and includes the null

hypothesis that there is no difference in PFS effectiveness between everolimus and sunitinib.

Table 31: HRs (95%CI) for disease progression or death in pancreatic NETs based on local radiology review

Intervention	Comparator	Data source	HR (95%CI)
Everolimus	Placebo	RADIANT-3[31]	0.35 (0.27, 0.45)
Sunitinib	Placebo	A6181111[45]	0.42 (0.26, 0.66)
Everolimus	Sunitinib	Calculated by AG	0.83 (0.49, 1.42)

Further data available from the company submission enabled an ITC for PFS from central radiology review. The indirect comparison of everolimus vs sunitinib for PFS based on central radiology review suggests no difference between the treatments (see Table 32).

Table 32: HRs (95%CI) for disease progression or death in pancreatic NETs based on central radiology review

Intervention	Comparator	Data source	HR (95%CI)
Everolimus+BSC	Placebo+BSC	RADIANT-3[31]	0.34 (0.26, 0.44)
Sunitinib+BSC	Placebo+BSC	From Pfizer submission (A6181111)	0.32 (0.18, 0.55)
Everolimus+BSC	Sunitinib+BSC	Calculated by AG	1.06 (0.57, 1.97)

4.2.5.2.2 Overall Survival

Table 33 shows the evidence used to inform the indirect comparison of everolimus with sunitinib for overall survival. The analysis suggests that there is 2.56 times greater hazard of dying from treatment with everolimus than sunitinib, which is statistically significant. However as these analyses are based on published HRs from RADIANT-3 and A6181111, which were not adjusted for treatment switching after disease progression, these results should not be relied upon.

Table 33: HRs (95%CI) for overall survival in pancreatic NETs

Intervention	Comparator	Data source	HR (95%CI)
Everolimus	Placebo	RADIANT-3[31]	1.05 (0.71, 1.55)
Sunitinib	Placebo	A6181111[45]	0.41 (0.19, 0.89)
Everolimus	Sunitinib	Calculated by AG	2.56 (1.08, 6.08)

Further data available from the company submission enabled an ITC of everolimus vs sunitinib for OS using the final follow-up data which suggests a lower hazard of death associated with sunitinib compared to everolimus. This, however, includes the null effect in the 95% CI, suggesting no statistically significant effect (see Table 34). This analysis does not account for the fact that approximately 70% of participants in the placebo and BSC arms of these two trials switched to receive the active treatment after disease progression, so should be interpreted with caution.

Table 34: HRs (95%CI) for death in pancreatic NETs based on final follow-up data

Intervention	Comparator	Data source	HR (95%CI)
Everolimus+BSC	Placebo+BSC	RADIANT-3[48]	0.94 (0.73, 1.20)
Sunitinib+BSC	Placebo+BSC	From Pfizer submission (A6181111)	0.73 (0.50, 1.06)
Everolimus+BSC	Sunitinib+BSC	Calculated by AG	1.26 (0.82, 2.02)

OS accounting for treatment switching using the Rank Preserving Structural Failure Time (RPSFT) method

The indirect comparison of everolimus vs sunitinib for OS where the companies have used the RPSFT method to adjust for treatment switching suggests a lower hazard of death associated with sunitinib compared to everolimus (as in the ITT analyses above), however the 95%CI is very wide and includes the null effect (see Table 35).

Table 35: HRs (95%CI) for death in pancreatic NETs adjusted for treatment switching

Intervention	Comparator	Data source	HR (95%CI)
Everolimus+BSC	Placebo+BSC	RADIANT-3[48]	0.60 (0.09, 3.95)
Sunitinib+BSC	Placebo+BSC	From Pfizer submission (A6181111)	0.34 (0.14, 3.95)
Everolimus+BSC	Sunitinib+BSC	Calculated by AG	1.76 (0.20, 15.78)

4.2.5.2.3 Response Rate

All ORs reported in Table 36 for the intervention compared to placebo were calculated by the AG, based on the number of individuals reported in RADIANT-3 and A6181111 having experienced these responses. The indirect treatment comparisons for everolimus and sunitinib were based on the AG calculated ORs from RADIANT-3 and A6181111. The indirect analysis suggests that there is an 82% increase in the odds of a partial response in individuals treated with sunitinib compared to everolimus. However, sunitinib was associated with a 52% increase in the odds of progressive disease when compared to everolimus. Everolimus was associated with a 2.3 times greater odds for disease stability than sunitinib. However, all of these indirect treatment comparisons were associated with wide 95% CIs, suggesting that there is little evidence of a difference in response rates between everolimus and sunitinib.

Table 36: HRs (95%CI) for response rates in pancreatic NETs

Outcome	Intervention	Comparator	Data source	OR (95%CI)
Partial Response	Everolimus	Placebo	RADIANT-3[a]	2.53 (0.78, 8.19)
	Sunitinib	Placebo	A6181111 [a]	13.81 (1.65, 115.85)
	Everolimus	Sunitinib	Calculated by AG	0.18 (0.02, 2.08)
Stable Disease	Everolimus	Placebo	RADIANT-3 [a]	2.62 (1.73, 3.95)
	Sunitinib	Placebo	A6181111 [a]	1.13 (0.61, 2.07)
	Everolimus	Sunitinib	Calculated by AG	2.33 (1.11, 4.86)
Progressive Disease	Everolimus	Placebo	RADIANT-3 [a]	0.23 (0.14, 0.37)
	Sunitinib	Placebo	A6181111 [a]	0.44 (0.20, 0.95)
	Everolimus	Sunitinib	Calculated by AG	0.52 (0.21, 1.30)

Notes: a, calculated by AG from response rates data retrieved data source

4.2.5.2.4 Adverse Events

An indirect treatment comparison was only completed for those AEs where data were available from both trials. All ORs reported in Table 37 (all grades of AE) and Table 38 (all grades 3/4 of AE) were calculated by the AG based on the number of participants experiencing these AEs (as reported in A6181111 and RADIANT-3). For all grades of AE, the indirect treatment comparison suggests that there is a 19% increase in the odds of experiencing stomatitis and a 42% increase in the odds of experiencing nausea with sunitinib compared to everolimus. For the other AEs (all grades), the evidence suggests an increase in the odds of experiencing the AE with everolimus compared to sunitinib. However, except for decreased appetite, all of these indirect treatment comparisons were associated with wide 95% CIs that included the null hypothesis of no difference, suggesting that there is

little evidence of a difference in AEs between everolimus and sunitinib. For all grades of decreased appetite, there was a statistically significant increase in the odds of experiencing the event with everolimus compared to sunitinib.

For the grade 3/4 AEs, the indirect comparison could only consider 7 AEs due to available data from the two trials. The evidence suggests an increased odds of experiencing grade 3/4 stomatitis, fatigue, diarrhoea, nausea and throbocytopenia with everolimus compared to sunitinib, and an increased odds of experiencing decreased appetite and asthenia with sunitinib compared to everolimus. However, all of the indirect treatment comparisons for grade 3/4 AEs were associated with wide 95% CIs, that included the null hypothesis of no difference, suggesting that there is little evidence of a difference in AEs between everolimus and sunitinib.

Table 37: ORs (95%CI) for adverse events all grade, in pancreatic NETs

Outcome	Intervention	Comparator	OR (95%CI)
Stomatitis	Everolimus	Placebo	8.92 (5.59, 14.22)
	Sunitinib	Placebo	11.08 (2.84, 43.26)
	Everolimus	Sunitinib	0.81 (0.19, 3.40)
Rash	Everolimus	Placebo	8.17 (4.82, 13.86)
	Sunitinib	Placebo	4.30 (1.43, 12.95)
	Everolimus	Sunitinib	1.90 (0.56, 6.45)
Fatigue	Everolimus	Placebo	2.74 (1.68, 4.49)
	Sunitinib	Placebo	1.31 (0.68, 2.56)
	Everolimus	Sunitinib	2.09 (0.91, 4.78)
Diarrhoea	Everolimus	Placebo	4.68 (2.71, 8.07)
	Sunitinib	Placebo	2.25 (1.21, 4.19)
	Everolimus	Sunitinib	2.08 (0.91, 4.74)
Nausea	Everolimus	Placebo	1.13 (0.69, 1.85)
	Sunitinib	Placebo	1.94 (1.03, 3.68)
	Everolimus	Sunitinib	0.58 (0.26, 1.30)
Dysgeusia	Everolimus	Placebo	5.05 (2.28, 11.18)
	Sunitinib	Placebo	5.02 (1.69, 14.93)
	Everolimus	Sunitinib	1.01 (0.26, 3.87)
Epistaxis	Everolimus	Placebo	83.88 (5.11, 1377.99)
	Sunitinib	Placebo	5.02 (1.69, 14.93)
	Everolimus	Sunitinib	16.97 (0.84, 341.97)
Decreased weight	Everolimus	Placebo	4.01 (1.86, 8.64)
	Sunitinib	Placebo	1.51 (0.61, 3.70)
	Everolimus	Sunitinib	2.66 (0.82, 8.67)
Thrombocytopenia	Everolimus	Placebo	30.81 (4.14, 229.09)
	Sunitinib	Placebo	3.96 (1.30, 12.01)
	Everolimus	Sunitinib	7.79 (0.79, 77.12)
Decreased appetite	Everolimus	Placebo	3.29 (1.73, 6.27)
	Sunitinib	Placebo	1.06 (0.50, 2.22)
	Everolimus	Sunitinib	3.11 (1.16, 8.30)
Headache	Everolimus	Placebo	3.45 (1.78, 6.69)
	Sunitinib	Placebo	1.42 (0.62, 3.29)
	Everolimus	Sunitinib	2.43 (0.84, 7.05)
Vomiting	Everolimus	Placebo	2.62 (1.33, 5.17)
	Sunitinib	Placebo	1.16 (0.61, 2.22)
	Everolimus	Sunitinib	2.26 (0.88, 5.78)
Asthenia	Everolimus	Placebo	1.60 (0.84, 3.05)
	Sunitinib	Placebo	1.39 (0.72, 2.70)
	Everolimus	Sunitinib	1.15 (0.46, 2.90)

Table 38: HRs (95%CI) for adverse events grade 3 and 4, in pancreatic NETs

Outcome	Intervention	Comparator	OR (95%CI)
Stomatitis	Everolimus	Placebo	29.99 (1.77, 507.09)
	Sunitinib	Placebo	6.19 (0.63, 60.73)
	Everolimus	Sunitinib	4.32 (0.12, 159.36)
Fatigue	Everolimus	Placebo	5.08 (0.59, 43.83)
	Sunitinib	Placebo	0.54 (0.15, 1.90)
	Everolimus	Sunitinib	9.36 (0.77, 113.29)
Diarrhoea	Everolimus	Placebo	14.46 (0.82, 256.56)
	Sunitinib	Placebo	2.03 (0.40, 10.13)
	Everolimus	Sunitinib	7.63 (0.28, 204.92)
Nausea	Everolimus	Placebo	10.23 (0.56, 188.42)
	Sunitinib	Placebo	0.99 (0.08, 12.64)
	Everolimus	Sunitinib	11.36 (0.24, 540.30)
Thrombocytopenia	Everolimus	Placebo	16.61 (0.95, 291.21)
	Sunitinib	Placebo	6.19 (0.63, 60.73)
	Everolimus	Sunitinib	2.45 (0.06, 92.93)
Decreased appetite	Everolimus	Placebo	0.25 (0.01, 5.48)
	Sunitinib	Placebo	2.00 (0.24, 16.98)
	Everolimus	Sunitinib	0.10 (0, 4.06)
Asthenia	Everolimus	Placebo	1.00 (0.14, 7.13)
	Sunitinib	Placebo	1.33 (0.31, 5.79)
	Everolimus	Sunitinib	0.75 (0.06, 8.70)

4.2.5.2.5 Subgroup analysis

Subgroup analysis based on whether or not participants had had previous somatostatin use, suggests very little difference in time to disease progression or death for everolimus compared to sunitinib (see Table 39).

Table 39: HR for local PFS by previous SSA use

Intervention	Comparator	Data source	HR (95%CI)	
			Previous use	No previous use
Everolimus+BSC	Placebo+BSC	RADIANT-3[31]	0.40 (0.28, 0.57)	0.36 (0.25, 0.51)
Sunitinib+BSC	Placebo+BSC	A6181111[45]	0.43 (0.21, 0.89)	0.41 (0.22, 0.75)
Everolimus+BSC	Sunitinib+BSC	Calculated by AG	0.93 (0.42, 2.08)	0.88 (0.43, 1.78)

4.2.5.3 Outcomes for RCT evidence for GI + Lung NETs

4.2.5.3.1 Progression Free Survival

RADIANT-4 reported PFS as the primary outcome and defined disease progression as, '*the time from randomisation to death or progression as per modified RECIST version 1.0 criteria'.*[44] RADIANT-4 reported both central radiology review and also local investigator review for PFS.

RADIANT-4 reported median PFS assessed by central review as 11.0 months (95% CI 9.2, 13.3) for the everolimus plus BSC arm and 3.9 months (95% CI 3.6, 7.4) for the placebo plus BSC arm. Everolimus was associated with a 52% reduction in the risk of disease progression or death for people with lung and GI NETs compared to placebo (HR 0.48 [95% CI 0.35, 0.67]; Table 40).

Locally assessed PFS was longer in duration in both arms compared to central review for RADIANT-4; 14.0 months (95% CI 11.2, 17.7) in the everolimus plus BSC arm compared to 5.5 months (95% CI 3.7, 7.4) in the placebo plus BSC arm. Everolimus was associated with a reduction (61%) in the risk of disease progression or death for people with lung and GI NETs compared to placebo (HR 0.39 [95%CI 0.28, 0.54]; Table 40).

Table 40: PFS – Lung and GI NETs

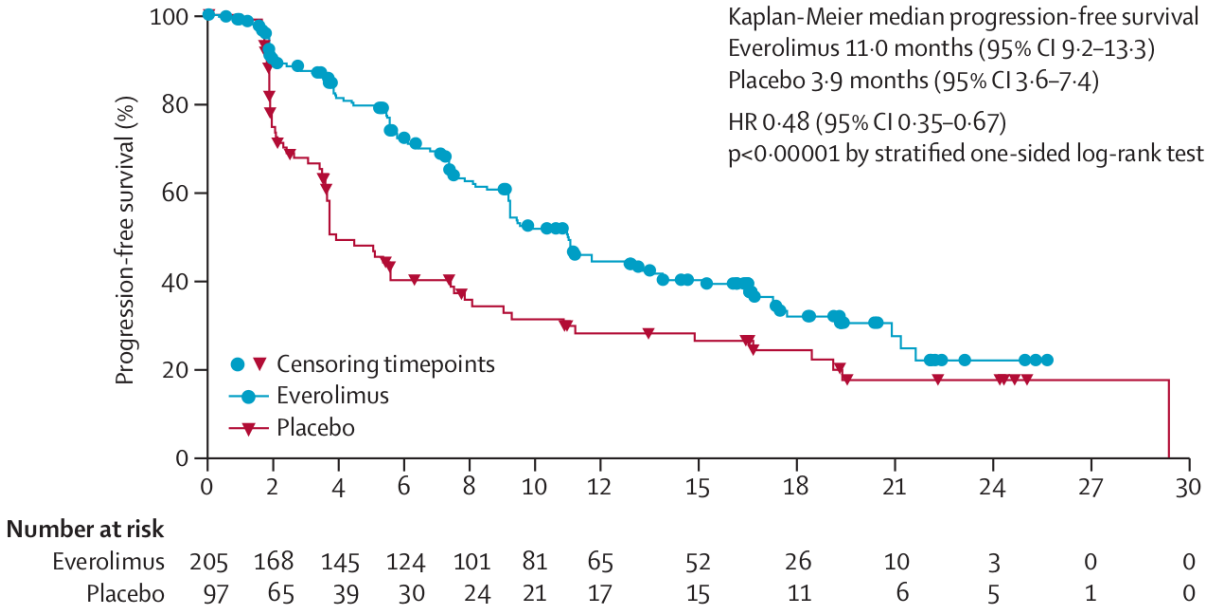
Study ID	Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
		CENTRAL RADIOLOGY REVIEW	
RADIANT-4	*Everolimus + BSC* (113/205) 11.0 (9.2-13.3)	*Placebo + BSC* (65/97) 3.9[a] (3.6-7.4)	0.48 (0.35-0.67) P<0.00001
		LOCAL INVESTIGATOR REVIEW	
	Everolimus + BSC (98/205) 14.0 (11.2-17.7)	*Placebo + BSC* (70/97) 5.5 (3.7-7.4)	0.39 (0.28-0.54) P<0.00001

Note: a, this was reported as both 3.0 and 3.9 months in the company submission, in Yao et al. 2016 it was 3.9 months
Source: Yao et al., Lancet, 2016 (RADIANT-4)

The company submission from Novartis made available secondary analysis of PFS, (one year and two days after the PFS analysis presented in the published paper[44]). Median PFS from central review was 14.39 months (95% CI 11.24, 17.97) for the everolimus plus BSC arm and 5.45 months (95% CI 3.71, 7.39) for the placebo plus BSC arm. Everolimus was associated with a 59% reduction in the risk of disease progression or death for people with lung and GI NETs compared to placebo (HR 0.41 [95% CI 0.30, 0.56]).

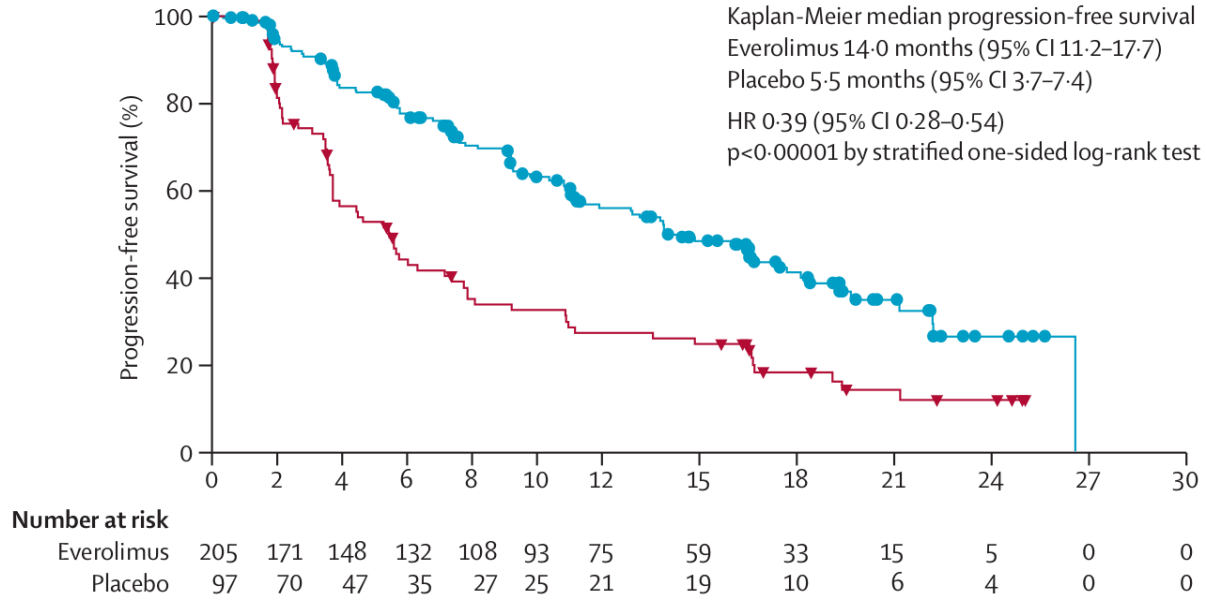
Kaplan-Meier curves were produced from RADIANT-4 for PFS from both central (Figure 18) and local (Figure 19) review with data from the primary cut-off point.

Figure 18: Kaplan-Meier plot for PFS as assessed by central review (primary cut off) RADIANT-4 (everolimus vs placebo)



Key: CI: confidence interval, HR: hazard ratio, PFS: progression-free survival.
Source: Novartis submission, Figure 5.3 (page 67)

Figure 19: Kaplan-Meier plot for PFS as assessed by local review (primary cut off) RADIANT-4 (everolimus vs placebo)



Key: CI: confidence interval, HR: hazard ratio, PFS: progression-free survival.
Source: Novartis submission, Figure 5.4 (page 68)

4.2.5.3.2 Overall Survival

RADIANT-4 presented interim OS analysis, once 70 deaths had been reached, in Yao at al. (2016). Data were not sufficiently mature to provide an estimation of median OS. In individuals with lung and GI NETs, Kaplan-Meier estimates for overall survival at the 25th percentile – 25% of individuals having died – were 23.7 months (95% CI 17.6, 27.3) for everolimus and 16.5 months (95% CI 9.0, 21.0) for placebo. Everolimus was associated with

a 36% improvement in OS for individuals with lung and GI NETs when compared to placebo (HR 0.64 [0.40, 1.05], Table 41)

In their company submission, Novartis, presented secondary analysis for OS from RADIANT-4, which was performed one year and two days after the published analysis presented by Yao et al. 2016.[44] This analysis was based on 101 deaths, corresponding to a 52.9% information fraction; median duration of follow-up was 33.4 months. Everolimus was associated with a 27% improvement in OS for individuals with lung and GI NETs when compared to placebo (HR 0.73 [95% CI 0.48, 1.11]).

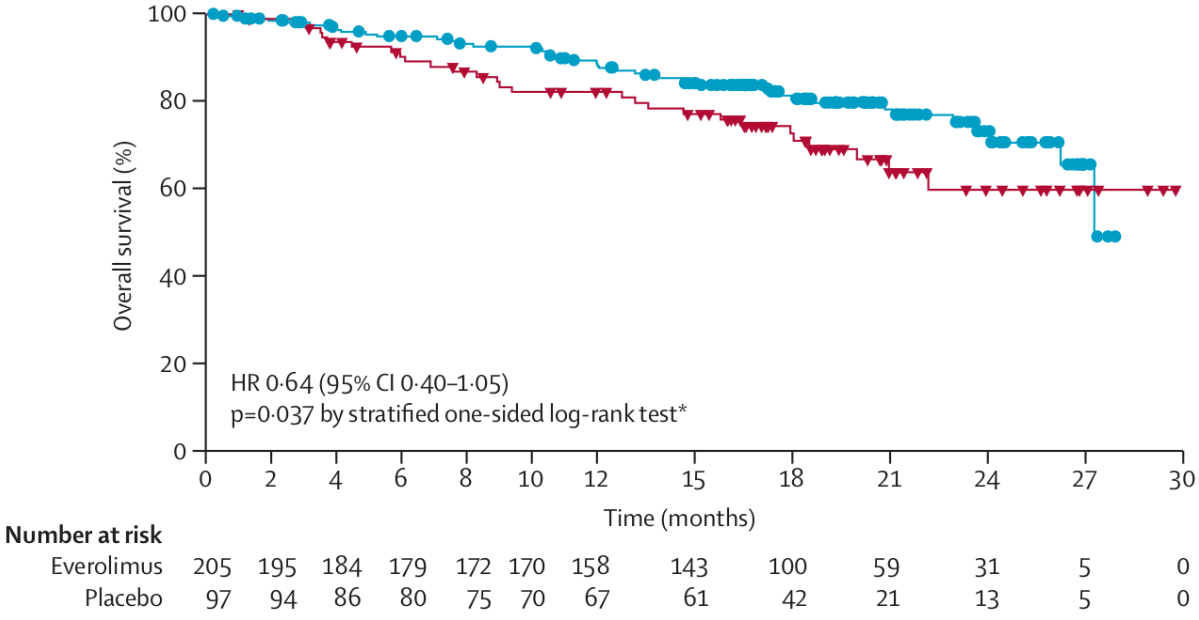
Table 41: Overall Survival – Lung and GI NETs

Study ID	Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
Primary cut-off	*Everolimus + BSC* (n=205) (42/205) 23.7 (17.6, 27.3)[b]	*Placebo + BSC* (n=97) (28/97) 16.5 (9.0, 21.0) [b]	0.64 (0.40, 1.05)[a] P=0.037
Secondary cut-off	66/205 25.7 (18.4, 28.6)	35/97 16.5 (9.0, 20.2)[c]	0.73 (0.48, 1.11) P=0.071

Notes: a, interim OS analysis from a total of 70 deaths; b, KM estimates for OS at the 25th percentile; c, reported in company submission as 2.18, assumed to read 20.18
Source: Yao et al., Lancet, 2016 (RADIANT-4) and Novartis submission, Table 5.5 (page 75)

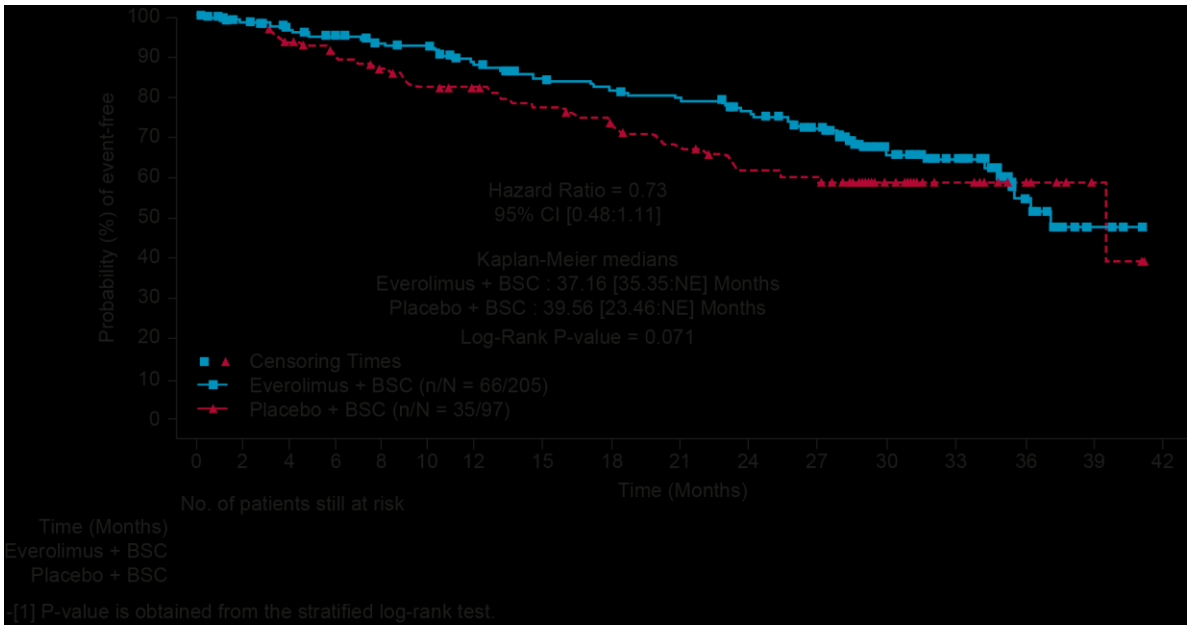
A Kaplan-Meier plot was produced for OS from RADIANT-4 at both the primary data cut-off point (Figure 20) and the secondary data cut-off point (Figure 21).

Figure 20: Kaplan-Meier plot for OS estimates at primary data cut-off RADIANT-4



Key: CI: confidence interval, HR: hazard ratio, OS: overall survival.
Source: Novartis submission Figure 5.11 (page 74)

Figure 21: Kaplan-Meier plot for OS estimates: secondary data cut-off



Key: CI: confidence interval, HR: hazard ratio, OS: overall survival.
Source: Novartis submission Figure 5.11 (page 75)

4.2.5.3.3 Response Rate

RADIANT-4 used a modified version of RECIST v1.0 to assess tumour response by central radiology review. Efficacy was assessed every 8 weeks following randomisation for the first 12 months and then every 12 weeks thereafter.

RADIANT-4 reported complete response, partial response, stable disease, progressive disease, objective response rate, disease control rate and tumour shrinkage, following central radiology review (Table 42). For all response rate outcomes, treatment with everolimus for lung and GI NETs, resulted in a favourable response in comparison to treatment with placebo except for complete response, which was not achieved in either arm.

Table 42: Response Rates – Lung and GI NETs

Study ID	Type of response	Experimental Arm n/N (%)	Control Arm n/N (%)
RADIANT-4 (Central radiology)		***Everolimus + BSC***	***Placebo + BSC***
	Complete response	0	0
	Partial response	4/205 (2)	1/97 (1)
	Stable disease	165/205 (81)	62/97 (64)
	Progressive disease	19/205 (9)	26/97 (27)
	Objective response rate [95% CI]	4/205 (2) [0.5-4.9]	1/97 (1) [0.0-5.6]
	Disease control rate, [95%CI]	169/205 (82.4) [76.5-87.4]	63/97 (64.9) [54.6-74.4]
	Tumour Shrinkage	117/184 (64)	22/85 (26)

Source: Yao et al., Lancet, 2016 (RADIANT-4)

4.2.5.3.4 Adverse Events

RADIANT-4 assessed their adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03. Treatment related adverse events (all grade and grade 3 and 4 combined), reported in at least 10% of the safety population, are presented in Table 43. Adverse events were more commonly reported following treatment with everolimus in comparison to placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-4) were stomatitis (63%), diarrhoea (31%), fatigue (31%), infections (29%) and rash (27%).

In their company submission, Novartis, also report AEs in patients regardless of study drug relationship of the safety population. This table can be found in Appendix 5.

Table 43: Adverse Events– Lung and GI NETs

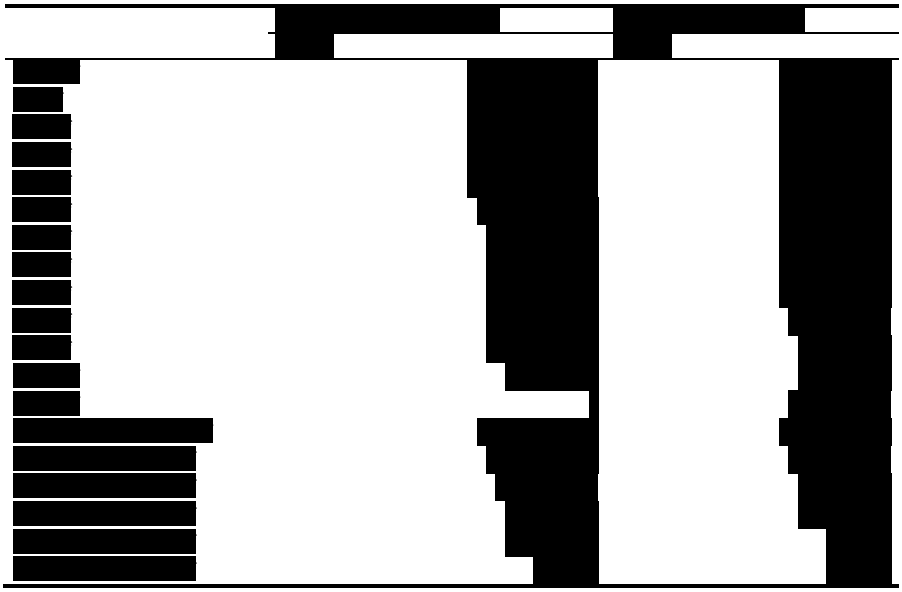
	All GRADE		GRADE 3+4	
Intervention	**Everolimus + BSC n/N (%)**	**Placebo + BSC n/N (%)**	**Everolimus + BSC n/N (%)**	**Placebo + BSC n/N (%)**
On treatment deaths	7/202 (4)	3/98 (3)		
Treatment discontinuation due to study drugs	24/202 (12)[a]	3/98 (3)[b]		
Any adverse event[c]	193/202 (96)	67/98 (68)	106/202 (53)	13/98 (13)
Anaemia	33/202 (16)	2/98 (2)	8/202 (4)	1/98 (1)
Asthenia	33/202 (16)	5/98 (5)	3/202 (3)	0/98 (0)
Cough	26/202 (13)	3/98 (3)	0/202 (0)	0/98 (0)
Decreased appetite	32/202 (16)	6/98 (6)	1/202 (<1)	0/98 (0)
Diarrhoea	63/202 (31)	16/98 (16)	15/202 (7)	2/98 (2)
Dysgeusia	30/202 (15)	4/98 (4)	1/202 (<1)	0/98 (0)
Dyspnoea	21/202 (10)	4/98 (4)	2/202 (1)	1/98 (1)
Fatigue	62/202 (31)	24/98 (24)	7/202 (3)	1/98 (1)
Hyperglycaemia	21/202 (10)	2/98 (2)	7/202 (3)	0/98 (0)
Infections	59/202 (29)	4/98 (4)	14/202 (7)	0/98 (0)
Nausea	35/202 (17)	10/98 (10)	3/202 (1)	0/98 (0)
Non-infectious Pneumonitis	32/202 (16)	1/98 (1)	3/202 (1)	0/98 (0)
Peripheral Oedema	52/202 (26)	4/98 (4)	4/202 (2)	1/98 (1)
Pruritus	26/202 (13)	4/98 (4)	1/202 (<1)	0/98 (0)
Pyrexia	22/202 (11)	5/98 (5)	4/202 (2)	0/98 (0)
Rash	55/202 (27)	8/98 (8)	1/202 (<1)	0/98 (0)
Stomatitis	127/202 (63)	19/98 (19)	18/202 (9)	0/98 (0)

Source: Yao et al., Lancet, 2016 (RADIANT-4)
Notes: a, reported as 59/202 (29%) in the company submission; b. reported as 7/98 (7%) in the company submission; c, data from company submission

4.2.5.3.5 Health Related Quality of Life

In their company submission, Novartis, present data on HRQoL from RADIANT-4 using the FACT-G questionnaire. The FACT-G is based on 27 items falling under four domains: physical well-being, social/family well-being; emotional well-being and functional well-being. Participant completion rates of the FACT-G questionnaire are presented in Table 44.

Table 44: Completion rates of patients on study at scheduled day with valid FACT-G questionnaire within time window



Source: Novartis company submission Table 5.6 (page 76)

Mean total score over time for the FACT-G questionnaire is presented in Figure 22. In their submission, Novartis, report that the, *'scores were well-balanced between the two arms and never exceeded the threshold of 7 points, defined as the minimal clinically important difference between treatment arms' (page 77 of Novartis submission)*

Figure 22: Change from baseline of FACT-G total score over time (on-treatment)

Key: BSC, best supportive care; FACT-G, Functional Assessment of Cancer Therapy – General questionnaire; n, number; SD, standard deviation.
Source: Novartis company submission Figure 5.13 (page 77)

The HR for definitive deterioration of the total FACT-G score was [redacted] Figure 23.

Figure 23: Kaplan-Meier plot of time to deterioration in FACT-G total score by at least 7 points (FAS)

Key: CI: confidence interval, BSC: best supportive care, FACT-G: Functional Assessment of Cancer Therapy – General questionnaire, FAS: full analysis set, NA: not accessible, WHO: World Health Organization.
Source: Novartis submission, Figure 5.14 (page 78)

4.2.5.3.6 Subgroup analysis

RADIANT-4 report PFS (central review) for everolimus vs placebo based on treatment naivety, previous chemotherapy use and previous long-acting SSA use (Table 45). There is little evidence of a difference in PFS within subgroups.

Table 45: Subgroup PFS from RADIANT-4

Covariate	Subgroup	N	HR (95% CI)
Treatment Naïve	Yes	177	0.65 (0.39, 1.08)
	No	185	0.51 (0.35, 0.76)

Previous chemotherapy	Yes	77	0.35 (0.19, 0.64)
	No	225	0.60 (0.42, 0.86)
Previous SSA Treatment	Yes	157	0.52 (0.34, 0.81)
	No	145	0.60 (0.30[a], 0.94)
Tumour Grade	Grade 1	194	0.57 (0.39, 0.84)
	Grade 2	107	0.49 (0.29, 0.83)

Source: Yao et al., New Eng J Med, 2011 (RADIANT-3)
Notes: a, reported as 0.39 in company submission but 0.30 in Yao et al. 2016

4.2.5.4 Outcomes for RCT evidence for GI NETs

Following a data request to Novartis, some of the outcomes from RADIANT-4 were provided for individuals with GI NETs alone, and also for individuals with lung NETs alone. The following section reports the baseline characteristics and outcomes provided by Novartis for individuals with GI NETs from RADIANT-4 alone. Tumour locations included under the umbrella GI were: stomach, colon, rectum, appendix, caecum, ileum, duodenum, jejunum, and the small intestine.

4.2.5.4.1 Baseline characteristics

Baseline characteristics for individuals with GI NETs only are presented in Table 46.

Table 46: Baseline characteristics for individuals with GI NETs

	Everolimus + BSC (n=118)	**Placebo + BSC (n=57)**
Age, yrs median (range)	63.0 (22-83)	60.0 (33-83)
Male n/N (%)	40.7%	54.4%
Tumour Functioning	100% non-functioning	100% non-functioning
Tumour Differentiation	Well: 50.8%	Well: 61.4%
	Mod: 5.1%	Mod:3.5 %
	Not defined: 44.1%	Not defined: 35.1%
WHO PS	0: 75.4%	0: 84.2%
	1: 24.6%	1: 15.8%
Previous Treatments	Somatostatin analogs: 59.0%	Somatostatin analogs: 63.0%
	Chemotherapy: 18.6%	Chemotherapy: 12.3%
	Surgery: 69.5%	Surgery: 84.2%
	Radiotherapy: [redacted]	Radiotherapy: [redacted]
	Locoregional + ablative therapy: [redacted]	Locoregional + ablative therapy: [redacted]

Source: Data on file from Novartis and ASCO poster

4.2.5.4.2 Progression Free Survival

Novartis provided data for PFS from the RADIANT-4 trial for patients with GI NETs. Median PFS assessed by central review was 13.1 months (95% CI 9.2, 17.3) for the everolimus plus BSC arm and 5.4 months (95% CI 3.6, 9.3) for the placebo plus BSC arm. Everolimus was associated with a 44% reduction in the risk of disease progression or death for people with GI NETs compared to placebo (0.56 [95%CI 0.37, 0.84]; Table 47).

Table 47: PFS –GI NETs

Study ID	**Experimental Arm (n/N) median months (95% CI)**	**Control Arm (n/N) median months (95% CI)**	**HR (95% CI)**
		CENTRAL RADIOLOGY REVIEW	
RADIANT-4	*Everolimus + BSC* (NR/118) 13.1 (9.2, 17.3)	*Placebo + BSC* (NR/57) 5.4 (3.6, 9.3)	0.56 (0.37, 0.84)

Source: Data on file from Novartis

4.2.5.4.3 Overall Survival

Novartis provided data for OS and Kaplan-Meier estimates of OS at the 25th percentile from the RADIANT-4 trial from patients with GI NETs (Table 48).

Table 48: Overall survival for GI subgroup

Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
Everolimus + BSC [redacted]	Placebo + BSC [redacted]	[redacted]

4.2.5.4.4 Response Rate

Novartis provided data for response rates from RADIANT-4 for patients with GI NETs (Table 49).

For all response rate outcomes, treatment with everolimus and BSC for GI NETs, resulted in a favourable response in comparison to treatment with placebo and BSC.

Table 49: Response rate GI subgroup

Study ID	Type of response	Experimental Arm n/N (%)	Control Arm n/N (%)
RADIANT-4		*Everolimus + BSC*	*Placebo + BSC*
	Complete response	[redacted]	[redacted]
	Stable disease		
	Progressive disease		
	Unknown response		
	Tumour shrinkage		
	Objective response rate [95% CI]		
	Disease control rate, [95%CI]		

Source: Data on file from Novartis

4.2.5.4.5 Adverse Events

Novartis provided data for adverse events from RADAINT-4 for individuals with GI NETs. Adverse events were more commonly reported following treatment with everolimus in comparison to placebo (Table 50). The five most common all grade adverse events following treatment with everolimus were Stomatitis (71.8%), infections (59%), diarrhoea (44.4%), Peripheral oedema (40.2%) and fatigue (36.8%).

Table 50: Adverse Events–GI NETs

	All GRADE		GRADE 3+4	
Intervention	Everolimus + BSC n/N (%) N=117[d]	Placebo + BSC n/N (%) N=58[d]	Everolimus + BSC n/N (%) N=117[d]	Placebo + BSC n/N (%) N=58[d]
Abdominal Pain	(19.7)	(27.6)	(5.1)	(6.9)
Anemia	(23.9)	(12.1)	(6.8)	(1.7)
Arthralgia	(16.2)	(10.3)	(0.9)	(0)
Asthenia	(21.4)	(10.3)	(2.6)	(0)
Cough	(26.5)	(22.4)	(0)	(0)
Decreased Appetite	(21.4)	(22.4)	(1.7)	(1.7)
Diarrhea	(44.4)	(43.1)	(11.1)	(3.4)
Dysgeusia	(22.2)	(5.2)	(0.9)	(0)
Dyspnea	(16.2)	(8.6)	(1.7)	(0)
Fatigue	(36.8)	(41.1)	(5.1)	(1.7)
Headache	(17.1)	(17.2)	(0)	(0)
Hypertension	(15.4)	(8.6)	(6.8)	(1.7)
Infections[b]	(59)	(22.4)	(12.8)	(3.4)
Nausea	(28.2)	(17.2)	(3.4)	(1.7)
Non-infectious Pnuemonitis[c]	(19.7)	(1.7)	(0.9)	(0)
Peripheral Edema	(40.2)	(6.9)	(2.6)	(1.7)
Pruritus	(18.8)	(10.3)	(0)	(0)
Pyrexia	(22.2)	(8.6)	(1.7)	(0)
Rash	(29.1)	(10.3)	(0.9)	(0)
Stomatitis[a]	(71.8)	(22.4)	(7.7)	(0)
Weight Decrease	(18.8)	(10.3)	(0)	(0)

Notes: a, includes stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration; b, includes all infections; c, includes pneumonitis, interstitial lung disease; d, in GI subgroup, 1 patient randomised to everolimus arm inadvertently received only placebo treatment because of dispensation error at site, therefore, included in placebo arm

Source: Novartis - ASCO poster

4.2.5.5 Outcomes for RCT evidence for Lung NETs

Following a data request to Novartis, some of the outcomes from RADIANT-4 were provided for individuals with lung NETs alone. The following section reports the baseline characteristics and outcomes provided by Novartis for just the individuals with lung NETs from RADIANT-4.

4.2.5.5.1 Baseline characteristics

Baseline characteristics for individuals with lung NETs only are reported in Table 51.

Table 51: Baseline characteristics for individuals with Lung NETs

	Everolimus + BSC (n=63)	Placebo + BSC (n=27)
Age, yrs median (range)	[redacted]	[redacted]
Male n/N (%)	[redacted]	[redacted]
Tumour Functioning	100% non-functioning	100% non-functioning
WHO PS n/N (%)	[redacted]	[redacted]
Previous Treatments n/N (%)	[redacted]	[redacted]

Source: Data on file from Novartis

4.2.5.5.2 Progression Free Survival

Novartis provided data for PFS from the RADIANT-4 trial from patients with lung NETs. There were 42 progression events out of 63 individuals assigned to everolimus plus BSC arm compared to 18 events out of 27 individuals for the placebo plus BSC arm. Everolimus was associated with a 50% reduction in the risk of disease progression or death for people with lung NETs compared to placebo (0.50 [95%CI 0.28, 0.88]; Table 52).

Table 52: PFS – Lung NETs

Study ID	Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
		CENTRAL RADIOLOGY REVIEW	
RADIANT-4	Everolimus + BSC (42/63) NR	Placebo + BSC (18/27) NR	0.50 (0.28-0.88)

Source: Data on file from Novartis and Yao et al. 2016

4.2.5.5.3 Overall Survival

Novartis provided data for OS from the RADIANT-4 trial from patients with lung NETs (Table 53 and **Source:** Data on file from Novartis

[redacted]). Hazard ratios were obtained from the unstratified Cox model.

Table 53: Overall survival for lung subgroup

Experimental Arm (n/N) median months (95% CI)	Control Arm (n/N) median months (95% CI)	HR (95% CI)
Everolimus + BSC ([redacted])	Placebo + BSC ([redacted])	[redacted]

Source: Data on file from Novartis

[redacted]

Source: Data on file from Novartis

4.2.5.5.4 Response Rate

Novartis provided data for response rates from RADIANT-4 for patients with lung NETs (Table 54).

For all response rate outcomes, treatment with everolimus and BSC for lung NETs, resulted in a favourable response in comparison to treatment with placebo and BSC.

Table 54: Response Rates – Lung NETs

Study ID	Type of response	Experimental Arm n/N (%)	Control Arm n/N (%)
RADIANT-4		***Everolimus + BSC***	***Placebo + BSC***
	Complete response	[redacted]	[redacted]
	Partial response	[redacted]	[redacted]
	Stable disease	[redacted]	[redacted]
	Progressive disease	[redacted]	[redacted]
	Unknown response	[redacted]	[redacted]
	Objective response rate [95% CI]	[redacted]	[redacted]
	Disease control rate, [95%CI]	[redacted]	[redacted]

Source: Data on file from Novartis

4.2.5.5.5 Adverse Events

Novartis provided data for adverse events from RADAINT-4 for individuals with lung NETs. Adverse events were more commonly reported following treatment with everolimus in comparison to placebo (Table 55). The five most common all grade adverse events following treatment with everolimus (RADIANT-4)

[redacted].

Table 55: Adverse Events–Lung NETs

	All GRADE		GRADE 3+4	
Intervention	**Everolimus + BSC n/N (%) N=62**	**Placebo + BSC n/N (%) N=27**	**Everolimus + BSC n/N (%) N=62**	**Placebo + BSC n/N (%) N=27**
Abdominal Pain (all)	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal Pain (upper)	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac Disorder	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dry Mouth	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]

Eye Disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral Oedema	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]

Source: data on file from Novartis

4.3 Methods for reviewing effectiveness for non-RCT for 177Lu-DOTATATE

This section details the methods used in the identification and synthesis of studies reporting non-randomised177Lu-DOTATATE data, since no relevant RCT data was available for 177Lu-DOTATATE.

4.3.1 Identification of studies

Study identification was undertaken in May 2016 and our bibliographic literature searching was updated in November 2016. Our literature searches were not limited by study design, so the same searches were used to identify randomised and non-randomised studies.

The searches are reported at section 4.1.2 and in Appendix 1.

4.3.2 Inclusion and exclusion criteria

Inclusion criteria were for any non-randomised study of individuals with pancreatic or GI NETs, receiving 177Lu-DOTATATE and reporting outcomes of interest (see Table 8).

4.3.3 Screening

Title and abstracts were independently double-screened by two reviewers. Studies meeting inclusion at title and abstract stage were ordered and the full-texts were double-screened by three reviewers.

4.3.4 Data extraction and management

A standardised data specification form was used and the data extracted were independently checked. Where multiple publications of the same study were identified, data were extracted and reported as if a single study.

Extracted and tabulated information included: country of study, number of participants, location of tumour, dose of 177Lu-DOTATATE, any additional drugs given, baseline characteristics of participants (age, % males, tumour functionality, tumour differentiation, ECOG or WHO performance status) and finally whether any previous treatments had been given. Outcomes extracted included, follow-up duration, PFS, OS, RR, AEs and HRQoL.

4.3.5 Critical appraisal strategy

Studies were not critically appraised.

4.3.6 Methods of data synthesis

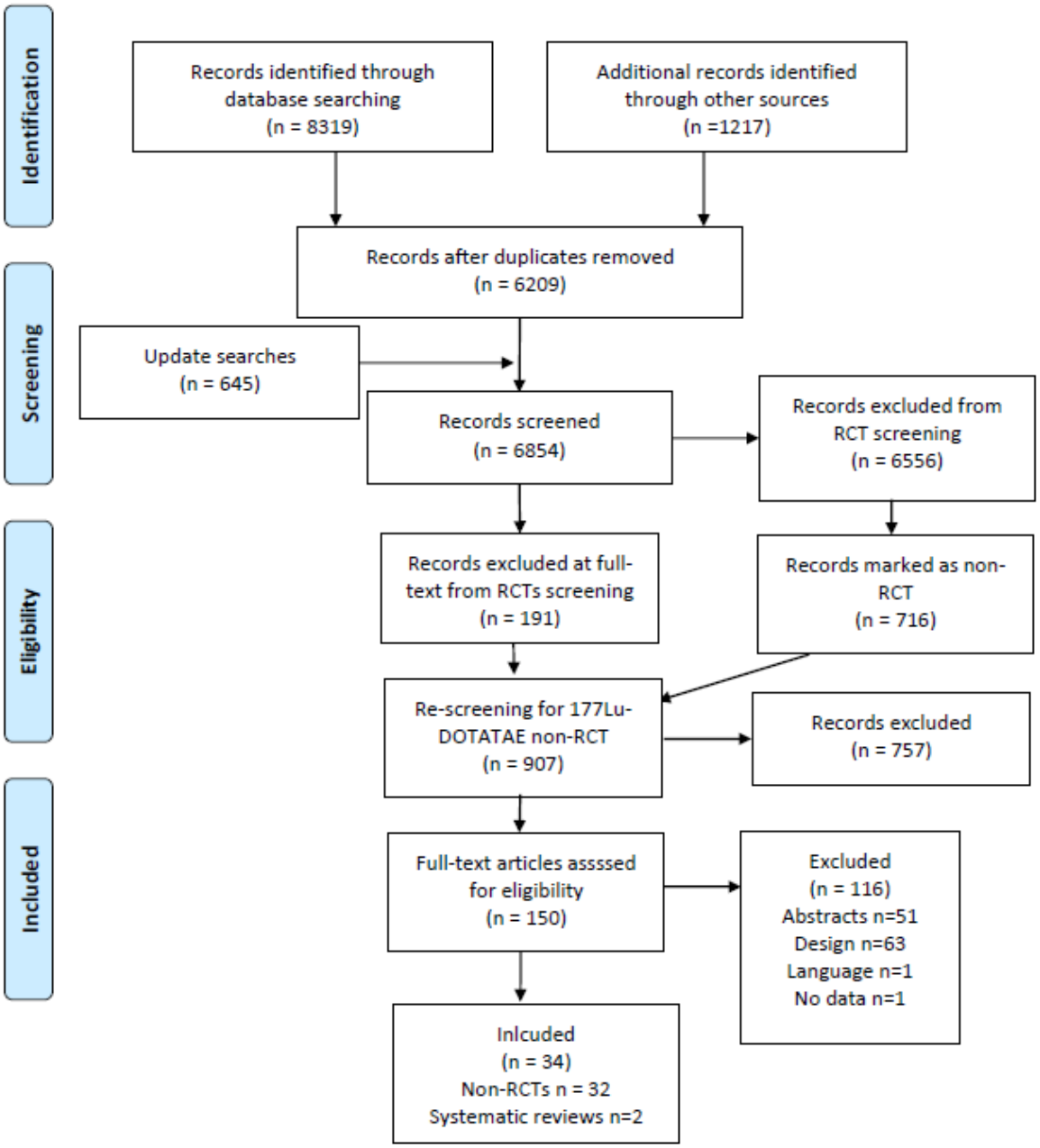
Data were presented in summary tables. The following outcomes have been narratively synthesised below; PFS, OS, response rate, HRQoL and adverse events.

4.4 Results for non-RCT

4.4.1 Quantity and quality of research available

PRISMA statement is presented in Figure 25.

Figure 25: PRISMA statement, non-randomised studies for 177Lu-DOTATATE



4.4.2 All 177Lu-DOTATATE trials tabulated

No non-RCT comparative trials were identified, however 32 single arm trials were. Baseline characteristics of these 32 trials are tabulated in Table 56 and outcomes in Table 57.

Table 56: Baseline characteristics from non-randomised studies for 177Lu-DOTATATE

Author and Year	Country	N	Location of NETS	Lutetium dose	Other drugs	Age (yrs)	Males n/N	Tumour Functioning n/N	Tumour Differentiation n/N	Previous Treatments n/N
Balter et al. 2016[49]	Uruguay	5	2 pNETs 2 ileum 1 bronchial	Cumulative dose of 4.44-22.2 GBq	NR	Range: 51-79 yrs	4/5 (80)	NR	NR	NR
Barber et al. 2012[50]	Australia[a]	5	4 pNETs 1 duodenum	7.0 to 10.0 GBq (mean 8.6GBq)	*Premedication:* Granisetron (3mg), Dexamethasone (8mg), Amino acid solution, *Concurrent:* 5FU chemotherapy (200mg/m^2/24h)	Range: 55-72 yrs Mean 68 yrs	5/5 (100)	Non-functioning: 5/5 (100)	5/5 (100) Well differentiated	Pancreatic 2/5 SSAs 1/5 Chemotherapy1/5 Incomplete resection Duodenum 1/5
Basu et al. 2016[51]	India[a]	5	1 lung 2 bronchial carcinoid 1 unknown 1 duodenum	16.1-25.6 GBq cumulative	NR	Range: 26 - 62 yrs	3/5 (60)	NR	3/5 (60) Well differentiated (3 thoracic NETs)	NR
Bodei et al. 2011[52]	Italy	51	5 bronchial 1 appendix 14 pancreatic 3 duodenal 19 ileum 2 sigma-rectal 3 unknown 3 paraganglioma 1 meningioma	*Group 1:* 3.7-5.18 GBq/cycle median in 6 cycles, 26.4GBq *Group 2:* 5.18-7.4 GBq/cycle; median in 4 cycles 25.2 GBq	100ml of physiological saline, 25g of lysine diluted in 1l of normal saline, 12.5g of lysine diluted in 500ml of normal saline	Range: 30-79 yrs Median 57 yrs	26/51 (51)	NR	35/37 (94.6) Well-differentiated	SSA 43/51
Bodei el al. 2016[53]	Italy	54	13 bronchial 35 GEP-NETs 6 unknown	PRRT-naïve patients (risk factors and no risk factors): 18.5 or 27.8 GBq in 4 cycles PRRT pre-treated: 14.8 in 4 cycles	NR	Range: 43-83 yrs Median 66 yrs	37/54 (69)	NR	6/35 (17.1) Well-differentiated (GEP NETs non-specified)	Surgery 32/54 SSA 44/54 Chemotherapy 21/54 Everolimus 5/54 Sunitinib 1/54 Interferon alpha 1/54 PRT 16/54 Radiotherapy 6/54 TACE 4/54

Claringbold et al. 2011[54]	Italy	33	10 pNETs 13 small bowel 2 large bowel 2 lung 6 unknown	7.8 GBq	Amino acids: 11.6g/l lysine and 23g/l arginine, at 250ml/h for 4 h. 5mg tropisetron and 2mg lorzaepam. 1,650mg/m2 capecitabine. Of the 19 patients with carcinoid, 18 were receiving regular octreotide analogue therapy for symptom control	Range: 32-82 yrs Median 60 yrs	21/33 (63)	Functioning 21/33 (64)	33 / 33 (100) Well- or moderately well differentiated NETs	Surgery 20/33 Octreotide 18/33 Chemotherapy 5/33
Claringbold et al. 2012[55]	Australia	35	15 bowel 17 GEP-NETs 2 lung	7.8 GBq	Capecitabine 1500mg/m2, temozolomide 200mg/m2. Amino acids: 11.6g/L lysine and 23g/L arginine at 240mL/h	Range: 33-81 yrs Median 63 yrs	24/35 (69)	Non-functioning: 16/35 (46) Functioning 13/35 (37)	35/35 (100) Well differentiated	Octreotide LAR 12/35 Chemotherapy 6/35 Surgery 12/35
Claringbold & Turner 2015a[56]	Australia	30	pNETs	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
Claringbold & Turner 2015b[57]	Australia	16	5 pNETS 11 small bowel	7.8GBq	Everolimus 5, 7.5 and 10 mg daily. Amino acids 11.6g/L lysine and 23g/L arginine at 240mL/hour. IV tropisetron and dexamethasone and oral aprepitant.	Range: 43-72 yrs Median 63 yrs	9/16 (56)	NR	NR	Surgery 8/16 SSA 11/16 Chemotherapy 6/16 PRRT 5/16 Sunitinib 1/16 ^{90}Y-microspheres 2/16
Delpassand et al. 2014[58]	USA	37	14 pNETS 12 small bowel 3 rectal 1 large bowel 7 unknown	200mCi (7.4 GBq; ±10%) administered up to cumulative dose of 800 mCi (29.6 GBq; ±10%)	Kidney protecting agents, 15 % Clinisol (1000ml), mixture composed by positively charged amino acids.	Range: 43-86 yrs Median 64 yrs	16/37 (43)	NR	NR	Sandostatin 28/37
Ezziddin et al. 2011a[59]	Australia	81	37 pNET 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 Functioning 18/81	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. 2011b[60]	German y	42	12 pNETs 30 non-pancreatic GEP NETs	Mean activity 8.1 ± 0.98 GBq per cycle	NR	Range: 44-88 yrs Mean 62 yrs	26/42 (70)	NR	42/42 (100) Well-differentiated	Surgery 22/42 Biotherapy 17/42 Chemotherapy 11/42 Locoregional treatment 2/42
Ezziddin et al. 2014a[61]	German y[a]	74	33 pNETs 41 non-pancreatic GEP NETs	Mean activity 7.9 GBq per cycle	Standard amino acid co-infusion (2.5% lysine and 2.5% arginine in 1 L of 0.9% NaCl; infusion of 250mL/h)	Range: 34-83 yrs Mean 62.5 yrs	42/74 (57)	Non-functioning 55/74 Functioning 9/74	74/74 (100) Well-differentiated	Surgery 38/74 Biotherapy 28/74 Chemotherapy 18/74 Locoregional treatment 13/74
Ezziddin et al. 2014b[62]	German y[a]	68	pNETs	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
Ilan et al. 2015[63]	Sweden	24	pNETs	Range activity 4.0-7.9 GBq per cycle	Kidney protection: 2L of mixed amino acids solution	Range: 43-78 yrs	13/24 (54)	NR	NR	NR
Kong et al. 2014[64]	Australia	68	33 pNETs, 35 non-pancreatic NET	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
Kunikowska et al. 2013[65]	Poland[a]	28	14 foregut, 9 midgut, 1 hindgut, 2 unknown primary, 2 other	7.4 GBq/m^2 with activity per course equaled 2.2-3.7 GBqY/Lu/DOTATATE	7.4 GBq/m2 with activity per course equalled 2.2-3.7 GBq of Y-DOTATATE. Amino-acid infusion, consisting of 11.3g of arginine and 9.0g lysine (1,000mL Vamin 18) and Ringer's solutions (500mL). Ondansetron (8mg)	Range: 39-78 yrs Mean: 55±10.9 yrs,	10/28 (36)	NR	NR	Chemotherapy 9/28
Kwekkeboom et al. 2003[66]	Netherlands	35	12 pNETS 12 carcinoid 8 unknown origin, 3 gastrinoma	100, 150 or 200 mCi to a final cumulative dose of 600-800mCi (27.8-29.6 GBq)	Granisetron 3mg, amino acids (lysine 2.5%, arginine 2.5% in 1 l 0.9% NaCl:250ml/h), 8 patients used sandostatin	Range: 19-78 yrs Mean 54 yrs	14/35 (40)	NR	NR	Surgery 12/35 Radiotherapy 1/35 Chemotherapy 3/25 Octreotide (Sandostatin) 14/35

Kwekkeboom et al. 2005[67]	Netherlands	129	8 gastrinoma, 2 insulinoma, 33 non-functioning endocrine pancreatic tumors, 18 endocrine tumors of unknown origin, 70 carcinoid tumours	600 to 800 mCi (22.2 to 29.6 GBq). Cycle dosages were 100mCi (3.7 GBq), 150 mCi (5.6GBq) and 200mCi (7.4GBq)	Granisetron 3mg, amino acids (lysine 2.5%, arginine 2.5% in 1 l 0.9% NaCl:250ml/h)	Range: 19-83 yrs Mean 56 yrs	65/129 (50)	NR	NR	Surgery 63/129 External beam radiation 6/129 Chemotherapy 20/129 SSA 66/129
Kwekkeboom et al. 2008[68]	Netherlands	310	188 carcinoid 72 non-functioning pNETs 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[69]	Italy	43	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 risk. Some treated with reduced dosage of 3.7GBq/cycle	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 over 1 hour twice the following day)	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
Sabet et al. 2013a[70]	Germany	68	23 pNETs, 45 non-pancreatic GEP-NETs	8.1 ±0.76GBq	NR	Range: 40-88 yrs Mean 63 yrs	39/68 (57)	NR	68/68 (100) Well-differentiated	Surgery 35/68 Biotherapy 30/68 Chemotherapy 18/68 Locoregional treatment 2/68
Sabet et al. 2013b[71]	Germany[a]	6	2 pNETs, 4 non-pancreatic NETs	48.7 GBq mean cumulative (29.6-96.7GBq)	2.6-3.3 GBq RE-HEDP, cumulative 5.9GPq	Range: 43-70 yrs	5/6 (83)	NR	NR	Radiation 1/6 Chemotherapy 5/6 Locoregional treatment 3/6 Biotherapy 4/6 Surgery 2/6
Sabet et al. 2014[72]	Germany	11	3 pNETs,	Mean dose of 6.95 GBq per cycle, aimed	Amino acids were co-administered to reduce the	Range: 40-78 yrs	7/11 (64)	NR	11/11 (100) Well-	Surgery 6/11 SSAs 6/11

			8 non-pancreatic GEP-NETs	at 4 courses and standard intervals of 3 mo	absorbed dose to the kidneys.	Mean 62yrs			differentiated	Chemotherapy 8/11 Locoregional treatment 2/11 PRRT 4/11
Sabet et al. 2015[73]	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 Functioning 44/61	61/61 (100) Well-differentiated	Biotherapy 53/61 Surgery 41/61 Chemotherapy 9/61 Locoregional treatment 10/61
Sansovini et al. 2013[74]	Italy	52	Advanced pNETs	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
Severi et al. 2015[75]	Italy	26	17 pNETs 5 ileum 1 appendix 1 colon 1 rectum 1 unknown	Total activity 14.8-18.5 GBq in 4 or 5 cycles, (median 16.5 GBq) Primary treatment: Median 10.8 GBq in five cycles Retreatment: Median 16.5 GBq in five cycles	Amino acids: lysine 70 mEq in 500 ml of saline (250ml over 30 min immediately before therapy, 250ml during therapy), lysine 70 mEq in 500ml of saline during the first 3h after therapy, and lysine 60 mEq in 500 ml of saline over 1 h twice the following day.	Range: 37-79 yrs Median 54 yrs	15/26 (58)	NR	NR	Surgery 13/26 Chemotherapy 13/26 Locoregional treatments 3/26 Somatostatin analogues 24/26
Soydal et al. 2016[76]	Turkey	29	9 pNETs 5 unknown 1 colon 2 stomach 2 lung 2 retroperitoneum 2 ovary 2 thyroid 3 ileum 1 appendix	7400 MBq each cycle	100 MBq of Ga-68 DOTATATE, 50g cocktail of 25g lysine and 25g of arginine diluted in 2L of normal saline.	Range: 19-76 yrs Mean 50.7±14.6 yrs	12/29 (41)	NR	24/27 Well differentiated 3/27 Moderately differentiated	Surgery 16/29 Chemotherapy 13/29 Radiotherapy 3/29 SSA 19/29
van Essen et al. 2007[77]	Netherlands	16	9 bronchial, 5 gastric 2 thymic carcinoids	22.2-29.6GBq Cumulative. cycle doses were 7.4 GBq. Dose could be reduced to 22.2-27.8 GBq.	3mg granisetron, amino acids (lysine 2.5%, arginine 2.5%)	Range: 37-76 yrs Median 57 yrs	10/16 (62)	NR	NR	Surgery 11/16 Chemotherapy 4/16 Radiotherapy 3/16

				Dose adjusted to 3.7 or 5.55 GBq						
van Essen et al. 2010[78]	Netherlands	33	8 pNETs, 5 unknown, 20 carcinoid (3 bronchial, 1 gastric, 1 rectal,15 midgut)	Intended cumulative dose of 14.8GBq in 2 cycles, cycle dose 7.4GBq or occasionally 3.7GBq.	3mg granisetron, amino acids (1L of arginine 2.5% and lysine 2.5%)	Range: 35-75 yrs Median 57	NR	NR	NR	NR
van Vliet et al. 2013[79]	Netherlands	268	72 pNETs, 178 GI or thoracic NETs (22 foregut, 145 midgut, 11 hindgut), 18 unknown	3.7 or 7.4GBq cumulative intended dose of 22.2-29.6GBq. If dosimetric calculations indicated that the radiation dose to the kidneys would exceed 23 Gy with a dose of 29.6 GBq, the cumulative dose was reduced to 22.2-27.8 GBq.	3mg granisetron, amino acids (1L of arginine 2.5% and lysine 2.5%)	Range: 23–83 yrs Mean 59 yrs	138/268 (52)	Non-functioning 61 (85) Functioning 11 (15)	NR	Octreotide142/268 Surgery 118/268 Chemotherapy 26/268 Radiotherapy 10/268
van Vliet et al. 2015[80]	Netherlands	119	pNETs G1: (n=15) borderline or unresectable pNETs G2 (n=14): borderline or unresectable pNETs and oligometastatic disease (< or = 3 liver metastasis) G3 (n=90): pNETS and more than 3 liver metastasis or other distant metastasis	Cycle dose of 7.4 GBq, cumulative dose of 22.2-29.6 GBq	3mg granisetron, amino acids (1L of arginine 2.5% and lysine 2.5%)	Range: 23–85 yrs Mean 55 yrs	54/119 (45)	Non-functioning 119 /119 (100)	NR	NR

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; PNETS, 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 57: 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
Balter et al. 2016[49]	3 months	NR	NR	pNETs: PR 1/2; SD 1/2 Ileal NET: PR 2/2 Bronchial NET: PR 1/1	NR	NR
Barber et al. 2012[50]	12-48 months	NR	5/5 (100)	Radiologic response: Pancreatic NET: 4/4 PR Duodenal NET: 1/1 SD	NR	NR
Basu et al. 2016[51]	10–27 months	27 months (duodenum) 10 months (unknown)	NR	Duodenum and unknown, partial response: 2/2	PRRT well tolerated: no haematological toxicity	Improved symptomatic palliation/QoL
Bodei et al. 2011[52]	4-66 month	Outcome not reported by tumour location	Outcome not reported by tumour location	Pancreas: PR 8/14; MR 1/14; SD 2/14; PD 3/14 Duodenum: CR 1/3, PR 1/3, PD 1/3 Ileum: PR 2/19, MR 6/19; SD 7/19; PD 4/19 Sigma-rectum: PR 1/2; PD 1/2 Unknown: MR 2/3; SD 1/3 Appendix: SD 1/1 Bronchial: PR 2/5; MR 2/5; SD 1/5 Paraganglia: MR 2/3; SD 1/3 Meninges: SD 1/1	Outcome not reported by tumour location	Outcome not reported by tumour location
Bodei el al. 2016[53]	Median 16 months Range 1-33 months	Median PFS was not achieved	NR	Responders (SD + PR +CR) were 71% GI; 93% pancreas	No serous side-effects with PRRT.	NR
Claringbold et al. 2011[54]	16 months Range 5-33 months	Outcome not reported by tumour location however for whole cohort: median PFS was not achieved at follow-up	Outcome not reported by tumour location	pNETs: PR 1/3; SD 1/3; PD 1/3 Small Bowel: PR 1/13; SD 12/13; Colon: SD 2/2 Lung: PR 1/2; SD 1/2 Unknown: SD 6/6 Pancreatic islet cell: PR 4/5; SD 1/5 Insulinoma: PR 1/1	Outcome not reported by tumour location	Outcome not reported by tumour location
Claringbold et al. 2012[55]	Median 18 months Range 12-33 months	Outcome not reported by tumour location	Outcome not reported by tumour location	GEP-NET: CR 3/17; PR 11/17 SD 2/17; PD 1/17 Bowel NET: CR 2/15; PR 2/15; SD 10/15; PD 1/15 Lung: SD 1/2; PD 1/2	Outcome not reported by tumour location	NR

Claringbold & Turner 2015a[56]	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
Claringbold & Turner 2015b[57]	Median 34 months Range 18-42 months	Outcomes not reported by tumour location	Median OS was not reached at 34 months	pNETS: PR 4/5; SD 1/5 GI-NETs: PR 3/11; SD 7/11; not assessable 1/11	Outcomes not reported by tumour location	NR
Delpassand et al. 2014[58]	Average 14.26 months Median 16.11 months Range 0.3-26.87 months	Median PFS not reached GI: KM survival estimate at 12 months: 72.7% (95% CI 49.1, 86.7) and at 24 months 72.7% (49.1, 86.7) Pancreas: 12 months: 79.5% (95% CI 39.3, 94.5) and at 24 months 63.6% (95% CI 22.2, 87.3)	Outcome not reported by tumour location	Outcome not reported by tumour location	Outcome not reported by tumour location	Outcome not reported by tumour location
Ezziddin et al. 2011a[59]	NR	NR	NR	pNETs: PR 57%; MR 13.5%; SD 16%; PD 13.5% GE-NETs: PR 23%; MR 13.5%; SD 45.5%; PD 18%	NR	NR
Ezziddin et al. 2011b[60]	Median 32 months (95% CI 29, 35)	pNETS: median 29 months (95% CI 18, 40) Other GEP-NETs: median 35 months (95%CI 16, 54)	Outcome not reported by tumour location	Regression (CR, PR and MR): pNETS: 7/12; other GEP-NETs: 14/30	NR	Outcome not reported by tumour location.
Ezziddin et al. 2014a[61]	Median 47 months (95% CI 44.5, 49.5)	Outcome not reported by tumour location	pNETs: median 57 months (95% CI 48, 66) Other GEP NETs: median 43 months (31, 55)	pNETs: 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[62]	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
Ilan et al. 2015[63]	3 months after termination of treatment	NR	NR	In all 24 patients, there was a significant correlation between absorbed dose and best tumour response.	NR	NR

Kong et al. 2014[64]	Median 60 months Range 5-86 months	NR	Outcomes not reported by tumour location	Partial and minor responses: pNETs: 55% Nonpancreatic NETs: 81% (OR 0.28, [95% CI 008, 0.94])	NR	NR
Kunikowska et al. 2013[65]	NR – other measure taken at 48 months	Event free survival 24.3 months; Time to progression 24.3 months	Median OS 49.8 months	NR	Grade 1+2 nephrotoxicity n=3/28 Mild nausea in both groups (38% of entire population)	NR
Kwekkeboom et al. 2003[66]	Average 9 months	NR	NR	pNETs: CR 1/12; PR 1/12; SD 7/12; PD 3/12 Carcinoid: PR 4/12; SD 6/12; PD 2/12 Unknown: PR 4/7; SD 1/7; PD 2/7 Gastrinoma: PR 3/3	Outcome not given by tumour location	Outcome not given by tumour location
Kwekkeboom et al. 2005[67]	Median 16 months Range 7-44 months	Outcome not given by tumour location	NR	pNETS: CR 3/32; PR 7/32; MR 7/32; SD 11/32; PD 4/32; Carcinoid: PR 13/66; MR 13/66; SD 28/66; PD 12;/66 Unknown origin: PR 6/17; MR 2/17; SD 4/17; PD 5/17 Gastrinoma: PR 5/8; MR 2/8; SD 1/8 Insulinoma: PR 1/2; PD 1/2	Outcome not given by tumour location	NR
Kwekkeboom et al. 2008[68]	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 pNETs: 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[69]	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. 2013a[70]	Median 48 months (95% CI 39, 54)	NR	pNETs: Median OS 48 months (95% CI 29, 67) Other GEP-NETs: Median OS 57 months (95% CI 36, 78)	Regression (CR, PR or MR) pNETs: 14/23 Other GEP-NETs: 19/45	Outcome not given by tumour location	NR
Sabet et al. 2013b[71]	NR	NR	OS for pancreatic NETs 5 months, OS for GI NETs, range 2-9 months	RR for pNETs: SD n=1/2; PD n=1/2; RR for GI NETs; SD 1/4;PD 3/4	Outcome not reported by tumour location	NR
Sabet et al. 2014[72]	NR	Outcome not reported by tumour location	NR	pNETs: PR 1/3; SD 2/3 GI NETs: PR 1/8; MR 1/8; SD 5/8; PD 1/8	Outcome not reported by tumour location	NR
Sabet et al. 2015[73]	Median 62 months (95% CI 57-67,) Range 4-102 months	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. Relevant haematotoxicity (grade 3/4) 5/61 No other relevant toxicities (including nephrotoxicity) or treatment-related deaths were observed.	NR
Sansovini et al. 2013[74]	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
Severi et al. 2015[75]	Median: 36 months Range 4–58 months	Outcome not reported by tumour location	Outcome not reported by tumour location	pNETS: PR 1/17; SD 14/17; PD 2/17 Ileum: SD 3/5; PD 2/5 Appendix: SD 1/1; Colon SD 1/1; Rectum CR 1/1; Unknown SD 1/1	Outcome not reported by tumour location	NR
Soydal et al. 2016[76]	NR	NR	NR	pNETs: PR 3/9; SD 5/9; PD 1/9 Other NETs (Unknown, Stomach, Colon, Retroperitoneum, Stomach, Ileum, Appendix) PR 3/14; SD 9/14; PD 2/14	NR	NR

van Essen et al. 2007[77]	18 and 21 months	Gastric carcinoids estimated median TTP 16 mo	NR	Gastric carcinoids: CR 1/5; MR 1/5; SD 2/5; PD 1/5	Not reported by tumour location	NR
van Essen et al. 2010[78]	Median 16 months Range 1–40 months	Median TTP in pNETS (n=8) 17 months Median TTP in carcinoid NETs (n=27) 20 months	Outcome not reported by tumour location	pNETs PD 5/8 Carcinoid NETs: PD 12/27	Treatment effects in patients with pancreatic neuroendocrine tumours were similar to those in patients with other gastroenteropancreatic neuroendocrine tumours.	NR
van Vliet et al. 2013[79]	NR	Outcome not reported by tumour location	Outcome not reported by tumour location	pNETS: OR (CR+PR+MR): 20/61; SD 22/61; PD 19/61 Midgut: OR 31/138; SD 80/138; PD 27/138	NR	NR
van Vliet et al. 2015[80]	NR	Median PFS (in 29 patients in groups 1 and 2) was 55 months (95% CI 37 – 73) Median PFS was 69 months for patients with successful surgery and 49 months for the other patients Median PFS (in 90 other patients in group 3) was 25 months.	Median OS (in 29 patients in groups 1 and 2) was more than 105 months. Median OS was more than 103 months for patients with successful surgery and 60 months for the other patients. Median OS (in 90 other patients in group 3) was 52 months.	Tumour response (3 months after last treatment): OR (complete response + partial response + minor response) in 72 / 119 (61%) patients; Stable disease in 24 / 119 (20%) and progressive disease in 21 (18%)	NR	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; pNETS, pancreatic neuroendocrine tumors; 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

4.4.3 Overview of results

All the 32 included studies presented were case series with no internal controls. There was a wide variation in the number of study participants (5 – 310), with only four out of 32 studies having more than 100 study participants. Studies were conducted in participants with a wide range of baseline characteristics.

For outcome measures, following treatment with 177Lu-DOTATATE, PFS ranged from 10 – 40 months and OS ranged from 34.2 – 105 months. In terms of response rates, complete response ranged from 2% - 27%; partial response ranged from 12% - 100% (with a SD range from 12% - 100%).

This wide variation in outcome measures are likely to be due to factors inherent in study design and compounded by wide variations in participant characteristics e.g. tumour sites, with outcomes often reported for mixed tumour locations e.g. data for gut, pancreas and lung NETS grouped together.

Twenty three of the 32 studies reported on adverse events, while six of the 32 studies reported on Health Related Quality of Life outcomes.

The extreme sensitivity of outcomes to apparently small variations in study features, particularly casemix, illustrates the great importance of having studies with parallel control groups, ideally ones which are randomly allocated, to assess the effectiveness of treatments. Without controlled studies it is very difficult to determine whether differences in outcome between case series for a new treatment (in this case 177Lu-DOTATATE) relative to separate case series for existing treatments are attributable to the difference in treatment or differences in prognostic factors.

4.5 Summary

4.5.1 Summary of clinical effectiveness systematic review

- Of 6209 titles/abstracts screened, three trials met the inclusion criteria for the clinical effectiveness systematic review.
- The three trials were made up from 56 citations (6 full texts, 1 errata and 49 conference abstracts).
- The risk of bias within the trials was low and it was found to be the same between the three studies in respect of selection, performance, detection, attrition and reporting bias.

4.5.2 Pancreatic NETs

- Two trials provided evidence for the effectiveness of everolimus (RADIANT-3) and sunitinib (A6181111) in the treatment of pNETs. Both interventions were compared to placebo. BSC was also given in both the intervention and placebo arms, for both trials.
    - Median PFS, assessed by central review, was 11.4 months for everolimus (RADIANT-3) and 12.6 months for sunitinib (A6181111) compared to 5.4 months and 5.8 months in the respective placebo arms.
        - Locally assessed PFS was also reported.

- Median OS was either not reached or immature in both trials from their first publication.
    - Longer follow-up data were available from later publications/company submissions. Median OS was 44.0 months for everolimus (RADIANT-3) and 38.6 months for sunitinib (A6181111) compared to 37.7 months and 29.1 months in the respective placebo arms.
        - Crossover from the placebo arm to the treatment arm (73% in RADIANT-3 and 69% in A6181111) significantly compromises the OS results.
- Tumour response rates were assessed locally for RADIANT-3 and assumed to be locally assessed for A6181111. Complete response was only achieved by 2 individuals receiving sunitinib (A6181111); it was not achieved in any of the other arms. Both trials report higher rates for partial response and stable disease and lower rates for progressive disease in the treatment arms (everolimus and sunitinib) when compared placebo.
- Overall, adverse events were more commonly reported following treatment with everolimus and sunitinib than with placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-3) were stomatitis (64%), rashes (49%), diarrhoea (34%), fatigue (31%) and infections (23%). Following treatment with sunitinib (A6181111) the five most common all grade AEs were diarrhoea (59%), nausea (45%), vomiting (34%), asthenia (34%) and fatigue (32%).
- HRQoL was assessed in A6181111 (sunitinib) using the EORTC QLQ-C30. There were no overall differences between study groups, except for diarrhoea (21.4 point) and insomnia (7.8 point) being higher in the sunitinib arm than the placebo arm. HRQoL data were not collected in RADIANT-3.

4.5.2.1 Indirect Treatment Comparison – Pancreatic NETs

- RADIANT-3 and A6181111 were used to compare everolimus to sunitinib in an ITC using the Bucher method.
- The ITC for PFS from central radiology review suggests no difference in the HR for the treatments (HR 1.06, 95%CI 0.57, 1.97).
- The ITC for PFS from local review suggests everolimus is associated with a 17% decrease in disease progression or death compared to sunitinib (HR 0.83, 95%CI 0.49, 1.42). The 95%CI is wide and includes the null hypothesis that there is no difference in PFS effectiveness between everolimus and sunitinib.
- For OS, the ITC suggests that there is 2.56 times greater hazard of dying from treatment with everolimus than sunitinib, which is statistically significant.
    - However as these analyses are based on published HRs from RADIANT-3 and A6181111, which were not adjusted for treatment switching after disease progression, these results should not be relied upon.
- The ITC for OS where the companies have used the RPSFT method to adjust for treatment switching suggests a lower hazard of death associated with sunitinib

compared to everolimus (HR 1.76 [0.20, 15.78]). However the 95% CI is very wide and includes the null effect.

- For response rates, the ITC suggests that there is an 82% increase in the odds of a partial response in individuals treated with sunitinib compared to everolimus. However, sunitinib was associated with a 52% increase in the odds of progressive disease when compared to everolimus. Everolimus was associated with a 2.3 times greater odds for disease stability than sunitinib. However, all of these indirect treatment comparisons were associated with wide 95% CIs, suggesting that there is little evidence of a difference in response rates between everolimus and sunitinib.
- An indirect treatment comparison was only completed for those AEs where data and events were available from both trials.
    - For all grades of AE, the ITC suggests a 19% increase in the odds of experiencing stomatitis and a 42% increase in the odds of experiencing nausea with sunitinib compared to everolimus. For rash, fatigue, diarrhoea, dysguesia, epistaxis, loss of weight, thrombocytopenia, decrease appetite, headache, vomiting and asthenia (all grades), the evidence suggests an increase in the odds of experiencing the AE with everolimus compared to sunitinib. However, except for decreased appetite, all of these indirect treatment comparisons were associated with wide 95% CIs that included the null hypothesis of no difference, suggesting that there is little evidence of a difference in AEs between everolimus and sunitinib. For all grades of decreased appetite, there was a statistically significant increase in the odds of experiencing the event with everolimus compared to sunitinib.
    - For the grade 3/4 AEs, the ITC could only consider 7 AEs due to available data from the two trials. The evidence suggests an increased odds of experiencing grade 3/4 stomatitis, fatigue, diarrhoea, nausea and thrombocytopenia with everolimus compared to sunitinib, and an increased odds of experiencing decreased appetite and asthenia with sunitinib compared to everolimus. However, all of the indirect treatment comparisons for grade 3/4 AEs were associated with wide 95% CIs, that included the null hypothesis of no difference, suggesting that there is little evidence of a difference in AEs between everolimus and sunitinib.

4.5.3 *Gastrointestinal and Lung NETs*

- One trial, RADIANT -4, provided evidence for the effectiveness of everolimus for treating GI and lung NETs. The intervention was compared to placebo and both arms received BSC.
- Median PFS for RADIANT-4, assessed by central review was 11.0 months for treatment with everolimus and 3.9 months for placebo.
    - Locally assessed PFS was also reported.
- Median OS was not reached. However, Kaplan-Meier estimates for overall survival at the 25th percentile were 23.7 months (95% CI 17.6, 27.3) in the everolimus arm compared to 16.5 months (95% CI 9.0, 21.0) in the placebo arm.

- Longer follow-up analysis of OS from the Novartis submission reported OS as 25.7 months compared to 16.5 months. Treatment switching was not permitted in RADIANT-4.

- Tumour response rates were assessed by central radiology review. No arm achieved complete response. Individuals receiving everolimus had a favourable response for partial disease, stable disease, progressive disease and tumour shrinkage in comparison to those in the placebo arm.
- Overall, adverse events were more commonly reported following treatment with everolimus compared to placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-4) were stomatitis (63%), diarrhoea (31%), fatigue (31%), infections (29%) and rash (27%).
- HRQoL was reported in the company submission from Novartis for RADIANT-4. The FACT-G questionnaire was used. [redacted]

4.5.4 Gastrointestinal NETs

- Following a data request from the AG to Novartis, results from RADIANT-4 were provided for individuals recruited with just GI NETs (n=118 for everolimus vs n=57 for placebo).
- Median PFS for GI NETs from RADIANT-4 was 13.1 months for treatment with everolimus and 5.4 months for placebo.
- Median OS estimated from a Kaplan-Meier at the 25th percentile was [redacted] in the everolimus arm compared to [redacted] in the placebo arm.
- [redacted]. Individuals receiving everolimus [redacted] response for stable disease, progressive disease and tumour shrinkage in comparison to those in the placebo arm.
- Overall, adverse events were more commonly reported following treatment than receiving placebo for individuals with GI NETs. The five most common all grade adverse events following treatment with everolimus were stomatitis (71.8%), infections (59%), diarrhoea (44.4%), peripheral oedema (40.2%) and fatigue (36.8%).

4.5.5 Lung NETs

- Following a data request from the AG to Novartis, results from RADIANT-4 were provided for individuals recruited with just lung NETs (n=62 for everolimus vs n=27 for placebo).
- There were [redacted] assigned to everolimus compared to [redacted] for the placebo arm. Everolimus was associated with a [redacted] in the risk of disease progression compared to placebo.
- There were [redacted] assigned to everolimus arm compared to [redacted] for the placebo arm. Survival was [redacted] following everolimus treatment compared with placebo.

- Rates of stable disease and progressive disease [redacted] with everolimus.

4.5.6 Overall, adverse events were more commonly reported following treatment with everolimus than placebo. The five most common all grade adverse events following treatment with everolimus (RADIANT-4)

[redacted]

Summary of non-randomised 177Lu-DOTATATE studies

- 32 non-randomised single arm trials were identified.
- There was a wide variation in outcome measures which are likely to be due to factors inherent in the single arm study design and compounded by wide variations in participant characteristics e.g. tumour sites, with outcomes often reported for mixed tumour locations e.g. data for gut, pancreas and lung NETs grouped together.

4.6 Ongoing Trials

The following trials registries were hand-searched for ongoing trials: Current Controlled Trials; ClinicalTrials.gov; the FDA website; and the EMA website (including European Public Assessment Reports [EPARs]); see Appendix 1 for search strategy used. All searches were carried out in May 2016. Three trials were considered relevant to this review (Table 58). Two trials were identified as recruiting and one was not yet open for recruitment. As two of the trials were investigating 177Lu-DOTATATE, the intervention we were unable to provide relevant RCT evidence for, we contacted the study organisers. We had replies from both study organisers. The CONTROL NETs trial is in progress, and data is not expected until 2018/2019. The OCCLURANDOM study has a total of 13 individuals recruited, and data was not expected to be ready before submission of this assessment report.

Table 58: Ongoing trials

Study ID	Sponsor/ Collaborators	Trial name	Sample size	Status
NCT02687958	Gruppo Oncologico Italiano di Ricerca Clinica	Study of Everolimus as Maintenance Therapy for Metastatic NEC With Pulmonary or Gastroenteropancreatic Origin	30	Recruiting
NCT02358356	Australasian Gastro-Intestinal Trials Group	Capecitabine ON Temozolomide Radionuclide Therapy Octreotate Lutetium-177 NeuroEndocrine Tumours Study (**CONTROL NETs**)	165	Not yet open for participant recruitment
NCT02230176	Gustave Roussy, Cancer Campus, Grand Paris	Antitumor Efficacy of Peptide Receptor Radionuclide Therapy With 177Lutetium -Octreotate Randomized vs Sunitinib in Unresectable Progressive Well-differentiated Neuroendocrine Pancreatic Carcinoma: First Randomized Phase II (**OCCLURANDOM**)	80	Recruiting

4.7 NETTER-1

DISCLAIMER

Normally, we would not report in detail the results of the NETTER-1 RCT, because it concerns a comparator which is not in the NICE Scope. However, we do this here on request from NICE, as it is the pivotal trial that will underpin the anticipated marketing authorisation for lutetium and informs our economic analysis for lutetium

NETTER-1 was identified through four published abstracts in accordance with the original NICE scope. NETTER-1 was not included in the systematic review from this assessment report as it did not meet the revised inclusion criteria of the updated scope issued by NICE on the 18th August 2016. As NETTER-1 is the only RCT to assess the effectiveness of 177Lu-DOTATATE, the AG have presented the findings from the trial here.

There are currently four published abstracts relating to NETTER-1 in the public domain. Data provided on NETTER-1 in this section is from AAA's company submission, or from data given to the AG following, a request to AAA. The data presented in the company submission is from taken from the clinical study report (CSR) from NETTER-1.

4.7.1 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.

The primary outcome was PFS. Secondary outcomes included ORR, OS, and time to progression, safety, tolerability and HRQoL. Median treatment follow-up was [redacted] for 177Lu-DOTATATE and [redacted] for Octreotide LAR. At the time of primary end-point analysis, [redacted] of the safety population had been exposed to [redacted] of 177Lu-DOTATATE. The study is still ongoing.

4.7.1.1 Rationale for the choice of comparator

Taken from the company submission, AAA report that, '*The use of octreotide LAR in the control arm was appropriate in terms of both study design and ethical considerations as to provide patients of the control arm with the best standard of care. A higher dose was required by the regulatory authorities at the time of the parallel scientific advice meeting with the FDA and EMA considering that the patients enrolled in the trial had have progressive disease following 20 or 30 mg octreotide LAR, and it was not ethical to maintain them on the same dose regimen. Consequently, 60 mg octreotide LAR at 4-week intervals dose was agreed for the control arm in the absence of an alternative efficacious treatment approved for this type of tumour'*(AAA company submission, page 44).

4.7.2 Baseline Characteristics NETTER-1

Baseline characteristics of participants recruited to NETTER-1 are presented in Table 59.

Table 59: 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

4.7.3 Outcomes – NETTER-1

4.7.3.1 Progression Free Survival

AAA report PFS as the primary outcome and is defined as, '*the time from randomisation to documented, centrally assessed disease progression, as evaluated by the independent reading centre, or death due to any cause.'* Progression was determined from the RECIST criteria version 1.1.

[redacted]

[redacted]**Table 60: Progression-free survival, full analysis set**

[redacted]

Figure 26: Progression-free survival, full analysis set

[redacted]

Source: AAA submission

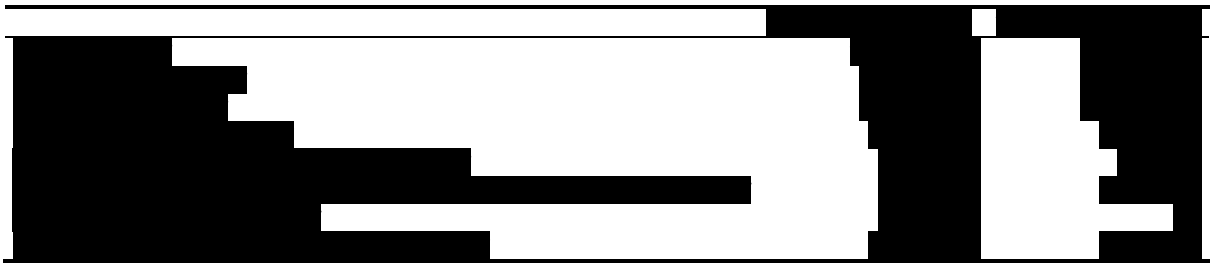
4.7.3.2 Overall Survival

[redacted]

4.7.3.3 Response Rate

[redacted]

4.7.3.4 Adverse Events



Key: TEAE, treatment-emergent adverse event

Table 64: Summary of adverse events reported in at least 10% of the patients who received 177Lu-DOTATE (regardless of whether treatment-related)

		Lutathera (N = 111)				Octreotide LAR (N = 110)			
		All grades		Grade 3 to 5		All grades		Grade 3 to 5	
SOC	PT	n_{pat}	%	n_{pat}	%	n_{pat}	%	n_{pat}	%
All SOCs	All PTs	105	94.6	46	41.4	92	83.6	36	32.4
Gastrointestinal disorders	Nausea	65	58.6	4	3.6	13	11.8	2	1.8
	Vomiting	52	46.8	8	7.2	11	10.0	1	0.9
	Diarrhoea	32	28.8	3	2.7	21	19.1	2	1.8
	Abdominal pain[1]	29	26.1	3	2.7	29	26.4	6	5.5
	Abdominal distension	14	12.6	0	0.0	15	13.6	0	0.0
General disorders and administration site conditions	Fatigue[2]	44	39.6	2	1.8	28	25.5	2	1.8
	Oedema peripheral	16	14.4	0	0.0	8	7.3	0	0.0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[3]	32	28.8	2	1.8	22	20.0	1	0.9
Blood and lymphatic system disorders	Thrombocytopenia[4]	28	25.2	2	1.8	1	0.9	0	0.0
	Lymphopenia[5]	20	18.0	10	9.0	2	1.8	0	0.0
	Anaemia[6]	16	14.4	0	0.0	6	5.5	0	0.0
	Leukopenia[7]	11	9.9	1	0.9	1	0.9	0	0.0
Metabolism and nutrition disorders	Decreased appetite	20	18.0	0	0.0	9	8.2	3	2.7
Nervous system disorders	Headache	18	16.2	0	0.0	5	4.5	0	0.0
	Dizziness	12	10.8	0	0.0	6	5.5	0	0.0
Vascular disorders	Flushing	14	12.6	1	0.9	10	9.1	0	0.0
Skin and subcutaneous tissue disorders	Alopecia	12	10.8	0	0.0	2	1.8	0	0.0
Respiratory, thoracic and mediastinal disorders	Cough	12	10.8	0	0.0	6	5.5	0	0.0

Key: N: number of patients in treatment group; n: number of patients;

Notes: 1 Includes 'Abdominal discomfort', 'Abdominal pain', 'Abdominal pain lower', 'Abdominal pain upper' and 'Gastrointestinal pain', 2 Includes 'Asthenia' and 'Fatigue', 3 Includes 'Arthralgia', 'Back pain', 'Bone pain', 'Flank pain', 'Groin pain', 'Musculoskeletal chest pain', 'Musculoskeletal discomfort', 'Musculoskeletal pain', 'Myalgia', 'Neck pain', 'Pain in extremity', 'Spinal pain', 4 Includes 'Thrombocytopenia' and 'Platelet count decreased', 5 Includes 'Lymphopenia' and 'Lymphocyte count decreased', 6 Includes 'Anaemia', 'Haemoglobin decreased', 'Normochromic normocytic anaemia', 7 Includes 'Leukopenia' and 'White blood cell count decreased'.

4.7.3.5 HRQoL

[redacted]

4.7.3.6 Subgroup Analysis

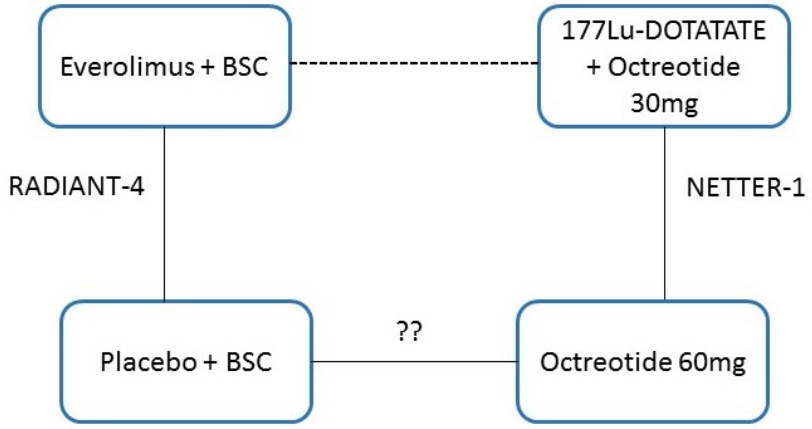
No subgroup analysis was carried out by AAA for NETTER-1.

4.7.4 Indirect treatment comparison

4.7.4.1 Methods – intended ITC

Data on the effectiveness of everolimus and 177Lu-DOTATATE in participants with GI NETs were identified from RADIANT-4 (everolimus + BSC vs placebo + BSC) and NETTER-1 (177Lu-DOTATATE + octreotide 30mg vs octreotide 60mg). The AG intended to indirectly compare everolimus to 177Lu-DOTATATE for GI NETs as shown in Figure 27.

Figure 27: Intended ITC for 177Lu-DOTATATE to Everolimus



To enable an indirect comparison, a trial connecting Placebo and BSC to Octreotide 60mg was required. The AG found no such trial in the primary searches so two supplementary bibliographic database searches were undertaken to find evidence to link these studies.

Search one: RCTs of Octreotide

The first search attempted to identify studies reporting RCTs of Octreotide. The search syntax took the following form: ((search terms for neuroendocrine tumours) AND (search terms for Octreotide (any dose) AND (a study design literature search filter for RCTs)).

This search was run in the following bibliographic databases: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); and CENTRAL (The Cochrane Library, Wiley Interface).

Search two: searches for dosing studies

The second search attempted to identify dosing or dose-ranging studies. The search syntax took the following form: ((search terms for Octreotide (any dose) AND (free text to capture reference to dosing studies)).

This search was run in the following bibliographic databases: MEDLINE (Ovid); MEDLINE-in-Process (Ovid) and EMBASE (Ovid).

The searches were not limited by language or date and both searches are fully reported in Appendix 2.

Results of searches:

Search one (RCTs of Octreotide) identified 83 citations for screening. Screening criteria was defined by; RCT, NETs population and octreotide given in doses equal to or over 30mg. One study was identified (PROMID) where Octreotide LAR 30mg was compared to placebo

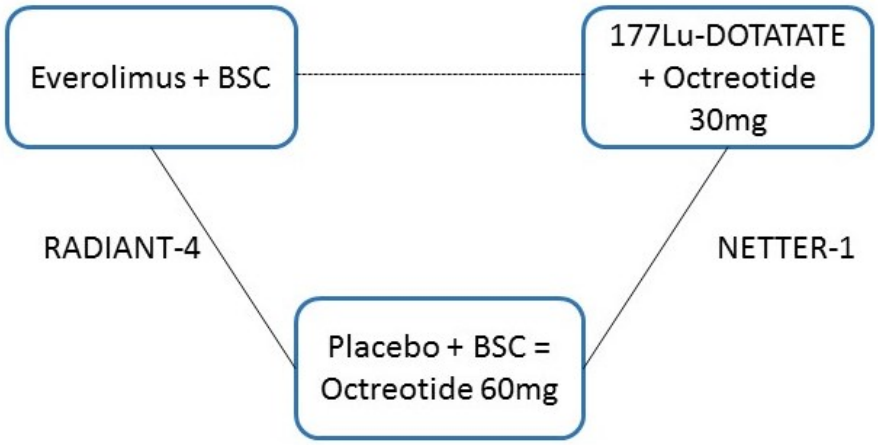
(n=42 vs n=43 respectively). Individuals recruited to the PROMID study were treatment-naïve. It was considered by the AG, following consultation with our clinicians, that the population of treatment-naïve was not comparable to the population from RADIANT-4 and NETTER-1 where at minimum of 59% of the population in RADIANT-4 and 100% of the population in NETTER-1 had had at least one previous treatment.

Search two (dosing studies) identified 180 citations for screening. Screening criteria was defined by RCT, NETs population and octreotide given in doses to include at least 30mg or 60 mg in one arm. No studies were identified.

4.7.4.2 Methods – actual ITC

Since additional searches identifying trials comparing placebo + BSC with octreotide 60mg, could not be found the intended ITC from Figure 27 could not be performed. In consultation with clinical experts, and in the absence of evidence to suggest otherwise, the AG did not think it was appropriate to link the RADIANT-4 and NETTER-1 trials by assuming that placebo + BSC (as observed in RADIANT-4) was equivalent to octreotide 60mg (as observed in NETTER-1; Figure 28)

Figure 28: Diagram of the indirect treatment comparison for GI NETs



However, as a sensitivity analysis, the AG have made the strong assumption that placebo and BSC can be considered equivalent to octreotide 60mg, but this indirect treatment comparison should be interpreted with caution Figure 28). Moreover, the data used for this network were obtained through a request for data by the AG to the companies as NETTER-1 is currently unpublished and RADIANT-4 does not report outcomes for the subgroup of participants with GI NETs only (instead RADIANT-4 reports outcomes for the combined group of GI + lung NETs).

In addition, a further caveat to this ITC is the different tumour locations included under the overarching term of GI in the two RCTs, and hence included in the ITC. NETTER-1 only recruited individuals with midgut NETs whereas RADIANT-4 recruited fore-, mid- and hind-gut. Table 61 reports the tumour locations of the individuals recruited to NETTER-1 and RADIANT-4.

Results reported for GI NETs only from RADIANT-4 in the clinical effectiveness Section 4.2.5.4 include all the tumour locations for GI in Table 61 except for unknown tumour location and one less participant in the group ‘other’ for everolimus + BSC (n=118 for

everolimus+ BSC and n=57 for placebo+BSC). The definition of GI NETs omitting the unknown location was used by Singh et al (2016) in their published poster.[81] The definition of GI used by Singh et al (2016) is the definition of GI that the AG have used in their ITC for NETTER-1.

Table 61: Tumour locations for GI NETs, comparison between NETTER-1 and RADIANT-4

	NETTER-1		RADIANT-4	
Tumour location	177Lu-DOTATATE n/N (%)	Octreotide 60mg n/N (%)	Everolimus + BSC n/N (%)	Placebo + BSC 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)

Despite the concerns raised above, the Bucher method[37] was used to indirectly compare everolimus to 177Lu-DOTATATE in individuals with GI NETs for the following outcomes: central review PFS, OS , RR and various AEs. Due to their only being two relevant trials for this synthesis we could not undertake any analyses for heterogeneity between the trials or inconsistency in the network.

For AEs, instead of providing data on all grades of AE and grades 3-4 AEs as the AG asked the company, AAA reported all grades of AEs and grade 3-5 AEs from NETTER-1. While Novartis provided the requested data for all grades and for grade 3-4 AEs from RADIANT-4. As grade 5 AEs are defined as death associated with AE, the AG attempted to identify whether any deaths associated with AEs had occurred in RADIANT-4.

[redacted]. It is therefore assumed that the grade 3-5 AEs provided by AAA can be compared with the grade 3-4 AEs provided by Novartis.

4.7.4.3 Results

Two RCTs were used to compare everolimus to 177Lu-DOTATATE: RADIANT-4 (everolimus + BSC vs placebo + BSC) and NETTER-1 (177Lu-DOTATATE + octreotide 30mg vs octreotide 60mg), see Figure 28.

For PFS, the indirect treatment comparison (Table 62) suggested that 177Lu-DOTATATE + octreotide 30mg is associated with a statistically significant reduction of 63% in disease progression or death compared to everolimus + BSC.

Table 62: HRs (95% CIs) for (central review of) disease progression or death in GI NETs

Intervention	Comparator	Data source	HR (95%CI)
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	0.37 (0.19, 0.69)

The results of the ITC for OS (Table 63) suggest a [redacted] in the hazard for death with 177Lu-DOTATATE + octreotide 30mg compared to everolimus + BSC, however this results is associated with a wide 95%CI [redacted].

Table 63: HRs (95% CIs) for OS in GI NETs

Intervention	Comparator	Data source	HR (95%CI)
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]

From the available data on response rates (see Table 64), the ITC results suggest that objective response and stable disease [redacted] with everolimus + BSC than 177Lu-DOTATATE + octreotide 30mg: objective response [redacted]; stable disease [redacted]. However, the evidence suggests [redacted] of progressive disease between 177Lu-DOTATATE + octreotide 30mg and everolimus + BSC [redacted].

Table 64: ORs (95% CIs) for response rates in GI NETs

Intervention	Comparator	Data source	Objective/overall response OR (95%CI)	Stable disease OR (95%CI)	Progressive disease OR (95%CI)
Everolimus+BSC	Placebo+BSC	RADIANT-4 (from AG data request to Novartis)[a]	[redacted]	[redacted]	[redacted]
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1 (from AG data request to AAA) [a]	[redacted]	[redacted]	[redacted]
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG	[redacted]	[redacted]	[redacted]

Notes: a, ORs calculated by AG from company response to data request

For all grades, data on 9 AEs could be compared from RADIANT-4 and NETTER-1.Table 65 shows the ORs for the AEs from each study and the results of the indirect treatment comparison. The findings suggest that 177Lu-DOTATATE is generally associated with [redacted] of experiencing AEs when compared to everolimus+BSC. This finding is statistically significant for the AEs of [redacted] but not for [redacted]. The [redacted] of experiencing fatigue associated with 177Lu-DOTATATE compared to everolimus+BSC is [redacted] For peripheral oedema, there is a

[redacted] of experiencing the AE with everolimus+BSC than with 177Lu-DOTATATE: [redacted]

Table 65: ORs (95% CIs) for all grade AEs in GI NETs

Outcome	Intervention	Comparator	OR (95%CI)
Abdominal pain	Everolimus+BSC	Placebo+BSC	0.64 (0.31, 1.33)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Anaemia	Everolimus+BSC	Everolimus +BSC	2.28 (0.95, 5.47)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Cough	Everolimus+BSC	Placebo+BSC	1.25 (0.60, 2.60)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Decreased appetite	Everolimus+BSC	Placebo+BSC	0.94 (0.45, 2.00)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Diarrhoea	Everolimus+BSC	Placebo+BSC	1.05 (0.56, 1.98)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Fatigue	Everolimus+BSC	Placebo+BSC	0.83 (0.44, 1.58)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Headache	Everolimus+BSC	Placebo+BSC	0.99 (0.44, 2.26)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Nausea	Everolimus+BSC	Placebo+BSC	1.89 (0.87, 4.12)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Peripheral oedema	Everolimus+BSC	Placebo+BSC	9.07 (3.24, 25.38)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]

Data on grade 3/4 AEs were only available for the indirect treatment comparison for five AEs: abdominal pain, decreased appetite, diarrhoea, fatigue and nausea. The ORs from the studies and those calculated in the indirect treatment comparison are shown in Table 66. For the grade 3/4 AEs, 177Lu-DOTATATE is associated with a [redacted] of experiencing the AE compared to everolimus+BSC, [redacted] between the two treatments.

Table 66: ORs (95% CIs) for grade 3/4 AEs in GI NETs

Outcome	Intervention	Comparator	OR (95%CI)
Abdominal pain	Everolimus+BSC	Placebo+BSC	0.73 (0.20, 2.57)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Decreased appetite	Everolimus+BSC	Placebo+BSC	1.00 (0.12, 8.57)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Diarrhoea	Everolimus+BSC	Placebo+BSC	3.55 (0.88, 14.35)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Fatigue	Everolimus+BSC	Placebo+BSC	3.11 (0.50, 19.27)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]
Nausea	Everolimus+BSC	Placebo+BSC	2.04 (0.30, 13.75)
	177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	[redacted]
	177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	[redacted]

4.8 Companies' reviews of clinical effectiveness

All three of the manufacturers – Advanced Accelerator Applications SA, Novartis and Pfizer – submitted clinical evidence for consideration for this MTA.

4.8.1 Advanced Accelerator Applications

AAA conducted a systematic literature review to, *'identify all studies that provide information on the clinical efficacy and safety of 177Lu-DOTATATE and relevant comparators in the treatment of patients with inoperable GEP-NETs*.' The literature searching for this submission was sufficient as was the inclusion/exclusion criteria used for screening. It was unclear whether title and abstract screening was completed in duplicate. Full-text screening was completed by two reviewers. As part of their inclusion criteria (company submission, Table 16, page 58) AAA included SSAs (octreotide and lanreotide). SSAs were removed from the NICE scope on the 18th August 2016. The exclusion criteria described by AAA in their submission (company submission, Table 16, page 58) states that conference abstracts are excluded. It is unclear therefore, why AAA have included the NETTER-1 trials as not only is it only currently published in abstract form (and so would not be identified by their systematic review) but its comparator is outside of the NICE scope. AAA included non-RCT evidence in addition to RCT evidence for all interventions and comparators (everolimus, sunitinib, octreotide, chemotherapy, lanreotide, interferon and 177Lu-DOTATATE). The AG did not find any RCT evidence for 177Lu-DOTATATE (as NETTER-1 was excluded, see section 4.2.1.1). The AG conducted a systematic review for non-RCT evidence for 177Lu-DOTATATE. The AG identified 34 trials (see section 4.4). AAA identified four non-RCTs for 177Lu-DOTATE (Kwekkeboom et al 2003/2005/2008 (ERASMUS);[66-68] Delpassand et al. 2014;[58] Paganelli et al. 2014[69] and Sansovini et al 2013[74]). All four non-RCTs were included. It is unclear why AAA did not include the additional 28 trials that the AG had identified.

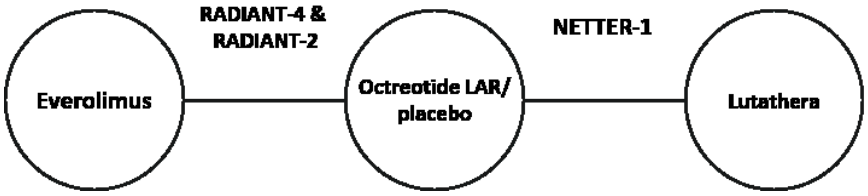
4.8.1.1 Network Meta-Analysis

AAA did not undertake a meta-analysis as they only found one trial for 177Lu-DOTATATE. Instead, they performed an ITC for GI NET, comparing everolimus with 177Lu-DOTATATE, and a mixed treatment comparison (MTC) for pNETs, comparing everolimus, sunitinib and 177Lu-DOTATATE, for the outcomes of PFS and OS.

Five trials identified from the systematic review were excluded from the analyses by AAA due to 96% of participants at baseline having stable disease (CLARINET),[82] no data on the number of participants with stable/progressive disease reported (PROMID),[83] or because they could not be connected to either the GI NETs or pNETs network (Faiss et al 2003, Meyer et al 2014 and Moertel et al 1992).[84-86].

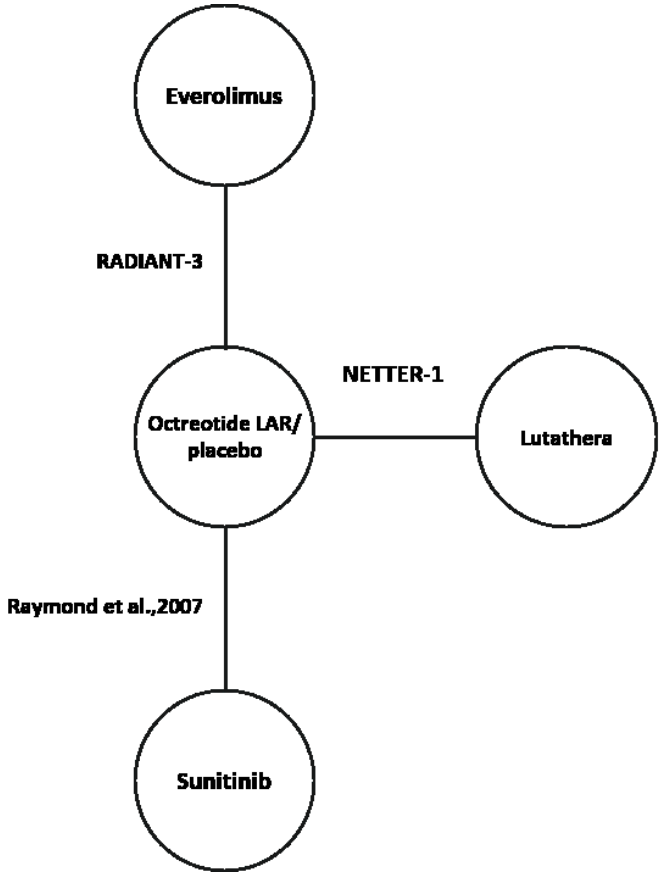
The three trials used in the ITC for GI NETs, were RADIANT-2, RADIANT-4 and NETTER-1 for GI NETS (see Figure 29). The three trials used in the MTC for pNETs were RADIANT-3, A6181111 and NETTER-1 for pNETs (see Figure 30).

Figure 29: GI NETs network for the MTC conducted by AAA for PFS and OS



Source: Reproduced from AAA submission Chapter 4 Figures 13, pages 71-72.

Figure 30: Pancreatic NETs network for the MTC conducted by AAA for PFS and OS



Note: Raymond et al 2007 is trial A6181111.
Source: Reproduced from AAA submission Chapter 4 Figures 12, pages 71-72.

Study and participant characteristics were compared across studies for GI NETs and pNETs by AAA. For somatostatin receptor status, AAA state that in NETTER-1 all participants were somatostatin receptor positive, but report that they were unable to obtain this information from RADIANT-2, RADIANT-3, RADIANT-4 and A6181111. It is therefore assumed by AAA that relative effectiveness between treatments does not alter by somatostatin receptor status.

For GI NETs, AAA highlight that the tumour functioning status differs between participants in the RADIANT-2, RADIANT-4 and NETTER-1 trials. They state that tumour function is not reported in RADIANT-2, that all participants in RADIANT-4 had non-functioning tumours, and in NETTER-1 participants with functioning and non-functioning tumours were eligible. Based on a lack of evidence to suggest a difference in the relative effectiveness between everolimus and 177Lu-DOTATATE for participants with functioning or non-functioning tumours, AAA assume that there is no difference. AAA state that the participant populations from RADIANT-2, RADIANT-4 and NETTER-1 are aligned with each other and with the NICE scope in terms of disease progression. AAA note that, although all patients in RADIANT-4 and NETTER-1 had received prior therapy, it was unclear whether this was the case in RADIANT-2.

AAA detail the data used from each trial in the networks by NETs location. For GI NETs, the company considers the populations to be in close alignment for PFS, see Table 67, but comment that there are differences in the populations for OS, see Table 67.

Table 67: GI NETs location data used by AAA from RADIANT-2, RADIANT-4 and NETTER-1

Trial	PFS	OS
NETTER-1	Midgut	Midgut
RADIANT-2	CRC	All NETs
RADIANT-4	GI	Lung + GI

For pNETs, AAA report that while NETTER-1 and A6181111 included participants with functioning and non-functioning tumours, RADIANT-3 did not report the tumour functioning status of their participants. As for GI NETs, AAA therefore assume that the relative effectiveness of everolimus compared to 177Lu-DOTATATE does not differ by tumour functioning status. AAA state that the participant populations in NETTER-1, RADIANT-3 and A6181111 had progressive disease which was assumed to be aligned with the NICE scope. AAA note that although all patients in NETTER-1 had received prior therapy, it was unclear whether this was the case in RADIANT-3 and A6181111.

AAA consider tumour location for RADIANT-3 and A6181111 to be aligned for PFS and OS, but that the population from NETTER-1 (GI NETs) is not aligned. Nevertheless, AAA include the GI NETs population from NETTER-1 in their MTC for pNETs (see Table 68).

Table 68: Pancreatic NETs location data used by AAA from RADIANT-3, A6181111 and NETTER-1

Trial	PFS	OS
NETTER-1	Midgut	Midgut
RADIANT-3	Pancreas	Pancreas
A6181111	Pancreas	Pancreas

For both tumour locations, AAA note “considerable variation” in the baseline characteristics across trials, yet consider the trials to be similar enough to synthesise.

AAA make three major assumptions to perform their MTCs: (1) that octreotide 60mg can be assumed to be equivalent to placebo and placebo + octreotide 30mg (in order to connect NETTER-1 to the other trials in the GI NETs network), (2) that octreotide 60mg is equivalent to placebo and placebo+BSC to connect NETTER-1 to the other trials for the pNETs network, and (3) that data from the NETTER-1 trial can be used to inform the network for pNETs even though no participants within NETTER-1 had pNETs.

AAA undertook a Bayesian analysis with Markov chain Monte Carlo (MCMC) simulation in R for both analyses using methods set out in Dias 2013.[87] They ran fixed and random effects models using the poisson/log model and the binomial/cloglog model. Prior distributions intended to be vague were used. A difference of >5 for the deviance information criteria (DIC) was used to identify the most appropriate model of the four types run: fixed effects poisson/log model, random effects poisson/log model, fixed effects binomial/cloglog model, random effects binomial/cloglog model. For each analysis, AAA report simulating 4 MCMC chains, with a burn-in of 10,000 iterations. Results were based on 50,000 iterations and a

thin rate of 4. AAA report assessing convergence using trace plots, autocorrelations and "other standard convergence diagnostics" (p210 of AAA submission), but do not state explicitly whether convergence was achieved in the models. Consistency of the networks could not be assessed as there were no closed loops, meaning that direct evidence between treatments compared within an RCT could not be compared to indirect evidence for that treatment comparison.

AAA report very little difference between the DICs from the 4 models for each network (see Table 27, p83 of AAA submission), therefore they present the results from the random effects Poisson model for both tumour locations and outcomes. Point estimates and 95% credibility intervals (CrIs) are reported for all treatment comparisons in Tables 23-26 (pp81-82) of their submission. The main results are summarised below in Table 69 and Table 70.

Table 69: GI-NETs HRs (95%CrIs)

Intervention	PFS	OS
177Lu-DOTATATE vs octreotode/placebo *everolimus vs octreotide/placebo* *177Lu-DOTATATE vs everolimus*	[redacted]	[redacted]

Table 70: pNETs HRs (95%CrIs)

Intervention	PFS	OS
177Lu-DOTATATE vs octreotode/placebo *everolimus vs octreotide/placebo* *sunitinib vs octreotide/placebo* *177Lu-DOTATATE vs everolimus* *177Lu-DOTATATE vs sunitinib* *everolimus vs sunitinib*	[redacted]	[redacted]

4.8.1.1.1 Limitations of AAA's MTC

We acknowledged the following important limitations of the MTC conducted by AAA, which limit the extent to which their findings can be relied upon: (1) RADIANT-2 should be excluded from this MTA as the population all have functioning tumours which is outside of the marketing license for everolimus for GI NETs, (2) NETTER-1 should be excluded from the pNETs network as it does not contain any patients with pNETs, (3) for the evaluation of GI NETs the populations for OS differ across the three studies (midgut NETs in NETTER-1, all NETs in RADIANT-2, GI and lung-NETs in RAD-4), (4) there is no justification for the assumption that octreotide LAR 60mg is equivalent to placebo, placebo+octreotide 30mg and placebo+BSC, (5) there is no consideration of the extent of treatment switching within RADIANT-2 (58% switched to active treatment), RADIANT-3 (73% switched to active treatment) and A6181111 (69% switched to active treatment) which limits the interpretation of results for OS, (6) the 95%CrIs are very wide indicating a great deal of uncertainty, more so than the results from the RCTs suggest, (7) results from the random effects Poisson model, and the fixed and random effects Binomial model, are not reported in the submission and so no comparison of any differences in point estimates or 95% CrIs between these models can be made.

4.8.1.2 Comparison with the AGs indirect treatment comparison

For GI NETs, RADIANT-2 was excluded from the AG's analysis as everolimus is not licensed for functioning tumours in GI and Lung NETs, and all participants in RADIANT-2

have functioning tumours. The AG did not identify any trials comparing placebo + BSC with octreotide 60mg to allow RADIANT-4 and NETTER-1 to be linked in a network. In consultation with clinical experts, and in the absence of evidence to suggest otherwise, the AG did not think it was appropriate to link the RADIANT-4 and NETTER-1 trials by assuming that placebo + BSC (as observed in RADIANT-4) was equivalent to octreotide 60mg (as observed in NETTER-1). However, as a sensitivity analysis, the AG have made the strong assumption that placebo+BSC can be considered equivalent to octreotide 60mg, but this indirect treatment comparison should be interpreted with caution.

From data requests sent by the AG to AAA, the AG were able to obtain GI only NETs data from RADIANT-4 (rather than GI + lung NETS data as used in AAA's indirect treatment comparison), but only for PFS and some AEs. Therefore, the results of the indirect comparison from the AG are different to that undertaken by AAA since RADIANT-2 is excluded from the AG analysis, only GI NETs are included in RADIANT-4, and an indirect comparison for OS was not conducted by the AG as this data was not received from the company.

For PFS, the HR for 177Lu-DOTATATE vs everolimus is estimated as 0.37 (95%CI 0.19, 0.69) from the AG, and 0.43 (95%CrI 0.05, 4.24) from AAA's analysis. The wide 95% CrIs from AAA's analysis is due to the use of a random effects model. These findings are similar in magnitude, however to accept these results it must be assumed that placebo + BSC is equivalent to octreotide 60mg. The AG also conducted IC of AEs, OS and RR.

For the pNETs network, the AG did not include NETTER-1 as none of the participants in the trial had pNETs. Therefore, only data from RADIANT-3 and A6181111 trials are included in the AG's indirect treatment comparison between everolimus and sunitinib. As well as PFS and OS, the AG also reported indirect comparison results for response rate and AEs. AAA only considered PFS and OS. For the comparison of everolimus with sunitinib for pNETs, point estimates calculated from AAA's MTC for PFS and OS are the same as those from the AG's indirect comparison, however the 95%CrIs from AAA's analysis are much wider than the 95%CIs from the AG's analysis. For example, the PFS HR (95%CrI) for everolimus compared to sunitinib from AAA's analysis is [redacted], while the HR (95%CI) from the AG's analysis is 0.83 (0.49, 1.42). It is likely that these differences in the width of the 95% credibility and confidence intervals are due AAA reporting the results from a random effects model, while the analysis conducted by the AG assumes a fixed effects model. As AAA do not report the results from a fixed effects model it is not possible to check that this is the reason for the uncertainty.

4.8.2 Novartis

Novartis conducted a systematic review aiming to identify, *'all relevant RCT and non-RCTs investigating everolimus, sunitinib or 177Lu-DOTATATE for the treatment of patients with advanced, metastatic or inoperable pNETs, and 177Lu-DOTATATE for advanced, metastatic or unresectable GEP-NETs' (company submission page 33).* The literature searching for this submission was sufficient, although there were minor errors in one of the searches of The Cochrane Library. It is unlikely that any studies were excluded from the review because of this error. The review followed the CRDs 'Guidance for Undertaking Reviews in Health Care'. The methods used by Novartis are described in brief and are adequate for the purpose of their submission. To minimise the risk of bias, it would have been preferable for

two reviewers to have reviewed all titles and abstracts, rather than one reviewer screening them all and the second screening 10% and all included citations.

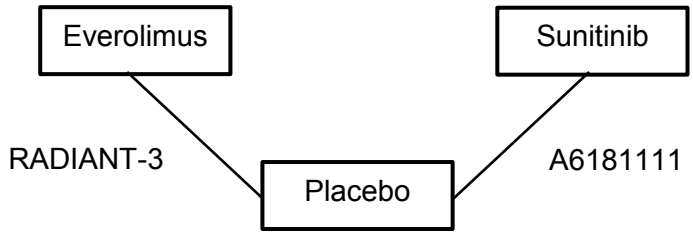
In relation to pNETs, Novartis identified five RCTs and 41 non-RCTs. From the five RCTs, four evaluated everolimus (RADIANT-3, COOPERATE-2, Yao *et al.* 2014, NCT01628913) and one evaluated sunitinib (A6181111). From the four RCTs that evaluated everolimus, only RADIANT-3 was included in the submission since COOPERATE-2 and NCT01628913 compared everolimus to comparators outside of scope. The results from the fourth identified RCT; Yao *et al* 2014 was retracted by the authors 6 months after publication. The inclusion of RADIANT-3 matches the RCT trial included by the AG for assessing everolimus in pNETs. RADIANT-3 is reported in detail in the company submission, with additional information presented in Appendix 3 of the company submission. Novartis also refer to OBLIQUE, a currently unpublished phase IV observational study, which assesses quality of life in individuals with pNETs receiving everolimus. Novartis also report on everolimus non-RCTs which represent 16 or 17 (n=16 referred to in the main company submission) document, whilst n=17 trials presented in results table (appendix 2 from their submission)) of the 41 identified non-RCTs. The non-RCT data was tabulated (appendix 2 of the company submission) and summarised in the main report (Chapter 4.8 of the company submission). The AG did not assess any non-randomised evidence for everolimus. Novartis conducted two further systematic literature reviews (SLR) aiming to identify, '*relevant clinical evidence on the efficacy and safety of everolimus for the treatment of GI NETs (SLR1) and lung NETs (SLR2) respectively'* (company submission page 59). The literature searching for this submission was sufficient and the methods of the review were the same as mentioned above. In terms of GI NETs, eight RCTs and five non-RCTs were identified by Novartis, of these eight and five trials, three RCTs and two non-RCTs also met the eligibility criteria for inclusion in the lung NETs SLR. Of the eight RCTs and five non-RCTs, only one RCT and one non-RCT was deemed relevant by Novartis in their submission (RADIANT-4 and Bajetta *et al.* 2014 respectively). Irrelevant RCTs were excluded based on the interventions not meeting the inclusion criteria from the scope (Yao et al. 2008; CLARINET; Faiss et al. 2003; Jacobsen et al. 1995; PROMID; Wolin et al. 2015) or that the population recruited was not within the marketing authorisation for everolimus (RADIANT-2). Irrelevant non-RCTs were also all excluded based on the interventions not being within scope (Ferolla et al. 2012; Campana et al. 2008; Grozinsky-Glasberg et al. 2008 and Panzuto et al. 2006). The AG did not include non-RCTs for everolimus and consequently from the two included studies from Novartis, the AG also identified RADIANT-4 (the RCT) but not Bajetta *et al.* 2014 (the non-RCT). RADIANT-4 is reported in detail in the company submission, with additional information presented in Appendix 7 of the company submission.

4.8.2.1 Network Meta-Analysis

Novartis did not conduct a MA, MTC or indirect comparison for GI and/or Lung NETs as they only identified the RADIANT-4 trial.

For pNETs, Novartis identified three trials from their systematic review that included everolimus (RADIANT-3, COOPERATE-2 and NCT01628913), and state that due to the different comparators in these three trials, a meta-analysis was not undertaken. Instead, an indirect comparison between everolimus and sunitinib is made using RADIANT-3 and A6181111. The network for Novartis's pNETs MTC is shown in Figure 31.

Figure 31: Pancreatic NETs network for the indirect comparison conducted by Novartis for PFS, OS, Concomitant SSA use and AEs



The network was used to compare PFS, OS, concomitant SSA use and 13 grade 3/4 AEs (where there was an incidence of ≥2% in either trial) between everolimus and sunitinib. For PFS, Novartis conducted two indirect comparisons, one using PFS defined by local review, and a second using PFS defined by a central blinded investigator review (referred to as BIRC in their submission). For OS, Novartis conducted an indirect comparison of OS based on ITT, and an indirect comparison of OS based on the RPSFT method, to account for treatment switching at disease progression that occurred in both trials.

A comparison of the study and participant characteristics between RADIANT-3 and A61811111 was conducted by Novartis, who deemed the trials to be similar enough to be combined. The outcomes contributing to the indirect treatment comparisons from both trials are presented in Table 4.8 of Novartis's submission.

Novartis also report the results of a published matched adjusted indirect comparison (MAIC)[88] which used individual participant data from RADIANT-3 with aggregate data from A6181111. The method was used to allow for matching of the characteristics of participants in RADIANT-3 to those in A6181111, and help to address the issue of approximately 70% of participants switching from the control arm to the active treatment arm in both trials after disease progression. However, Novartis argue (p49 of their submission) that the limitations of the MAIC method, which includes the inability to match on characteristics not accounted for in both trials, the unknown impact of unobserved differences in study and/or patient characteristics, and the fact that the Scottish Medicines Consortium (SMC), for which the MAIC had been included in an HTA they appraised on this clinical questions, referred to the MAIC as "non-standard", have led them to consider the more straightforward approach of Bucher et al[37] to calculate an indirect comparison between everolimus and sunitinib. Using the MAIC method partially corrects for some of the bias associated with comparing two different populations from the two trials, whereas there are no corrections for patient population differences with the Bucher method. In any case, the MAIC analysis serves as a robustness check of the Bucher results. The results of these analyses are summarised in Table 71 and Table 72 below (see Tables 4.11, 4.12, 4.13, 4.14 and 4.15 in Novartis's submission for all data used and MTC results).

Table 71: Results of Novartis's Pancreatic NETs indirect comparison of everolimus vs sunitinib for PFS, OS and concomitant SSA use[a]

Outcome	everolimus vs placebo	sunitinib vs placebo	everolimus vs sunitinib
Local investigator defined PFS	0.35 (0.27, 0.45)	0.42 (0.26, 0.66)	0.83 (0.49, 1.42)
Blinded independent review defined PFS	0.34 (0.26, 0.44)	0.32 (0.18, 0.55)	1.08 (0.59, 1.99)
ITT OS	0.94 (0.73, 1.20)	0.71 (0.47, 1.09)	1.32 (0.81, 2.16)
RPSFT OS	0.60 (0.09, 3.95)	0.43 (0.17, 1.20)	1.40 (0.17, 11.72)
Concomitant SSA use	0.91 (0.61, 1.36)	0.88 (0.45, 1.71)	1.04 (0.48, 2.26)

Notes: a, rounded to 2 decimal places by AG
Key: ITT, intention to treat; RPSFT, rank-preserving structural failure time

Table 72: Results of Novartis's Pancreatic NETs indirect comparison of sunitinib vs everolimus for grade 3/4 AEs[a]

Outcome	sunitinib vs everolimus[a]
Neutropenia	23.71 (0.19, 3037.28)
Hypertension	18.68 (0.15, 2414.14)
PPE syndrome	11.62 (0.09, 1540.16)
Leukopenia	11.62 (0.09, 1540.16)
Diarrhoea	0.57 (0.03, 12.113)
Stomatitis	0.23 (0.01, 14.06)
Thrombocytopenia	0.41 (0.01, 25.31)
Anaemia	0.04 (0, 4.76)
Hyperglycaemia	0.35 (0.01, 21.02)
Fatigue	0.20 (0.01, 17.25)
Infections	0.20 (0.01, 17.25)
Pneumonitis	0.09 (0.01, 11.67)
Nausea	0.09 (0.01, 11.67)
Sum	4.48 (0.51, 39.38)

Notes: a, Note that in Table 4.15 of Novartis's submission (results for indirect comparison of AEs), the upper and lower 95% CIs are were incorrectly labelled as lower and upper, respectively.
Key: PPE, palmar-plantar erythrodysesthesia

Novartis conclude that there are no significant differences for (locally and centrally defined) PFS, (ITT or RPSFT) OS, or concomitant SSA use between everolimus and sunitinib. They report that the indirect comparison for AEs suggests a higher odds of grade 3/4 for neutropenia, hypertension, PPE syndrome and leukopenia events with sunitinib than with everolimus. While for the remaining AEs, a higher odds is associated with everolimus than sunitinib. However, none of the ORs are statistically significant and all have very wide 95%CIs.

4.8.2.1.1 Limitations of Novartis's indirect treatment comparison

The AG note the following limitations with the indirect comparison calculated by Novartis: (1) it is unclear where Novartis obtained the HR for BICR PFS from A6181111 as the AG was unable to identify this from the published literature, (2) the justification for using the Bucher method of indirect comparison is not clear when a MAIC analysis would have been possible. The AG note that the conclusions of the published MAIC are similar to those from the Bucher method reported by Novartis even though the methods used differ and the OS data used by Novartis for the Bucher method are more mature than that used in the published MAIC analysis.

4.8.2.1.2 Comparison with the AGs indirect treatment comparison

The AG identified the same two RCTs for pNETs and used the same method for the ITC (Bucher) as Novartis. The ITC results were exactly the same for local PFS between Novartis and the AG, and very slightly different for central PFS even though the input HRs and

95%Cis for RADIANT-3 and A6181111 were the same. The AG believe this very slight different is possibly related to Novartis using more precise data than the AG had use of. For OS, the AG used data for A61811111 from Pfizer's submission rather than data from Raymond et al which is what Novartis used. Therefore there are some differences in the HRs and 95%Cis between the AG and Novartis. However, both sets of results (AG and Novartis) for PFS and OS indicate no statistically significant difference between everolimus and sunitinib. Similarly, the ITCs for grade 3/4 AEs from the AG and Novartis all show very wide 95% Cis suggesting no statistically significant difference between everolimus and sunitinib.

4.8.3 Pfizer

Pfizer did not conduct a systematic review in order to identify relevant trials for this decision problem. Pfizer were confident that the only trial conducted with sunitinib in its licensed indication for pNETs was the A6181111 trial. This matches the AGs trial identification for sunitinib. Pfizer report data primarily from the principal study publication Raymond et al. 2011.[45] In addition, other data sources for the A6181111 trial include the Clinical Study Report and updated survival analysis from a conference abstract. In their submission Pfizer report incidence rates for AEs using the CSR (referenced as published in 2009) as the source for the data. The AEs published in Raymond et al. 2011[45] are different and on average higher (by n=1 or 2) for all grade AEs.

4.8.3.1 Critique of MAIC analyses by Pfizer

Pfizer presented a MAIC of everolimus and sunitinib using placebo-controlled treatment effects on PFS and OS from the A6181111 trial of sunitinib vs placebo and RADIANT-3 trial of everolimus vs. placebo. These analyses follow previously published work by Signorovitch and colleagues,[88] who first applied the method to this question. Pfizer used updated OS data and matched the sunitinib and placebo arms of A6181111 to the baseline characteristics in RADIANT-3. The direction of matching, i.e. of the A6181111 to the RADIANT-3 population, was determined by the availability of individual patient data on the former trial and only summary data for the latter. In contrast, the prior study was sponsored by Novartis and had available RADIANT-3 individual patient data and only aggregate data for the A6181111 trial of sunitinib, which determined that matching was in the opposite direction, i.e. of RADIANT-3 to the A6181111 population.

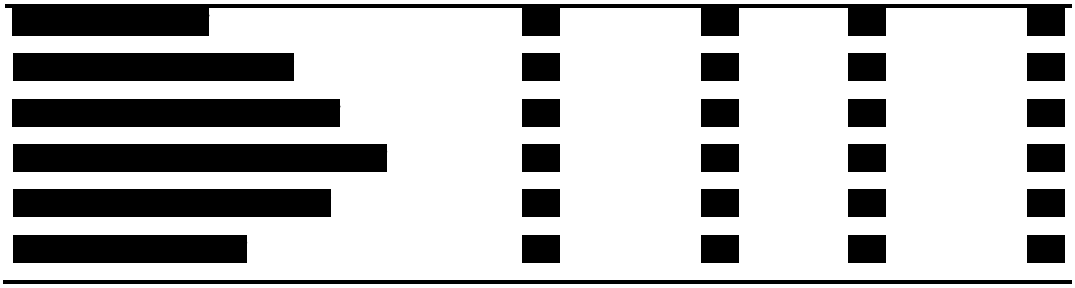
Briefly, a MAIC involves estimating sampling weights by regression analysis and applying these weights to data form individual patients to adjust their relative contribution to the analysis of outcome data from the 'index' trial, i.e. A6181111; the weights reflect the likelihood that an individual with a mix of baseline characteristics is found in the population of a 'target' trial, i.e. RADIANT-3. In practice logistic regression is used to obtain the weights, following the methodology of propensity score matching for observational data.[89] As a resulted the weighted summary characteristics at baseline match the baseline characteristics of the target population in RADIANT-3. In the present case, where no individual patient data but only summary baseline characteristics are available for the target population, a modified approach using the method of moments was used by Pfizer to obtain the matching weights.[88]

Pfizer's justification for their use of MAIC, as opposed to simpler methods such as Bucher, to indirectly compare sunitinib vs everolimus is that simpler indirect methods based on a

common comparator or anchor may fail to account for confounding when the populations of the trials in the network differ markedly or trial designs or implementation vary. The company acknowledges, however, that its MAIC analysis could not adjust for differences in study design across trials. The main justification offered by the company for its MAIC, however, is in relation to the effect on cross-over in OS. Since 69% and 85% of placebo patients in A6181111 and RADIANT-3 crossed over to the active treatment in open label extension phase studies, the OS outcomes in the placebo arm are 'contaminated' by the active treatments and would not serve as common comparator or anchor. In contrast, the MAIC by matching the sunitinib arm of A6181111 to the population of the everolimus arm in RADIANT-3 is feasible in this case.

While the two RCTs investigated patient populations with progressive, advanced well- or moderately differentiated pNETs, important differences were noted between them. These included the early termination of A618111 due to improved PFS with sunitinib, the smaller size of such trial relative to RADIANT-3, and the more frequent imaging schedule in A6181111 (eight weeks vs. 12 weeks in RADIANT-3), which may result in earlier detection of disease progression. Unlike A6181111, RADIANT-3 included patients with performance status 2, but since they constituted only 3% of the trial sample this had limited effect on the results produced by Pfizer.

As evidenced in**Error! Reference source not found.**, while randomisation produced a balanced distribution of baseline characteristics in RADIANT-3, it



Source: Reproduced from Pfizer submission, Table 11, page 59

Two approaches were taken by Pfizer to the MAIC, one for PFS and another for OS. For PFS, where a common BSC plus placebo comparator was available in both trials, the 'comparator based' approach was followed, involving the following steps:

1. The sunitinib and BSC pus placebo arms of A6181111 were separately matched to the everolimus arm.
2. The sunitinib vs. BSC plus placebo HR was estimated on the matched A6181111 individual patient data.
3. Bucher indirect comparison of everolimus vs sunitinib was estimated using the HR of the matched sunitinib vs BSC plus placebo data from A6181111 and the reported HR of everolimus vs. BSC plus placebo in RADIANT-3.

The 95% CI of the resulting MAIC HR of PFS was calculated from the standard errors of the log hazard ratio of sunitinib vs. BSC plus placebo, adjusted for the effective sample size, and of the HR of everolimus vs. BSC plus placebo in RADIANT-3, as approximated from its reported point estimate and 95% CI

Due to the contamination by cross-over, the MAIC of OS was conducted on by directly matching the sunitinib arm to the everolimus arm. In this analysis, the following steps were followed:

1. The sunitinib arm of A6181111 was matched to the everolimus arm.
2. The individual patient OS data for everolimus was recreated from digitised Kaplan-Meier curves using the algorithm by Hoyle and Henley.[90]
3. The HR of sunitinib vs everolimus was estimated from the matched individual patient data from the sunitinib arm and the recreated individual patient data in RADIANT-3.

The 95% CI of the resulting HR was obtained from step III, after adjusting for the effective sample size in the matching weights applied to the sunitinib data.

Table 73.

Table 73: MAIC PFS and OS results in Pfizer submission vs. Bucher estimates.

	PFS		OS	
Comparison	N	HR (95% CI)	N	HR (95% CI)
Bucher IC[1]				
Sunitinib vs. placebo			-	-

Everolimus vs placebo	[redacted]	[redacted]	-	-
Sunitinib vs. everolimus	[redacted]	[redacted]	-	-
Matched Adjusted IC				
Sunitinib vs placebo[a]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus vs placebo[b]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib vs. everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Unmatched IC				
Sunitinib vs everolimus	[redacted]	[redacted]	[redacted]	[redacted]

Note: a, Based on individual patient data weighted to match the population of RADIANT-3 as described by summary characteristics in [redacted]above.b, Based on published data (Raymond et al. 2011; Yao et al. 2011) [2]

[redacted] In particular, Pfizer compared the matching-adjusted Kaplan-Meier curve of the placebo arm in A6181111 with the respective curve from recreated individual patient data for the placebo arm of RADIANT-3, and [redacted]. However, given the differences in the timing of scheduled imaging assessments to determine disease status between the two trials discussed above, adjusting for the placebo PFS outcomes in the common comparator approach seems warranted nonetheless.

In relation to its OS results, Pfizer acknowledges the limitation of the data available. In particular the available sample for the sunitinib arm is small, especially after matching, which effectively halved its size. [redacted].

[redacted]

Source: Taken from Pfizer submission, Figure 9, page 70

Pfizer provides a clear justification for the MAIC evidence submitted to NICE. This was based on updating the previous analysis[88] with new OS data, and methodological improvements on the previous work by adding more variables on which to match the two indirectly compared trials. The first argument is unquestionable given that final OS analyses have been published since the previous MAIC study. The second argument is however less firm, as discussed below.

The analysis by Pfizer provides a clear description and adequate detail of the methods used in and results obtained from its MAIC. The discussion also acknowledges the main strengths

and limitations of this analysis, and provides an adequate explanation of the reasons for the [redacted]. This discussion provided the valuable insight that much of the [redacted]. This highlights the limitations associated with the small sample of this trial.

The AG notes that matching-adjusted indirect comparisons in small samples implies a difficult balance to strike between internally valid comparisons and generalisability to the relevant patient populations. We have discussed this issue before.[91] The estimates of relative effectiveness for sunitinib derived from this indirect comparative assessment by Pfizer may be relevant to a small group of patients, those that are represented in both the A6181111 and RADIANT-3, but may not be generalisable to the subgroup of patients not represented in RADIANT-3 but present in A6181111. Thus, while Pfizer presents its findings as improved evidence upon the previous study by Novartis on the basis of their use of additional variables for matching the samples from the two trials, any additional variable used for matching reduces the generalisability of the MIAC findings to the original A6181111 population. This is in addition to the limitations due to increased sampling uncertainty, which as Pfizer notes increases as the effective sample size declines with increased variables on which to match.

As Pfizer acknowledges, the MAIC of OS between sunitinib and everolimus is affected by high levels of uncertainty, due to the lack a within trial placebo control available for indirect comparison, and the problems of sample size. Further research is needed that performs a MAIC analysis with a within trial placebo control that is itself adjusted for cross-over to active treatment. Due to the small sample sizes of A6181111, the most fruitful approach would be to match the sample of RADIANT-3 to the population of A6181111 as Signorovitch and colleagues have done,[88] rather than the other way around, which Pfizer has done. This would produce estimates of relative effectiveness with lower levels of uncertainty and risk of bias due to few observations.

Pfizer provided individual patient data on A6181111 to NICE, which the AG used to conduct some sensitivity analyses of their MAIC. [redacted].

5 Assessment of Cost-Effectiveness

5.1 Review of cost-effectiveness evidence

The purpose of this section of the report is to review existing evidence on the cost-effectiveness of sunitinib, everolimus and lutetium relative to chemotherapy or best supportive care in patients with unresectable or metastatic, progressive NETs.

5.1.1 Methods

5.1.1.1 Searches

Bibliographic literature searching was conducted the 19th May 2016 and forward citation searching completed on 17th August 2016. The searches took the following form: (terms for neuroendocrine or pancreatic or gastrointestinal or lung) AND (metastatic or unresectable or advanced) AND (terms for the interventions under review) AND (a costs or economic literature search filter). The search was not date limited, not limited by language and was not limited to human only studies.

The following databases were searched: Medline (OVID), Embase (OVID), NHS EEDs (via Wiley), Web of Science (ISI – including conference proceedings), and Econlit (Ebsco Host). The search strategies are recorded in Appendix 1.

5.1.1.2 Screening

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review (Section 4.1.3), with the following exceptions (as specified in the appraisal protocol):

- Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.)
- Studies that measure only costs but not health benefits will be excluded except for stand alone cost analyses from the perspective of the UK NHS.

Titles and abstracts were screened for relevance by two reviewers (RMM and IT), with disagreements resolved by discussion. Full texts were retrieved for references judged to be relevant and were screened for eligibility by the same reviewers, with disagreements resolved by discussion.

The bibliographies of included studies and review articles, which were not judged eligible for inclusion, were examined by one reviewer (RM) to identify other potentially relevant references. These references were retrieved and checked for eligibility in the same way as full texts from database searches.

5.1.1.3 Quality assessment

Studies meeting the criteria for inclusion were assessed by one reviewer (RMM) using the checklist developed by Evers et al. (2005).[92] Studies based on decision models were further quality assessed using the checklist developed by Philips et al. (2004; 2006).[93, 94]

5.1.1.4 Synthesis

Economic studies were summarised and synthesised using tabulated data and narrative synthesis.

5.1.2 Results

5.1.2.1 Identified studies

The electronic database search for cost-effectiveness evidence identified 1143 records and 6 additional records were identified by other means. After de-duplication 896 records remained, all of which were screened by title and abstract. Of these, 30 full texts were assessed for eligibility. Eight of these were deemed to meet the eligibility criteria for the review. The study selection process is detailed in Figure 32.

Four of the eight full texts were journal articles and the remaining four were posters presented at conferences. Three of the four articles were full economic evaluations (Casciano et al. 2012; Muciño-Ortega et al. 2012, Walczak et al. 2012).[95-97] One journal article (Marty, Roze and Kurth, 2012)[98] was an analysis of costs of administration of lanreotide and octreotide; due to the limited scope of this study and since the revision of the NICE scope removed these two treatment options from the present technology assessment review, this study was excluded from the review. Of the four identified conference poster presentations, two reported full economic evaluations (Johns et al. 2012, Soares et al. 2011)[99, 100]. The remaining two posters were evaluations of lanreotide and octreotide (Ayyagari et al. 2016, Roze et al. 2011)[101, 102], one of which (Roze et al, 2011)[102] was a preliminary report of the excluded article (Marty Roze and Kurth, 2012)[98] and was therefore excluded; the other poster reported a full economic evaluation (Ayyagari et al. 2016)[101] and was reviewed for its methodological content but without considering its results given their irrelevance to the revised NICE scope. Given the limited evidence found and since no recent conference abstracts were found that reported economic evaluations update searches were not conducted.

The three included studies reported in peer reviewed journal article form were evaluations of treatments for pNETs; one study was an evaluation of sunitinib versus everolimus in the US healthcare setting (Casciano et al. 2012)[95], another was an evaluation of sunitinib versus best supportive care in the Mexican healthcare system (Muciño-Ortega et al. 2012)[96] and the third study was a comparison of sunitinib versus best supportive care in the Polish healthcare system (Walczak et al. 2012)[97]. One of the two studies presented in conference posters was an evaluation of sunitinib versus best supportive care for pNETs patients in Scotland and Wales (Johns et al. 2012)[99] and the other study investigated the same question for the Portuguese healthcare system (Soares et al 2011).[100] The third poster, included only for methodological review, was the only one report of those found in poster or journal article form that related to an economic evaluation of treatments for Gastrointestinal NETs (Ayyagari et al. 2016).[101]

Table 74 describes the characteristics of included studies. All studies were sponsored by the industry or co-authored by an individual person affiliated with a company manufacturing or commercialising one of the evaluated treatments.

Figure 32: PRISMA Flow Chart

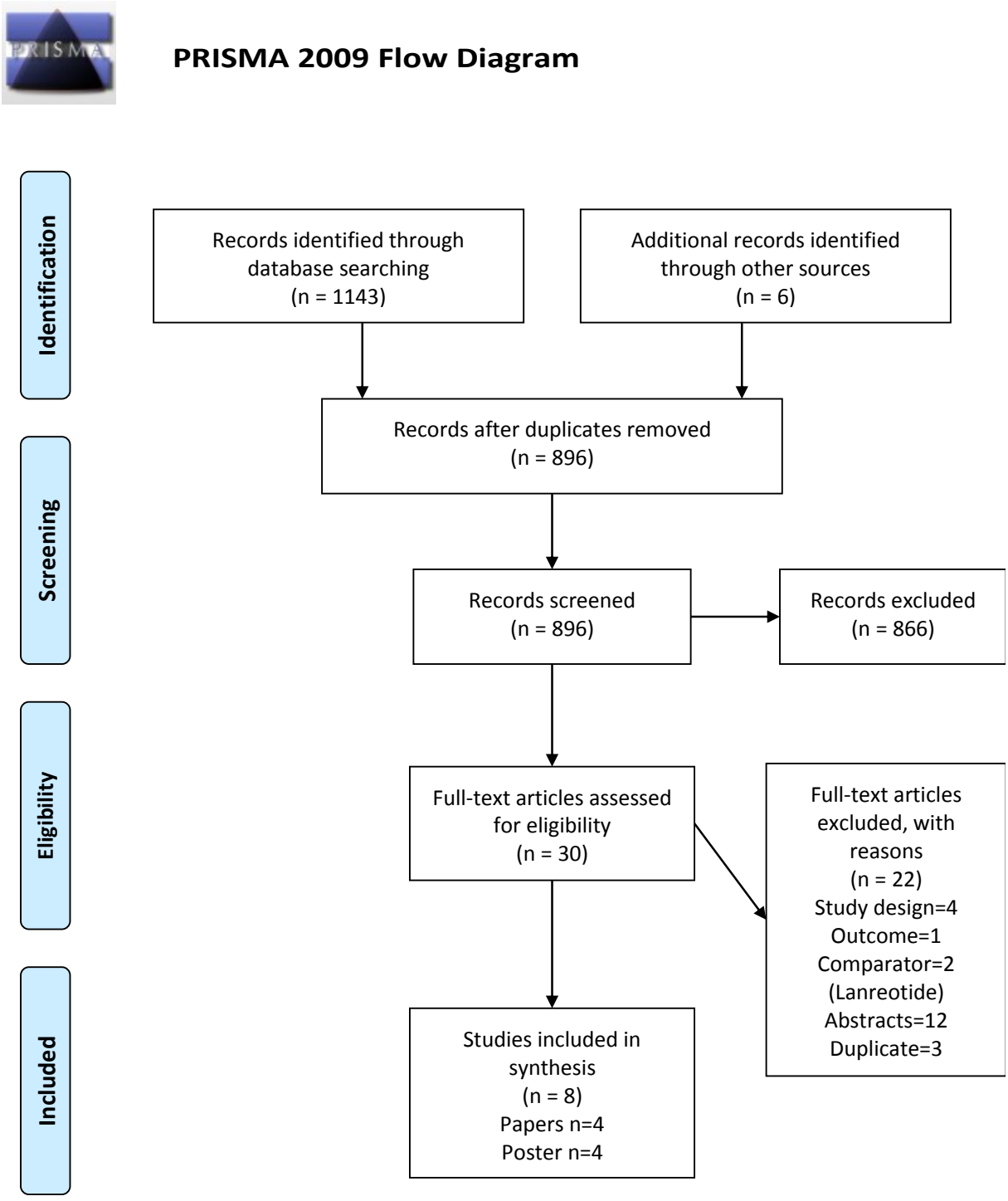


Table 74: Characteristics of submitted models

Author	Country	Regimens	Population	Study type	Perspective	Outcomes considered	Horizon	Model based?	Sponsor
Casciano et al. 2012[95]	US	Sunitinib vs Everolimus	Advanced (i.e. unresectable and/or metastatic) progressive pNETs (mean years)	Cost-utility analysis	Hospital	Total healthcare costs per patient Cost per QALY gained	20 years	Yes	Funded by Novartis
Mucino-Ortega et al. 2012[96]	Mexico	Sunitinib with Best supportive care vs. Best supportive care only	Advanced well-differentiated pNETs	Cost-utility analysis	Mexican Public Social Health Insurer Institution, IMSS	Total health care costs per patient Cost per QALY gained	10 years	Yes	Funded by Pfizer
Walczak et al. 2012[97]	Poland	Sunitinib with BSC vs. BSC only	Advanced well-differentiated pNETs with disease progression	Cost-utility analysis	Public payer for health services, Polish National Health Fund and the patient's	Total health care costs per patient Cost per QALY gained	Lifetime	Yes	Funded by Pfizer
Johns, Eatock and Johal 2012[99]	UK	Sunitinib with BSC vs. BSC only	Advanced pNETs	Cost-utility analysis	NHS	Total care costs Cost per QALYs gained	10 years	Yes	Funded by Pfizer

Key: BSC: Best supportive care; pNETs: pancreatic neuroendocrine tumours; QALY: Quality adjusted life year; CEA: cost-effectiveness analysis; CUA = cost utility analyses

Notes: a, Includes studies reporting UK costs and effects without economic evaluation, and standalone cost analyses based in the UK NHS

5.1.2.2 Pancreatic studies

Casciano et al. 2012[95]

The only study comparing targeted therapies evaluated everolimus versus sunitinib in patients with advanced (unresectable or metastatic) progressive pNETs from a US health insurer perspective. In the absence of head to head study of the two treatments, this study was based on the results of a previous indirect comparison of AEs, PFS and OS outcomes with everolimus and sunitinib across their respective pivotal phase III trials (Signorovitch et al. 2013)[88] Data on outcomes of everolimus relative to placebo were those reported in RADIANT-3 trial (Yao et al. 2011)[31] whilst the sunitinib outcomes were obtained from the A6181111 trial.[45]

The analysis modelled the experience of a cohort of patients who receive either everolimus plus BSC or sunitinib plus BSC, from the start treatment until 20 years post-treatment. Patients were assumed to be in an initial stable disease (SD) health state where they could remain until death or experience disease progression and move to a deteriorated health state, progressive disease (PD), with higher costs and lower utility values. In turn those who experience disease progression would, according to the model remain there until death. This model was implemented as a semi-Markov model where patients could move between the three health states (SD, PD and death) in discrete time points every month. In each of these monthly cycles patients would accumulate costs and utilities specific to the health state, and different costs and utilities were accumulated in SD between the two initial treatments (sunitinib and everolimus), whereas costs and utilities in PD and death were the same under the two treatments (death incurred costs and utilities of zero). The study reported that four health states were used, however, two of these were SD states only differentiated by the presence or absence of adverse events, which did not affect the transition probabilities to the other health states (PD or death) but only the costs and utility associated with the cycle. Since the rate of AE varied with each cycle, in effect this was a Markov model of three health states with variable costs and utility pay-offs for the SD state.

Given that transitions in the model were unidirectional (i.e. once a transition to PD from SD occurred the patient could not make a transition back to SD, and after a transition to death the patient remained in such state), the transition probabilities across states with each successive cycle were derived by partitioning survival into overall survival time and survival time free from disease progression. In each cycle, the difference in the proportion of the cohort still alive and that in alive and progression free (i.e. in stable disease) was the proportion who were in the PD state. To estimate the PFS and OS curves for each treatment, the matched-adjusted indirect comparison (MAIC) method was used (Signorovitch et al.2013).[88] In this application, this consisted in weighting individual patient data from one placebo controlled trial (i.e.RADIANT-3 trial of everolimus) to match the distribution of summary baseline characteristics in the other trial (the A6181111 trial of sunitinib, for which no individual patient data were available to the analysts). The resulting weighted placebo-controlled HRs for PFS and OS were applied to Weibull parametric curves of PFS and OS data from the everolimus arm of RADIANT-3. As for AEs, cycle specific event rates were derived from the observed grade 3/4 AEs rates with each successive cycle in the everolimus arm of RADIANT-3, scaled by the overall ratio of pre to post weighted rates of grade 3/4 AEs with everolimus and the ratio of sunitinib event rates to MAIC weighted everolimus rates.

Data on resource utilisation were obtained from a survey of physicians with experience in treatment of NETs in the US, who were asked about the experience of a total of 40 patients recently treated by them (Casciano et al. 2012).[95] The survey differentiated between a baseline stable disease phase, the period following a first disease progression, and the period after a second progression. Data collected covered actual patient management in the baseline and first post-progression periods, which was taken to reflect the SD health state in the model (since the patients population was defined as advanced, progressive NETs), whereas second progression period, which was assumed to correspond to the PD heath state of the model, was mostly based on hypothetical treatment scenarios (Casciano et al. 2012).[95]

Drug acquisition costs for everolimus 10mg/day and sunitinib 37.5mg/day which were given in RADIANT-3 and A6181111 until disease progression or dose reduction or discontinuation due to intolerance, were adjusted for dose intensities of 85.9% and 91.3, respectively. Other costs referred to BSC, which was defined as SSA, physician visits, imaging and lab tests, hospitalised treatment for grade 3/4 AEs, post-progression therapy, and end of life care.

Health state utility values were obtained from a TTO preference elicitation study in heathy individuals of health state descriptors (vignettes) constructed by physicians for the purpose of this economic model evaluation. Values for the SD and PD were elicited as well as disutilities of a selected number of AEs (Swinburn et al. 2012).[103] This was used to calculate a SD utility value constituted by a AE-free utility value common to both treatments from which a weighted average of disutilities according to their AE profiles in RADIANT-3 and A6181111 was subtracted, as well as a PD utility value common to both treatment arms of the model.

Everolimus and sunitinib resulted in mean PFS duration of 1.19 and 1.04 years (0.15 year difference), and 3.30 and 2.85 life years (0.45 year difference). Everolimus increased annually discounted (at 3%) QALYs relative to sunitinib by 0.304 while increased discounted (at 3%) health care costs by $12,673 (in 2014 prices, purchasing power adjusted prices £9276) per patient, corresponding to a cost per QALY gained of $41,702 (£30,524).

Deterministic sensitivity analysis showed that results were most sensitive to the PFS HR, treatment dose intensity, costs of PD, and AEs costs. Probabilistic sensitivity analysis revealed a 69% probability that the incremental cost-effectiveness ratio (ICER) for everolimus was below US$100,000 and that the 95% CI ellipsoid covered all four possible combinations of outcomes (i.e. everolimus: increased costs and increased QALYs, decreased costs and increased QALYs, increased costs and decreased QALYs and decreased costs and decreased QALYs). In this sense the study was inconclusive, although the authors argue that these results suggest everolimus is cost-effective.

Critique

The study's main contribution is the provision of evidence on the costs and health benefits of choosing one of two targeted therapies available to treat advanced, progressive pNETs. It makes a comprehensive account of uncertainty in the available evidence, which emerges primarily from the fact that no direct head to head comparative studies of the two treatments exist and that given the rare nature of the disease and treatment practice heterogeneity, standard methods of indirect comparison (e.g. Bucher et al. 1997)[37] are likely to lead to biased results. The results of this study thus suggest that any comparison between the two treatments is unlikely to lead to conclusive results and that measurement of costs and utility differences is crucial for informing treatment choice in this patient population.

The main limitation of this study is the omission of a BSC arm from the analysis. This is an important omission especially for the adequate interpretation of the extent of uncertainty in the effectiveness and cost-effectiveness evidence. Another key limitation is the source of utility data, which was derived from TTO valuations of health state vignettes formulated by clinical experts as opposed to being derived from HRQoL measurements of patient reported outcomes. Although the authors may have felt justified for their chose of values in the fact that their source of effectiveness data for everolimus, the RADIANT-3 RCT, did not collect such HRQoL patient reported outcomes , the authors could have employed the HRQoL outcomes reported by the RCT source of sunitinib data, the A6181111 trial, with mapping algorithms to derive EQ-5D values. Finally the authors acknowledged the lack of adequate resource utilisation data for progressive disease.

Mucino-Ortega et al. 2012[96]

A study in Mexico compared Sunitinib additional to BSC with BSC alone, using the data from the A6181111 trial.[45] The study used the same three state Markov model structure as the study by Casciano et al. 2012[95], but using a 2 week instead of a 4-week cycle length, to model the costs and QALYs of each treatment over a 10 year period. The study adopted the perspective of the Mexican public health insurance system covering people with current or past history of formal employment. At least one of the co-authors was affiliated to Pfizer, the sponsor of sunitinib.

The effectiveness data to populate model parameters was obtained from a time to event analysis using a Weibull parametric model of PFS and OS data in A6181111. The relative treatment effects of Sunitinib were estimated relative to these models, as proportional hazards (ref). Adverse events rates in the model were obtained from the same trial.

The cost analysis included costs of drug acquisition, medical management, including specialist consultations, laboratory and imaging tests, pain management, and palliative care. The resource utilization data on were obtained from a survey of 15 clinical oncologists from institutions located in four large cities in the country. The unit costs were obtained from government procurement tariffs and public health insurer institution costs of services at the tertiary level.

Health state utility values were obtained from analysis of data collected in the A6181111 trial, using the EORTC-QLQ-C30. Such data were mapped into EQ-5D scores using the linear algorithm of McKenzie and van der Pol (2009).[104] The mapped EQ-5D scores were then analysed in a linear mixed model with covariates for treatment allocation, cycle number and baseline mapped EQ-5D value.

The study found that Sunitinib plus BSC resulted in an extra 1.18 (discounted) life years over BSC alone, and in an extra (discounted) QALYs of 0.70. Sunitinib plus BSC was also more expensive than BSC alone by US$20,854 (£12,925) in 2011 prices (£13,410 reflated to 2015 prices; adjusted for Purchasing Power Parity [PPP], £22,977). The corresponding incremental cost per QALY gained was £29,808 (£18,475; £19,168 in 2015 prices; adjusted for PPP, £32,842). The most influential parameters on these results, in order of importance, were: Routine medical management costs before progression, HR progression free survival, HR overall survival, sunitinib acquisition costs, utility of post-progression health state, and routine medical management costs after disease progression.

Critique

This study's main strengths is its clarity of reporting, in defining the population, intervention, and comparators and the institutional and medical practice context within which the treatments are given. The study clearly presents the derivation of resource use and costs parameters associated with adverse events reported in the trial (Raymond et al. 2011),[45] and heath state utility values from patients' responses to a disease specific (EORTC-QLQ-C30) tool mapped into EQ-5D.

The main limitation of the study is its analysis of overall survival, which did not adjust for cross-over to sunitinib in patients on the placebo arm. Cross-over occurred in 69% of patients under placebo (Johns, Eatock and Johal 2012);[99] since the relevant comparison in this analysis is between a state of their world where Sunitinib is available and the alternative where it is not, the analysis is likely to underestimate life years and QALY gains by sunitinib over BSC (provided sunitinib extends life and disease progression-free life). The study did not account for subsequent treatments; this information was not collected in the trial (Pfizer communication through NICE October, 2016).

Another limitation of this study is its reliance on a panel of oncologist' opinions to obtain resource use quantities of medical management, which turned out to be one of the most important sources of uncertainty in the study. The study did not analyse the extent of structural uncertainty in results; there is no report of any testing for the proportional hazards assumptions on which the results heavily rely and there was no sensitivity analyses performed using different parametric functions to extrapolate the overall survival and progression free survival curves.

It is an open question, therefore, whether the estimated extension of life free of disease and overall life extension found by this study of 0.49 and 1.18, respectively, are robust to different parametric assumptions about the distribution of time to such events.

In summary, this study provides evidence on the potential cost-effectiveness of sunitinib relative to BSC in pNETs. However the results on costs and, consequently, cost-effectiveness may be not generalizable to the UK setting due to important differences in relative prices between staff inputs and drug acquisition costs. Nevertheless, the study provides valuable evidence on health state utility values in pancreatic patients.

Johns, Eatock and Johal 2012[99]

The only published cost-effectiveness analysis in the UK is a conference poster presenting the evidence submitted by Pfizer to the SMC in January 2011 and to the AWSMG in March 2011 for the purpose and which resulted in a positive recommendation for the drug as treatment in advanced pNETs in Scotland and Wales. This analysis used the most recent data at the time (and currently) from the Phase III A6181111 trial of sunitinib vs. placebo to model incremental costs and QALY gains using the same methods of Mucino-Ortega[96], but with the addition of an adjustment to overall survival outcomes in the placebo arm for the effect of cross-over to sunitinib in the blinded and extension phases of the study (ref).

It is reported that adjustment of OS data for cross-over using the RPSFT model resulted in a HR at the latest cut-off date of 0.499 (95%CI: 0.351-0.947), citing a conference abstract source (Valle et al. 2011).[105] However, it was reported that the CEA analysis was based on an estimate of RPSFT model HR 0.24 (95% CI: 0.08-1.07) based on an 'intermediate data cut' dated December 2009 and citing 'Pfizer data on file' (Johns, Eatock, Johal 2012)[99]. This analysis used a proportional hazards model for both PFS and OS time to event analyses, where PFS was analysed using a Weibull parametric regression form with a binary covariate

indicating the randomly allocated treatment group, and where OS in the sunitinib arm was modelled using a Weibull form and the placebo OS outcomes were obtained from applying the HR from RSFTM to the Weibull placebo distribution. However, the Weibull parameters values used to extrapolate PFS and OS rates in the model were not reported.

It is reported that the probabilities of AEs and treatment discontinuation were obtained from the A6181111 trial. Resource utilisation data for BSC and AE management, where only Grade 3/4 events were considered, were obtained from UK clinical expert opinion, without citing sources. Utilities were obtained from mapping the EORTC-QLQ-C30 patient data from A6181111 into EQ-5D using McKenzie and van der Pol's algorithm (McKenzie and van der Pol 2009).[104] It was reported that "the mean baseline utility value was 0.73 for the sunitinib plus BSC and placebo plus BSC arms" and that the 0.60 used for the PD phase in both arms, was the mean utility value of those measured during the last study cycle for patients who experienced disease progression. The quoted statement is unclear about the role the base-line utility value played in the analysis, especially since it is utility values post-baseline and before progression which are relevant to estimate utility in the SD phase.

The study reported that sunitinib increased discounted PFS years, discounted life years and discounted QALYs by 0.53, 2.33 and 1.39, respectively, whilst it resulted in incremental costs of £31,416 (in 2010 prices), almost two third of which was due to sunitinib drug acquisition. The resulting ICER was £22,587 (£24,244 at 2015 prices). Besides the use of ITT values of OS HR as opposed to cross-over adjusted values, which was most influential, parameters to which results were most sensitive included the post-progression utility, sunitinib acquisition cost, and the PFS HR. The authors state that the results were robust to variations in assumptions about concomitant SSA use and parametric forms used to extrapolate OS and PFS.

Critique

The limited information available on this study prevents assessing its quality. Indeed, it is not possible to replicate the results with the information presented in the poster, since, for example, the Weibull parameter values used to extrapolate PFS or OS curves in the model were not reported. It is noteworthy that this study adjusted placebo OS outcomes for cross-over to sunitinib, although their reported choice of data cut-off date appears to be different from the latest. This study suggests that adjustment for cross-over from placebo to the targeted treatment in RCTs in this area may determine whether a treatment is cost-effective.

On the other hand, the study suffers from their omission of everolimus as a competing treatment option. The methods used to estimate utilities were not clearly presented, although results presented in the Tornado sensitivity analysis appear to imply that they followed those detailed in Mucino-Ortega (2012).[96] In common with other studies, this analysis suffers from the lack of actual resource use data, as it was based entirely on experts' opinions in this regard. According to these results the cost per QALY gained with sunitinib may be between £20,000 and £30,000.

Walczak et al. 2012[97]

The same study question has been investigated from a Polish Health Payer's perspective in a separate study by Pfizer (Walczak et al. 2012).[97] This study provide a detailed account of their use of systematic methods to search for the effectiveness evidence on sunitinib compared with BSC, following principles in the Cochrane Collaboration and the National Polish Agency for HTA. The search was conducted in March 2012. Only one study, the

A6181111 trial, met the inclusion PICOS criteria requiring effectiveness, safety and HRQoL outcomes reported by head to head RCT of the two treatment options for advanced, progressive pNETs conducted in parallel groups.

The Polish study adopted the same Markov and partitioned survival analysis method of modelling the costs and health outcomes as in the analysis submitted to the SMC and the AWSMG in 2011 by Pfizer and reported by Johns and colleagues (Johns, Eatock and Johal 2012).[99] Also as in Johns and colleagues' study, the Polish analysis adopted the estimates of OS effectiveness based on an interim data cut-off date of April 15, 2009,[45, 106] with HR of 0.18 (95% CI: 0.06 – 0.68) as opposed to the latest estimates available at the time with cut-off date of June 2010 (Valle et al. 2011),[105] which resulted in HR 0.49 (95% CI: 0.35 – 0.94) based on the RPSFT model. The (inverse) HR was applied to extrapolated OS rates obtained from a parametric Weibull function fitted to the sunitinib arm, to derive the placebo curves that would have occurred in the absence of cross-over (counterfactual placebo OS rates). The authors reported that a Weibull function with a binary treatment indicator was fitted to the PFS data from A6181111 to extrapolate PFS rates in the two trial arms, and ultimately partition OS time into SD and PD, which equals the difference between extrapolated 0S and PFS rates. However, the authors reported the following parameter values (Table 75), which suggest Weibull functions were fit to each arm separately:

Table 75: Parameter values (95% CI) for Weibull extrapolating models of PFS and OS in base-case pNETs

		Walczak et al. 2012		Casciano et al. 2012	
		Sunitinib	BCS	Sunitinib	Everolimus
PFS	Shape	0.79	1.16	1.195	1.195
	Scale	19.89 [1]	6.31 [1]	7.27 [2]	6.103 [2]
	Mean years	1.89	0.49	0.97 [4]	1.15 [4]
OS	Shape	1.63	1.63	1.379	1.379
	Scale	40.04 [1]	7.20 [1]	5.88 [2]	7.263 [2]
	Mean years*	2.98	0.54[5]	2.89 [3]	3.57 [3]

Notes: [1] Scale in months, as reported in Walczak et al. 2012; [2] Scale in days, as reported in Casciano et al. 2012. [3] Figures are based on integral of the survival Weibull formula; i.e. the gamma function which overestimates mean survival as it extends over infinite time horizon; to see the extent of the inaccuracy, compare results on mean years of OS for everolimus in this table and those reported by Casciano, which are summarised in Table 77 i.e. 2.89 vs. 2.85, respectively; i.e. an overestimation of 1.4%. The percentage overestimation of Walczak's figures is similarly small although larger than those of everolimus in Casciano, since Walczak's time horizon is shorter than Casciano's, i.e. 10 years vs. 20 years. [4]These figures contrast with Casciano's which reports mean years of PFS of 1.19 (14.35 months) and 1.04 (12.51 months), for everolimus and sunitinib. [5] The study reported using a HR of 0.18. Using the latest HR estimate referred to by the authors, 0.499 (Valle et al. 2011) results in a mean life expectancy of 1.49.

In terms of costs drug acquisition, administration, diagnostic and monitoring (including CT every two months for the first six months and every three months thereafter until disease progression), SSA use, BSC, Grade 3/4 AEs management and palliative care were measured. Sunitinib and SSA treatment costs were measured using median treatment duration, which was stopped due to AE, disease progression or death, and alternatively, treatment duration until disease progression was used in scenario analysis. A compliance rate of 91.3% defined as administered relative to the number of planned doses at 37.5 mg daily was used and obtained from the main trial report.[45] End of life care was also measured, as the costs of hospice at home care for the last week of life.

The study found that sunitinib with BSC had an extra 0.98 QALYs and an ICER of €20,441 (£33,866 at PPP in 2005 prices) per QALY gained relative to BSC only. The parameters to which results were most sensitive to the duration of sunitinib use.

Critique

The study documents a systematic search of the RCT literature comparing sunitinib versus BSC, which identified only one study, the phase III A6181111 trial. The authors reported a detailed assessment of the quality of this study and account of the main findings.

A strength of this study is its application of a method to adjust OS outcomes for cross-over of patients in the placebo arm to the targeted therapy arm in A6181111. However, the authors reported their use of an estimate of OS effectiveness based on trial data from a cut-off date of 2009 when an updated 2010 estimate, which was less favourable to the targeted treatment, was available.

In common with other economic studies funded by Pfizer and reviewed here, this study omitted a relevant comparator, everolimus. The RADIANT-3 trial may have been identified by the systematic search had it been designed to include such targeted therapy.

As other studies in NETs, this evaluation suffered from its reliance on a Weibull function to extrapolate PFS and OS outcomes beyond the end of the trial. For the OS analysis this methodological choice may have been determined by the need to use a parametric extrapolating function that was consistent with proportional hazard assumption so that the available estimate of effectiveness estimate, which was in hazard ratio form, could be adopted in the analysis. For PFS however, no such justification existed, as there was no cross-over adjustment to deal with, and the authors should have provided at least a sensitivity analysis of the parametric extrapolation functions used for each arm.

The study also lacked adequate reporting of model inputs on the duration of sunitinib treatment use in the model, and of model outputs in terms of life years and mean PFS time.

Overall, this study is the only complete study report of an economic evaluation in Europe. However, given the different country setting and relative prices that it corresponds to, and the limitations of the report itself, the evidence provided by this study is of limited value to guide decisions in a UK NHS context.

5.1.2.3 GI studies

The only study identified in the GI location evaluated lanreotide relative to octreotide, both of which are out of the NICE scope for the current assessment (Ayyagari et al. 2016).[101] For the present purposes, it is relevant that this study adopted the same three health state semi-Markov structure as the analyses in pNETs just reviewed, using a 3 year and lifetime time horizons. This was presented in a conference poster format and given the limited information thus provided is not subject to any formal critique.

Table 76: Characteristics of included studies

Study	Population	Comparators	Horizon	Model structure	Health states/events modelled	Utilities	Costs	Key individual parameters (sensitivity analysis)	Source of effectiveness parameters	Comments
Casciano et al., 2008[95]	Advanced pNETs US	Everolimus vs Sunitinib	20 years	Semi-Markov – partitioned survival with monthly cycles Proportional hazards model PFS and OS with baseline Weibull form	-SD without AEs - SD with AEs -PD -Death	SD with no AE SD with AE: Everolimus SD with AE: Sunitinib DP Death (0)	Drug acquisition and administration For each health state (entry and follow-up states): Symptomatic care Procedures/tests Physician visits Hospitalisations. Also post-progression treatments Death (end of life care).	-PFS HR -Active treatment dose intensity -Post-progression treatment costs -Adverse events costs	HR: MAIC of HRs of (updated) A6181111 RCT (Sunitinib) vs. RADIANT-3 (Everolimus) outcome data [Signorovitch et al. 2012]	Discount rate Did the model adjust for treatment crossover in all arms? Were PFS, OS and treatment duration estimated from publicly available data? Were the mean treatment cycles provided?
Mucino-Ortega et al. 2012[96]	Advanced well-differentiated pNETs Mexico	Sunitinib with BSC vs. BSC	10 years	Markov - partitioned survival with 2-weekly cycles Proportional hazards model PFS and OS with baseline Weibull form	-SD -PD -Death	Treatment specific SD values from mapping EORTC-QLQ-C30 data from A6181111 into EQ-5D (Raymond et al. 2011) with McKenzie & van der Pol 2012 algorithm	Drug acquisition Adverse event management For each health state: Procedures/tests Physician visits Palliative care. The source of resource use data was a survey of 15 oncologists in public hospitals of 4 different cities	HR PFS HR OS Cycle costs of routine care before progression Acquisition costs of sunitinib per cycle Utility of post-progression	HR A6181111 RCT for OS and PFS	Discount rate 5% The model did not report adjustments for cross-over in any treatment arm PFS and OS were estimated from the publicly available data from main trials
Walczak et al. 2012[97]	Unresectable or metastatic, well differentiated pNETs with disease progression Poland	Sunitinib with BSC vs. BSC	Lifetime	Markov – partitioned survival with 4 weekly cycles Proportional hazards model PFS and OS with baseline Weibull form	-SD -PD -Death	Treatment specific SD values from mapping EORTC-QLQ-C30 data from A6181111 into EQ-5D (Raymond et al. 2011)	Direct medical costs: sunitinib, the administration of the drug, diagnostic and monitoring, somatostatin analogues, BSC, Grade 3/4 severe AEs, palliative care and end of life care.	Sunitinib treatment duration	OS, PFS HRs in A6181111 RCT (data at 2009 cut-off)	Discount rate of 5% for costs and 3.5% for QALYs OS RPSFTM adjusted for cross over Systematic review of the effectiveness, safety and HRQoL literature; date of search: March 2012

John, Eatock, Johal 2012[99]	Advanced or metastatic pNETs	Sunitinib with BSC vs. BSC	10 years (described as 'lifetime')	Markov - partitioned survival Proportional hazards model PFS and OS with baseline Weibull form	-SD -PD -Death	Treatment specific SD values Mapping EORTC-QLQ-C30 data from A6181111 into EQ-5D (Raymond et al. 2011) with McKenzie & van der Pol 2012 algorithm	Drug acquisition Grade 3/4 Adverse event management BSC patient management Outpatient visits CT scans End of life care	OS: ITT vs. Cross-over adjusted Utility PD Sunitinib Drug acquisition HR PFS	HRs of (updated) A6181111 RCT (Sunitinib)	Discount rate 3.5% OS RPSFTM adjusted for cross-over Cycle length not stated

Table 77: Results of cost effectiveness studies

Study	Regiments compared	Patient characteristics	Time horizon	PFS years	Life years (un-discounted)	Mean treatment duration (months)	Discounted incremental QALYs	Discounted Incremental costs (£)	ICER Incremental cost per QALY	Notes on ICER
Casciano et al. 2012[95]	Everolimus vs Sunitinib	As in A6181111 (Sunitinib) by MAIC	20 yrs	Eve: 1.196 Sun:1.043.	Eve: 3.29 Sun: 2.85	Eve: 11.896 Sun: 10.967	0.304	US$12,673	US$41,702	Costs & ICER are adjusted to 3.5% discounting of costs and life years gained, and are in 1999 prices Was treatment duration also based on MAIC?
Mucino-Ortega et al. 2012[96]	Sunitinib+ BSC vs BSC	As in A6181111 trial	10 years	Sun+BSC: 1.02 BSC: 0.52	Sun: 2.76 BSC: 1.58 (discounted)	NR	0.70	US$20,854	US$29,807	Costs, QALYs & ICER are discounted at 5% annual rate, and prices are in 2011 US dollars
Johns, Eatock and Johal 2012[99]	Sunitinib+ BSC vs BSC	As in A6181111 trial	10 years	Discounted TTP: Sun+BSC: 1.10 BSC: 0.57	Discounted: Sun+BSC: 3.49 BSC: 1.16	NR	1.39	£31,416	£22,587	Costs, QALYs & ICER are discounted at 3.5% annual rate, and prices are in 2010 £s
Walczak et al. 2012[97]	Sunitinib + BSC vs BSC	As in A6181111 trial	Lifetime	NR	NR	NR	0.98	€21,770	€20,441	Costs discounted at 5%, QALYs discounted at 3.5%. Prices according to Polish National Health Fund regulations applicable in 2012 (exchange rate with Euro from 2011) Median duration of drug use, accounted for discontinuation due to an AE, disease progression and death, was used to estimate the cost of sunitinib and somatostatin analogues

Table 78: Evers checklist (Evers 2005) –Review of published economic evaluation studies

		Casciano et al. 2012[95]	Mucino Ortega et al. 2012[96]	Walczak et al. 2014[97]	Ayaggari, et al. 2016[101]
	Location	**Pancreatic**	**Pancreatic**	**Pancreatic**	**GI**
1.	Is the study population clearly described?	No	Yes	Yes	Yes
2.	Are competing alternatives clearly described?	Yes	Yes	Yes	No
3.	Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes
4.	Is the economic study design appropriate to the stated objective?	No	Yes	No	Yes
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	No	No	No	Yes
6.	Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes
7.	Are all important and relevant costs for each alternative identified?	No	No	Yes	No
8.	Are all costs measured appropriately in physical units?	Yes	No	No	Yes
9.	Are costs valued appropriately?	Yes	Yes	Yes	Yes
10.	Are all important and relevant outcomes for each alternative identified?	No	No	No	No
11.	Are all outcomes measured appropriately?	No	No	No	No
12.	Are outcomes valued appropriately?	No	Yes	No	No
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	No	Yes	Yes
14.	Are all future costs and outcomes discounted appropriately?	Yes	Yes	No	Yes
15.	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Yes	Yes	Yes
16.	Do the conclusions follow from the data reported?	Yes	Yes	Yes	Yes
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?	No	No	No	No
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	No	No	No	No
19.	Are ethical and distributional issues discussed appropriately?	No	No	No	No

6 Critical Appraisal of Company Submissions

Two companies submitted economic models to NICE, AAA and Novartis. Novartis submitted an economic evaluation in patients with pNETs and, separately, patients with GI and Lung NETs. AAA presented an economic evaluation in pNETs and another in midgut carcinoid tumours. Pfizer did not submit a cost-effectiveness model; it stated that "Previous technology appraisals (SMC and AWMSG) have challenged the data limitations relating to uncertainty associated with modelling the clinical OS benefits of sunitinib in PNET due to the extensive crossover of patients in study A6181111. Because A6181111 is the only clinical trial for sunitinib in this indication, the limitations in the data for certain key model attributes remain. For these reasons, any cost-effectiveness evidence submitted would continue to be associated with considerable uncertainty." (Pfizer submission, p. 84).

6.1 Novartis submission

6.1.1 Economic evaluation of everolimus in pNETs

6.1.1.1 Overview

In pNETs, the company evaluated everolimus with BSC relative to sunitinib with BSC. The company based this analysis on an indirect treatment comparison of results in RADIANT-3, a phase III pivotal trial of the everolimus 10mg once daily with BSC versus placebo with BSC, and the A6181111, a phase III RCT of sunitinib [redacted] with BSC relative to placebo with BSC. These RCTs were the only available relevant evidence identified from a systematic review of RCTs and non-RCTs of everolimus, sunitinib or 177Lu-DOTATATE for treating patients with advanced, metastatic or inoperable pNETs, and 177Lu-DOTATATE for advanced, metastatic or unresectable GEP-NETs. The company did not provide reasons for omitting BSC from the analysis, for which head-to-head trial data were available against each of the targeted treatments in RADIANT-3 and A6181111.

The ITC of everolimus and sunitinib found no statistically significant differences in PFS and OS outcomes, with estimated differences having wide confidence intervals. The company found that everolimus had a lower frequency of grade 3/4 AEs and different tolerability profile (see section 4.2 above).

Everolimus was found to dominate sunitinib. It generated lower discounted costs and more discounted QALYs, which were calculated on the assumption that the two treatments produced the same mean PFS and OS. Since the model assumed only two disease states, stable disease and disease progression, and utilities in the latter state were assumed to be the same across treatments, the QALY differences rested on the health state utility in stable disease under the two treatments, which in turn reflected their differences in toxicity and AEs. Critically, these utility values were based on clinical experts' valuations of health related quality of life descriptors (vignettes) of stable disease in general and the impact of treatment specific AEs, as opposed to health-related quality of life outcomes in actual patients.

6.1.1.2 Efficacy, effectiveness and safety evidence

The systematic review by Novartis involved searching major electronic libraries (see section 4 and section 5 from company submission) on 21 July 2016, as well as hand searches of

conference proceedings on 8 August 2016. The two identified trials are described before in this report (section 4.2). Here only the major results and design features for the purposes of economic analyses are summarized.

RADIANT-3, a phase III double blind RCT, assessed everolimus 10mg given orally and with BSC relative to matched placebo with BSC in 410 adult, mTOR inhibitor-naïve patients with progressive and advanced pNETs. They were randomised on a 1:1 ratio to the two treatments, in stratified fashion according to their baseline status in terms of prior chemotherapy (receipt vs. no receipt), and WHO Performance Status (0 vs. 1/2).

According to the effectiveness section of the Novartis submission, the median follow-up period in RADIANT-3 was 17 months, with median treatment durations of [redacted] for everolimus versus 3.74 months with placebo. However, in the economic analysis section, 6.5.2.2, the median treatment duration with everolimus is reported as 8.61 (Novartis submission, p. 101). At the time the primary publication was written (cut-off date 28 February 2010) 32% of patients in everolimus group and 13% of patients in the placebo group were still receiving the allocated treatment; 44% in the everolimus group had stopped due to disease progression and 80% in the placebo group had done so for the same reason (Yao et al. 2011).[31]Patients in the placebo arm whose disease subsequently progressed were eligible to cross-over to open-label everolimus. Of those patients initially randomized to placebo 85% received open-label everolimus. Further, both trial arms included a BSC, which involved SSA use in 37.7% and 39.9% of patients in the everolimus and placebo arms.

The primary analysis (based on assessment by local investigator) found that median PFS in everolimus was 11.0 (8.4-13.9) versus 4.6 (3.1-5.4) months for placebo, and a HR for disease progression or death with everolimus of 0.35 (95% CI: 0.27 – 0.45). The assessment by central review found a HR of 0.34 (95% CI: 0.26-0.44). The final OS analysis, which was unadjusted for cross-over to everolimus, performed with data available on 5th March 2014 produced median OS of 44.0 months for the everolimus group versus 37.7 months for the placebo and a HR with everolimus of 0.94 (95% CI: 0.73 – 1.20). The Novartis submission acknowledges that these results “may be confounded due to the high level of cross-over from placebo to everolimus and the receipt of subsequent anti-neoplastic therapies”. In particular, [redacted] of everolimus patients received antineoplastic therapies since discontinuation of study drug, versus [redacted] of placebo patients. Twenty-three percent of patients in the everolimus arm received a targeted therapy and 19.2% in the placebo did so, whilst 29% of patients in each arm received chemotherapy.

The company conducted an OS analysis in which it adjusted for the effect of cross-over from the placebo to the everolimus arm, whether as a result of disease progression or after completing the core phase and entering the open-label phase of the study. The method used for this purpose was the RPSFT model, which assumes the effect of treatment on OS is the same whenever the patient receives the treatment, e.g. at the start of the trial, after disease progression or after completing the core phase of the study. While the duration of follow-up in RADIANT-3 trial was 72-78 months, the RPSFTM analysis effectively required limiting the follow-up to 24 months after the start of treatment and produced a HR of 0.60 (95% CI 0.09 – 3.95).[107]

The other RCT identified by the company’s systematic review was the A6181111 that compared sunitinib 37.5mg daily given with BSC against placebo with BSC. [45] As the RADIANT-3 trial of everolimus, the A6181111 was conducted in patients with progressive, advanced and well or moderately differentiated pNETs, and measured the same primary

outcome, PFS. Likewise, patients randomized to placebo were allowed to cross-over to open-label active treatment, sunitinib, following disease progression. Fifty-one percent of patients in the sunitinib arm (44/86) and 69% of patients in the placebo (59/85) entered the open label extension study.[45] The median treatment duration with sunitinib was 4.6 months versus 3.7 months in placebo. The most common reasons for study discontinuation were disease progression (occurring in 22% of sunitinib and 55% of placebo cases), termination of the trial (48% and 19%) and adverse events (17% and 8%).[45] In a separate report referred to by Pfizer in its submission, it is stated that 38, i.e. two thirds, of placebo patients who crossed-over did so following disease progression, while 21 placebo patients started sunitinib after study closure.[108] (See review of clinical effectiveness results, section 4.2. for details on A6181111).

In the absence of head to head RCT evidence , Novartis resorted to an indirect comparison of everolimus with sunitinib based on their respective relative outcomes against placebo in RADIANT-3 and A6181111 using the method by Bucher.[37] The relative effect on OS was estimated using ITT and, alternatively, RPSFT model-adjusted HRs. For the comparison based on the RPSFT model OS estimates, Novartis cites a HR for sunitinib of 0.43 (95% CI 0.17 – 1.20) without clear reference as to the source. In contrast, in its submission, Pfizer cites a HR for sunitinib relative to placebo of 0.34 (95%CI 0.14 – 1.28).[108]

Novartis reported a PFS HR of 1.08 (95%CI 0.59-1.99; blinded independent review committee) and ITT OS HR of 1.32 (0.81-2.16) and RPFST model-adjusted OS HR of 1.39 (95% CI 0.17-11.72).

The company also found that the HR of SSA use as part of BSC with everolimus was 1.04 (95% CI 0.48-2.26) relative to sunitinib. The company concluded that there was no significant difference between the treatments in terms of these outcomes.

In terms of AEs, the company's Bucher IC analysis resulted in an overall OR of 4.47 (95% CI 0.5-39.4) for an overall rate of grade 3-4 AE of 0.35 with everolimus against an indirectly estimated overall rate of 0.71 with sunitinib. These data were used by Novartis to estimate the relative incidence of AEs and associated costs and utilities in the economic model, by assuming that the adverse events in question only occurred once for each individual. Since the types of grade 3-4 AEs where sunitinib had excess risks over everolimus occurred less frequently (i.e. neutropenia, hypertension, leukopenia and PPE syndrome occurred in less than 1% of patients), than those where everolimus had worse outcomes (i.e. diarrhoea, stomatitis, thrombocytopenia, anaemia, hyperglycemia, fatigue, infections, pneumonitis, nausea, occurred in 3 to 7%), the excess risks estimated by the Bucher method across individual AE categories added up to a larger total with everolimus than sunitinib. Thus, while sunitinib had a higher incidence of any of the 13 grade 3/4 AEs considered, the IC of individual categories produced absolute AEs rates that implied the opposite, i.e. that everolimus was associated with more of any of these events. As described below, the company addressed this contradiction in an ad-hoc manner in the economic evaluation.

In their submission, Novartis also included the results of a published indirect comparative study between everolimus and sunitinib that analysed placebo controlled outcome data from the RADIANT-3 and A6181111 trials using the Matched-adjusted Indirect Comparison (MAIC) method (Signorovitch et al. 2013).[88] A detailed discussion of this evidence is presented in section 4.2. The MAIC PFS HR for everolimus vs. sunitinib was estimated to be 0.84 (0.46–1.53). This estimate was smaller although statistically indistinguishable from the

HR PFS estimate of 0.90 (0.53–1.53) before matching, and from the PFS HR of 1.08 from the Bucher analyses by Novartis cited above.

Matching to the A6181111 trial sample reduced the relative effectiveness of everolimus vs. sunitinib from the unadjusted OS HR of 0.69 (0.46–1.05) to the MAIC OS HR 0.81 (0.49–1.31).

The MAIC of AEs covered 14 categories of grade 3/4 AEs. The MAIC pooled placebo-adjusted OR of sunitinib versus everolimus was 1.37 in the 14 Grade 3/4 AEs analysed by Signorovitch et al. (calculated by the AG); the MAIC pooled OR on the subset of eight AEs included in both the Bucher and MAIC analyses (Neutropenia, Hypertension, PPE syndrome, Diarrhoea, Stomatitis, Thrombocytopenia, Anaemia, Fatigue) was 1.16, was 1.16, which is smaller than the corresponding Bucher IC estimate,1.37 (calculated by PenTAG from data in Novartis submission; see Appendix 9). More importantly, unlike the Bucher IC estimates used by Novartis to populate the economic model, the MAIC AE rate estimates added up to similar totals for sunitinib and everolimus in the subset of common categories (0.38 vs. 0.37 respectively) (In contrast, the Bucher rates were 0.15 vs 0.29, respectively; PenTAG calculations of Novartis data submitted to NICE).

The company concluded that there was no evidence of any difference in terms of PFS, OS, SSA use between everolimus and sunitinib. It also concluded that sunitinib led to a higher risk of Grade 3/4 AEs with a different tolerability profile between the two treatments. This led the company to adopt a base case where both treatments had equal PFS and OS effectiveness. In addition, it cautioned about the potential bias due to heterogeneity between the populations in the trials (RADIANT-3 and A6181111) used in the Bucher IC, which was used as the source of the economic model parameters.

(These AE estimates were obtained from the primary analysis cut-off date of 28 February 2010. In addition, Novartis presented updated results on AE that occurred in the double blind and extension phases of RADIANT-3 with cut-off date of 5th March 2014; see Table 168 in Appendix 5. These are not discussed here as they were not used in the Novartis economic evaluation.

The company also presented CiC data on a non-randomised, unpublished study, the OBLIQUE trial, in advanced pNETs patients treated with everolimus 10 mg in routine practice. The study involved 46 patients who were followed up for 6 months from treatment initiation and measured EORTC-QLQ C30, EORTC-QLQ G.I.NET 21, and the EQ-5D. This study found that HRQoL was maintained over the observation period. In particular, the mean EQ-5D score (95% CI) at baseline was 0.72 (0.67-0.77), 0.67 (0.61-0.73) at 3 months and 0.73 (0.67-0.78) at 6 months. This study is important as it is the only identified source by the AG on utility values of patients on everolimus in the advanced pNETs population (see section 7.1.5.5 on AG's review of utilities). However, Novartis did not discuss how the population from which these utility values were measured differs from the trial populations of RADIANT-3 and A6181111.

6.1.1.3 Novartis review of economic models and their results

Novartis conducted a systematic literature review of economic evaluation studies, including studies on resource utilization, costs and utilities. They identified two studies as relevant to the NICE scope for this assessment, namely, the economic evaluations of sunitinib plus BSC relative to BSC and of everolimus relative to sunitinib or BSC in progressive, advanced pNETs, as reported in previous company submission to the SMC[109, 110] and AMWSG.[111, 112]

One of the identified studies is the poster publication by Johns and colleagues, reviewed in section 5.1 above, which found sunitinib to have an ICER of £22,587 per QALY gained compared to placebo. The other study was the SMC and AWMSG submission on everolimus, which for in the analysis presented for Scotland was found to have an ICER of £14,562 per QALY gained compared to sunitinib and £24,998 per QALY gained compared with BSC; in the analysis for Wales, the respective values were £12,894 and £24,999.

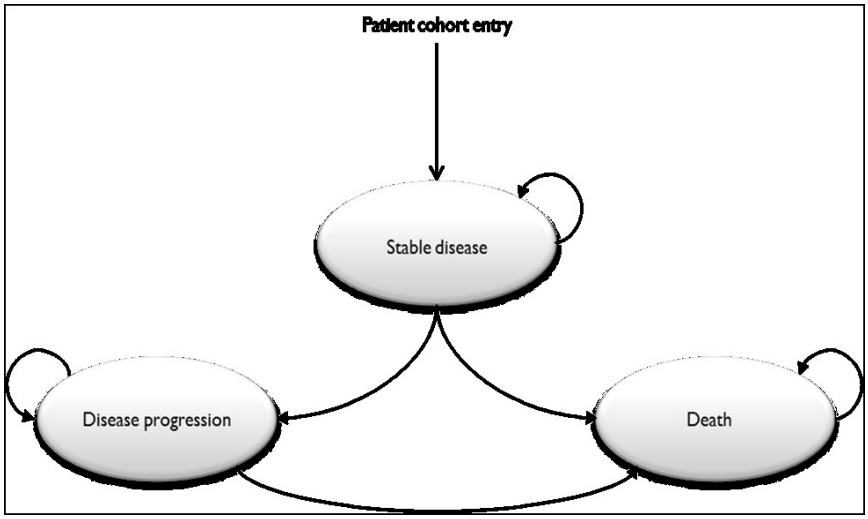
The above evidence is likely to have been outdated by recently updated data and analyses, particularly in relation to evidence adjusted for treatment cross-over, and therefore would warrant updated review and analyses.

6.1.1.4 Novartis economic evaluation

- Description of the model structure, health states, cycle lengths, including a background summary on the sources of evidence (e.g. update to main trial data and indirect comparison evidence) used

Novartis evaluated the costs and health benefits of Everolimus with BSC relative to Sunitinib with BSC in advanced, well or moderately differentiated pNETs patients with progressive disease from an NHS or PSS perspective. A semi-Markov model of monthly health state cycles experienced by a patient cohort was used to synthesize the evidence on effectiveness, resource use, costs and health state utilities, over a period of 20 years following the start of treatment. The main source of evidence was an indirect comparison of PFS, OS, concomitant SSA use, treatment duration, and Grade 3/4 AEs outcomes in the A6181111 trial of sunitinib and the RADIANT-3 trial of everolimus (see Section 4.2.5.2 and section 6.1.1.2). The model consisted in three health states, representing SD, PD or death, each associated with different costs and utilities, as illustrated in Figure 33.

Figure 33: Model Structure in pNETs



Source: Reproduced from Novartis Submission, Figure 6.1

In order to allocate the distribution of patients across the health states for each treatment at a given point in the modelled time, the rate of survival in the patient cohort as obtained from a parametric OS curve fitted to the trial data was partitioned between the two alive health states using a parametric PFS curve also estimated from the trial data for each treatment

arm. Thus in each treatment cycle the residual between the OS and PFS rates was used as the estimator for the proportion of patients in the PD phase.

The resource utilisation data were obtained from a survey of 32 clinical experts in the UK. Health state utility values elicited for a set of vignettes describing health states in pNETs from a sample of members of the general public were used for health states with and without AEs, since no HRQoL or utility data were recorded in RADIANT-3; sensitivity analyses adopted alternative values for the sunitinib arm derived from HRQoL outcomes measured in the A6181111 trial of sunitinib vs. placebo.

The model accounts for the costs of subsequent treatments after disease progression by including a fixed cost of radiotherapy, chemoembolization and chemotherapy use in the first cycle of the progressive disease state of the model. Similarly, a fixed cost of end of life care is included upon transition to the death state.

6.1.1.4.1 Data and Methods

Efficacy and effectiveness data used in the model

The model used parametric curves fitted to the PFS individual patient data from the everolimus arm of RADIANT-3 to estimate the proportion of patients on SD during the observed period in the trial (up to 25 months) and to extrapolate beyond it up to 20 years. The sunitinib arm PFS was estimated by applying estimates of the PFS HR from the ITC analyses described above (see Section 4.2.5.2 and section 6.1.1.2). OS for both treatments was derived using the same approach as for PFS, to estimate the proportion of patients alive and, by subtracting the proportion of PFS at a given time, in the PD state during the 74-month trial observation period and up to 20 years.

Novartis explored different parametric failure time distributions to model PFS and OS of the everolimus arm of RADIANT-3, including the exponential, Weibull, Gompertz, log-normal, log-logistic. To select their base case, three criteria were used: the Bayesian Information Criteria, as a measure of goodness-of-fit that penalises model complexity (i.e. the number of model parameters); the visual fit to the non-parametric Kaplan-Meier curves; and visual fit to the empirical hazard rates (i.e. the instantaneous probability of failure). In addition, for the OS distributions Novartis used external registry data from the SEER database to validate the candidate models; in particular the 15 year survival rate after diagnosis of 6% in SEER was used to judge whether a model extrapolation beyond the end of the trial follow-up was plausible. Finally, Novartis discarded PFS distributions that crossed the preferred OS parametric curve, which turned out to be the Weibull distribution. This led to the choice of the Weibull parametric distribution for the PFS with everolimus, in preference over the log-logistic and log-normal distributions since these crossed the OS curve in the early part of the trial follow-up. Other parametric functions not chosen for the base case were used in sensitivity analyses.

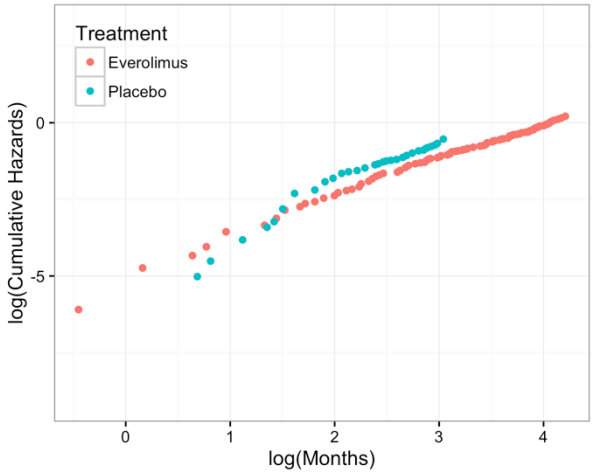
The adopted approach to derive the OS and PFS curves for sunitinib implied the assumption of constant proportional hazards and, as the company acknowledged, that there were no confounders affecting the relative treatment effects between everolimus and sunitinib. In support of the second assumption, the submission states that the available subgroup analyses from both the RADIANT-3 and A6181111 do not suggest that treatment effects relative to placebo are modified by measured characteristics. In support of the proportional hazards assumption, plots of the log cumulative hazard against the log of trial follow-up time

(log-log plots) were presented, suggesting a parallel pattern between the active and placebo arms in each trial.

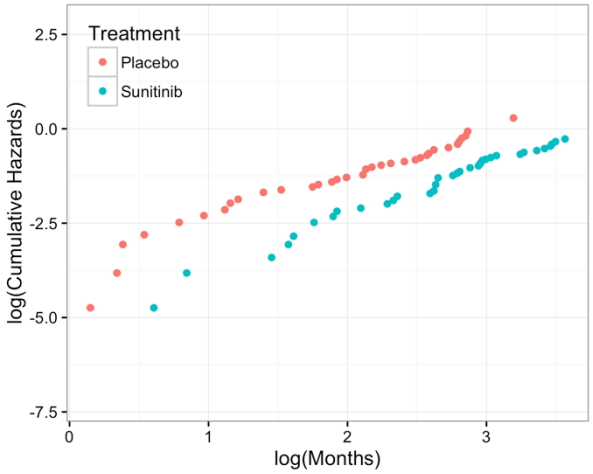
The company warns that because of cross-over to the active treatment in the placebo arms of the two trials, the OS HR derived from the Bucher IC may be biased due to differences in the method used to adjust for treatment cross-over in the RADIANT-3 trial and the A6181111, which was conducted by Pfizer and available only to Novartis from aggregate results submitted to the SMC and AWMSG. In particular, Novartis argues that, as illustrated by the comparative log-log plots of the two analyses (see Figure 34), the extent of recensoring needed for valid adjustment of the placebo arm of RADIANT-3 with the RPSFT method, produced a placebo OS curve (graph on the left) that was much shorter than the corresponding curve for placebo (graph on the right) under the Pfizer RPSFT analysis of A6181111 trial. This led Novartis to propose that Pfizer may not have applied recensoring in their analyses, which is needed for valid estimation of treatment effect.[113] The AG sought to verify this question by requesting from Pfizer the individual patient data and statistical analysis code needed to replicate the company's RPSFT analyses. In response, Pfizer provided the individual patient data without the analysis code, which prevented the AG to replicate and determine whether the RPFST analyses by the two companies were comparable.

Figure 34: Plots of log(-log[survival]) versus log(time) for OS for both arms of RADIANT-3 and A6181111

A. OS RADIANT-3



B. OS A6181111



Source: Reproduced from Figure 6.12 in Novartis submission

On the basis of the Bucher IC results showing that the everolimus vs sunitinib HR for OS (RPSFT adjusted: 1.39, 95% CI: 0.166–11.723) and PFS (local review: 0.833, 95% CI: 0.490–1.417; BIRC: 1.079, 95% CI: 0.586–1.990) had wide confidence intervals around 1, Novartis adopted this value in the base case, i.e. the assumption of no difference in effect between the two treatments in terms of both PFS and OS outcomes.

As discussed early, these OS figures and the log-log plots from A6181111 in Figure 34, are not different from the latest OS results for that trial (Raymond et al. 2016), [108] which are presented by the Pfizer submission to NICE. Using the latest RPSFT-adjusted OS HR for sunitinib vs placebo, 0.34, and the corresponding estimate for everolimus used by Novartis to derive the base case (Bucher) HR of everolimus vs. sunitinib, 0.60, results in a (Bucher) HR

of everolimus vs. sunitinib of 1.76. (Pfizer conducted a MAIC analysis of everolimus versus. sunitinib and resulted in MAIC OS HR of [redacted] although this was derived by matching to the A6181111 population and therefore not comparable to the figures in this section, which are matched to the RADIANT-3 population; Pfizer submission, p. 68; see section 6.1.1.2).

Adverse events

The model measured only the costs and health related quality of life (disutility) effect of treatment-related Grade 3/4 AEs since the "grade 1 and 2 events [observed in RADIANT-3] would not be associated with any meaningful management costs or impact on HRQoL" (Novartis submission, p. 97). An overall AE rate of 7% for the everolimus arm of the model and a 26% rate for sunitinib from cycle 0 to cycle 25 were applied and set to 0 thereafter [Columns P & Q in 'Survival' Novartis pNETs excel model sheet]. While the everolimus rate was obtained from RADIANT-3 trial data, the sunitinib rate was obtained by scaling up this rate according to the OR 4.479 of sunitinib vs. everolimus for any Grade 3/4 AEs from the Bucher IC conducted by Novartis (see section 4.8.2). However, new grade 3/4 data provided by Pfizer as part of its submission to NICE suggests the rate is too high. Updating the Bucher analyses submitted by Novartis with the new Pfizer data results in a pooled Grade 3/4 HR with everolimus of 1.37. In any case, as Novartis acknowledges, the validity of this approach to estimate the economic impact of AEs hinges on the unverifiable and unlikely assumption that patients did not experience multiple instances of the same Grade 3/4 adverse event.

Although the model does not explicitly account for the effect of AEs on treatment use, it included a measure of relative dose intensity for the targeted therapies recorded during the study period in the RADIANT-3 and A6181111 trials.

Similarly, costs of AEs in the model were assumed to apply only to the first 25 cycles. The role of AE in terms of treatment discontinuation was not explicitly modelled but accounted for independently by adjustments to the dose intensity and treatment duration.

Novartis presented additional published estimates on the relative incidence of AEs between sunitinib and everolimus from matched adjusted indirect comparison analysis of AE data from an earlier cut-off point[88] than the data cut-off of the Bucher IC analysis that informed their economic model. Although the two sources may refer to different populations; i.e. the MAIC was adjusted to the A6181111 and Bucher to the RADIANT-3, comparison of the two set of estimates suggests that the Bucher IC leads to misleading AE rate estimates for the cost-effectiveness analyses. However, the company decided not to use the MAIC estimates in the economic analysis since the previous submission to the SMC resulted in the appraisal committee's opinion that the method was "non-standard with uncertainty as to the robustness of this type of analysis". (Novartis submission p. 49). However, the overall balance of Grade 3/4 AE risk implied by the individual AE rates obtained from the Bucher IC was inconsistent with the pooled OR from the same method. Novartis used the Bucher AE rates adjusted for this inconsistency.

The manner in which the difference in the profile of AEs experienced under the two treatment options determined costs and, was the sole factor behind utility differences in the base case, given that everolimus and sunitinib were assumed to have equal PFS and OS outcomes. As discussed in section 6.1.1.2, the rates of individual types of AEs were determined by IC using the Bucher method. This led to differences in Grade 3/4 adverse event rates between the two treatments that were inconsistent with the ranking of the two treatments in terms of pooled

AE: whilst the pooled OR indicated sunitinib was associated with a higher incidence of adverse events, the individual rates for the thirteen AEs considered in the Novartis model combined implied the opposite. To address this contradiction, the company calculated costs and disutilities of AEs as weighted averages of the costs and disutilities associated with managing and experiencing individual AE types, using the Bucher derived individual AE rates as weights. These weighted averages were then multiplied by the overall incidence of any Grade 3/4 in RADIANT-3, for everolimus, and by the Bucher pooled OR, for sunitinib, in their pNETs economic model. Table 79 presents how the disutility of any AEs were calculated. The same approach was used to estimate costs of AEs.

Costs and benefits were discounted at the 3.5% annual rate as indicated by the NICE reference case.

Utility values

The utility values in the model were obtained by a Time Trade-Off (TTO) preference elicitation exercise conducted with 100 members of the general public. Individuals were asked to evaluate descriptors of health states previously designed by clinical experts as representative of those experienced by pNETs patients in routine practice. The analysis was generic in the sense that the vignettes assessed by participants in the exercise were not told about any particular treatment but instead presented with states that described stable disease or progressive disease states, where stable disease was with and without adverse events, including diarrhoea, hand-foot syndrome, hyperglycaemia, nausea/vomiting, pneumonitis, rash, stomatitis, and thrombocytopenia (Swinburn et al. 2012).[103] This study was sponsored by Novartis. A discussion of this study is presented in the review of utility values section 5.1.1.3 and 7.1.5.5.

The company used the disutilities estimated from the preference elicitation exercise to impute treatment specific utility values of stable disease to the two treatments, after applying the weighted average method based on AE rates discussed in section 7.1.5.5. The same PD utility value was applied to both treatment arms. The values of SD with adverse events are summarised in Table 79, which illustrates that the average severity of events experienced with everolimus was marginally larger than that experienced with sunitinib (i.e. 0.647 vs. 0.656).

Table 79: List of AEs and summary of utility values for SD with AEs

Adverse reactions	Mean utility	AE rate (everolimus)	Adjusted rate (everolimus)	AE rate (sunitinib - from Bucher IC)	Adjusted rate (sunitinib)	Adjusted utility (everolimus)	Adjusted utility (sunitinib)
Neutropenia	0.690		0.007		0.224	0.005	0.155
Hypertension	0.643		0.007		0.179	0.004	0.115
Hand-foot syndrome	0.583		0.007		0.113	0.004	0.066
Leukopenia	0.690		0.007		0.113	0.005	0.078
Diarrhoea	0.600		0.092		0.081	0.055	0.049
Stomatitis	0.557		0.189		0.071	0.105	0.039
Thrombocytopenia	0.690		0.111		0.071	0.077	0.049
Anaemia	0.643		0.163		0.010	0.105	0.006
Hyperglycaemia	0.771		0.144		0.079	0.111	0.061
Fatigue	0.643		0.065		0.020	0.042	0.013
Infections	0.612		0.065		0.020	0.040	0.012
Pneumonitis	0.612		0.072		0.010	0.044	0.006
Nausea	0.710		0.072		0.010	0.051	0.007
SD + AE						0.647	0.656

Key: AE: adverse event, SD: stable disease
Source: Reproduced from Table 6.5 in Novartis submission, extended with data reported in Novartis model files

Some of the utility values of SD with AEs in Table 79 were based on assumption. These are described in Table 80, which may be interpreted by comparison with the SD value without AE used in the model, 0.771. The assumption that hypertension, which was not measured in the preference elicitation study, had an average disutility equal to the average of all AEs in SD, 0.128 (=0.771-0.643) is particularly implausible since national EQ-5D data in large samples suggests the disutility of hypertension in patients with cancer in the last 5 years is negligible.[114] The disutility of anaemia, which was imputed the same value as for hypertension, is higher than the 0.085 identified in previous reviews of chemotherapy induced anaemia.[115] Likewise, the imputation of the 0.128 disutility value for all AEs to Grade 3/4 fatigue by Novartis is questionable in view of lower TTO estimates found by previous studies.[115, 116]

Table 80: Mean utility values of SD with specific grade 3/4 AEs included in the model

Adverse event	Mean Utility Vale	SE	Reference/Assumption
Neutropenia	0.690	0.024	Assumed similar to thrombocytopenia
Hypertension	0.643	0.023	Average of all AEs
Hand-foot syndrome*	0.583	0.023	Swinburn *et al.* 2012[103]
Leukopenia	0.690	0.024	Assumed similar to thrombocytopenia
Diarrhoea	0.600	0.025	Swinburn *et al.* 2012[103]
Stomatitis	0.557	0.024	Swinburn *et al.* 2012[103]
Thrombocytopenia	0.690	0.024	Swinburn *et al.* 2012[103]
Anaemia	0.643	0.023	Average of all AEs
Hyperglycaemia	0.771	0.020	Higher than SD with no AE, which is unlikely; thus assumed similar to SD with no AE
Fatigue	0.643	0.023	Average of all AEs
Infections	0.612	0.026	Assumed similar to pneumonitis
Pneumonitis	0.612	0.026	Swinburn *et al.* 2012[103]
Nausea	0.710	0.021	Swinburn *et al.* 2012[103]

Key: AE: adverse event, PD: progressive disease, SD: stable disease
Notes: *Hand-foot syndrome= Palmar-plantar erythrodysesthesia syndrome (PPE)
Source: Reproduced from Table 6.4 in Novartis submission

Table 81: Summary of utility values for cost-effectiveness analysis

Health State	Source			
	Swinburn et al. 2012[103] Utility value: mean (SE)	95% CI	A6181111 Utility value: mean (SE)*	95% CI
SD without AEs	0.771	0.731 – 0.810	NA	NR
SD with AEs (everolimus)	0.647 (0.023)	0.601 – 0.693	0.730 (00.73)	NR
SD with AEs (sunitinib)	0.656 (0.024)	0.610 – 0.702	NA	NR
PD	0.612	0.564 – 0.659	0.596 (0.06)	NR

Key: AE: adverse event, CI: confidence interval, PD: progressive disease, SD: stable disease, SE: standard error, NA: not applicable, NR: not reported *SE not reported for the sunitinib trial values thus assumed to be 10%

Source: Reproduced from Novartis submission Table 6.5; Swinburn *et al.* 2012; [103] Raymond *et al.* 2011[45]

No disutility for end of life care costs was included in the analysis nor any adjustment for the effect of age on background utility considered.

Costs

Novartis included costs of drug acquisition and administration (for first and subsequent treatments and treatments defined as BSC), disease monitoring, management of treatment-related Grade 3/4 AE, and death.

The acquisition costs of everolimus of £2,673.00 for 30 tablets of 10 mg adopted in the model was based on 2016 BNF prices. The company presented analyses with and without a [redacted] PAS discount, which reduced the drug acquisition cost to [redacted]. The costs of everolimus in each (monthly) cycle were calculated as the product of the monthly cost of everolimus acquisition and administration, i.e. a dispensing fee, and the proportion of patients on treatment at each cycle in the everolimus arm of RADIANT-3, where everolimus treatment was given for a median duration of 8.61 months and mean duration of [redacted]. The cost of everolimus was adjusted by the relative dose intensity (RDI) of 85.9% recorded in RADIANT-3, which accounted for everolimus treatment interruptions and dose reductions.

The acquisition costs of sunitinib were £2522.40 for 30 tablets of 37.5 mg, from 2016 BNF prices. The company assumed a PAS whereby sunitinib is given free of charge to the NHS for the first cycle, as is the case in Scotland, and adjusted costs by a RDI of 91.3% as reported for sunitinib in A6181111 (Raymond et al. 2011).[45] In its base case analysis, Novartis assumed that the cost of sunitinib drug acquisition and dispending was incurred for the same number of mean treatment cycles as everolimus, on the basis that their indirect treatment comparison found no difference in PFS duration between the two treatments. This assumption seems untenable in the light of the available data on treatment duration from A6181111 and RADIANT-3. The company performed sensitivity analysis using an alternative figure of 9.66 months of sunitinib treatment duration, which the company attributes to the literature without providing reference. It also cites a submission by Pfizer to the AWMSG where the company is reported to have assumed “patients receive an average of 293 days of treatment per year”. However, in their submission to NICE, Pfizer reported an average duration of sunitinib of 8.3 months in clinical practice (253 days; Pfizer submission to NICE, p. 17). Further, the median treatment duration with sunitinib in A6181111 was 4.64 months (Raymond et al. 2011)[45] as opposed to the [redacted] of everolimus use in RADIANT-3.

The costs of drug administration involved a dispensing fee to cover a hospital pharmacist’s time required to dispense an oral medication, obtained from PSSRU sources, and the costs

of delivering chemotherapies for intravenously administered drugs, from NHS Reference costs. The same administration costs were thus applied to everolimus and sunitinib.

As for the costs of monitoring treatment and disease, data on 13 advanced pNETs (6 well-differentiated and 7 moderately-differentiated) patients, as provided by a survey of 34 UK clinicians, as part of a survey of 197 clinicians in six countries, with experience of treating advanced NETs, was used in the company model. The main publication reporting the methods and findings of the survey is included in the systematic review of cost-effectiveness studies section 5.1.2 (Casciano et al. 2013).[117] The survey asked clinicians about the treatment received and healthcare resources used for the two most recent patients they had treated, for each of three disease stages, including a baseline period, a first progression period and a second progression period. The baseline period was described in the survey as the period following diagnosis with advanced pNETs, up to the first time tumour progression was recorded. The first progression followed the baseline period and ended when the patient was diagnosed with further measurable disease progression of advanced pNETs.

For the purposes of deriving data for its economic analysis Novartis considered the first progression phase as the SD phase of the model, and the second progression as the PD phase of the model. The survey produced actual resource utilisation data on 8 (60%) pNET patients for the SD phase and no patients in for the PD phase. Due to limited available data on NETs in general for the PD phase, the survey asked clinicians to provide hypothetical data on the 13 pNET patients. The majority of patients (n=7; 54%) were in the 51-65 age range and had ECOG 0-1 (n=6; 46% - 4 had no recorded status).

Data were collected via web, on resource use, including clinician visits, procedures and tests (e.g. CT scans, biomarker, including Chromogranin A, and other tests) and hospitalisations. In addition, symptomatic (SSA and other) drug use in SD, and symptomatic treatment and chemotherapy in PD were collected. The clinicians were asked to estimate the duration in SD of patients, whereas for PD they were asked to assume that they would spend 12 months in that state. By dividing the reported amount of resources for the whole SD and PD periods by their respective duration, the average cost of a monthly cycle was derived for use in the model. Since more clinician visits were obtained for the first cycle of the PD phase, the Novartis model allowed for different healthcare costs in the first and subsequent cycles after progression. Unit costs were obtained from NHS Reference costs.

The resulting values used for populating the model are presented in Table 82, which is reproduced from the Novartis submission. It may be seen that 84% of the total healthcare costs in SD, which amounts to £87 (physician visits+ tests + hospitalisations), is associated with physician visits, £55 per month, and CT scans, £18 per month. Life in the PD state for the first month after disease progression generates total healthcare costs of £376 (first cycle), and £170 per month subsequently; the difference is due to 0.4 additional visit to the primary physician and one additional visit to other physicians in the first month after progression. In subsequent months of the PD state, 95% of the costs are due to physician visits, at £106 per month, CT scans, £22 per month, and hospitalisations, £34 per month.

Table 82: Healthcare resource utilisation and costs in stable and progressive disease states

Resource	Unit Cost	Unit	Stable Disease		Progressive Disease 1st Cycle		Progressive Disease Subsequent Cycle	
			Frequency per cycle	Cycle Cost	Frequency per cycle	Cycle Cost	Frequency per cycle	Cycle Cost
Physician visits								
Follow-Up (Primary Phys.)	158.54	Visit	0.274	43.39	0.744	117.91	0.338	53.58
Follow-Up (Another Phys.)	139.99	Visit	0.080	11.27	1.385	193.83	0.378	52.86
Subtotal				**54.65**		**311.74**		**106.44**
Procedures and tests								
Ultrasound	55.17	Procedure	0.024	1.33	0.032	1.77	0.032	1.77
CT	124.53	Procedure	0.145	18.04	0.173	21.55	0.173	21.55
SRS	806.32	Procedure	0.008	6.49	0.000	0.00	0.000	0.00
MRI	181.76	Procedure	0.024	4.39	0.019	3.50	0.019	3.50
Chest x-ray	42.12	Procedure	0.000	0.00	0.013	0.54	0.013	0.54
Neuron-specific enolase (NSE)	1.19	Test	0.000	0.00	0.006	0.01	0.006	0.01
Chromogranin A	1.19	Test	0.056	0.07	0.083	0.10	0.083	0.10
Pancreatic hormone (PP)	1.19	Test	0.024	0.03	0.026	0.03	0.026	0.03
Plasma vasoactive intestinal peptide (VIP) total	1.19	Test	0.016	0.02	0.032	0.04	0.032	0.04
Serum marker	1.19	Test	0.016	0.02	0.026	0.03	0.026	0.03
Ki-67	1.19	Test	0.016	0.02	0.026	0.03	0.026	0.03
5-Hydroxyindoleacetic acid (5-HIAA)	1.19	Test	0.064	0.08	0.083	0.10	0.083	0.10
Plasma Substance P	1.19	Test	0.016	0.02	0.026	0.03	0.026	0.03
Plasma vasoactive intestinal peptide (VIP) total free T4	1.19	Test	0.016	0.02	0.026	0.03	0.026	0.03
CBC blood test	3.01	Test	0.121	0.36	0.179	0.54	0.179	0.54
Blood urea nitrogen (BUN)	3.01	Test	0.121	0.36	0.141	0.42	0.141	0.42
Serum glucose	3.01	Test	0.121	0.36	0.128	0.39	0.128	0.39
Serum creatinine	3.01	Test	0.121	0.36	0.179	0.54	0.179	0.54
Lipid profile	3.01	Test	0.089	0.27	0.077	0.23	0.077	0.23
Subtotal				**32.24**		**29.87**		**29.87**
Hospitalisations								
General hospitalisation	586.93	Hospitalisation	0.000	0.00	0.058	33.86	0.058	33.86
Subtotal				**0.00**		**33.86**		**33.86**

Source: Resource Utilisation Survey conducted in the UK, NHS reference costs 2014/2015[118]

The costs of managing adverse events covered treatment related Grade 3/4 AE that occurred in the SD phase of the model. Only AE that were recorded in >2% of patients in any of the active treatment arms of the A6181111 and RADIANT-3 trials were accounted for. Details on the AE types the methods used for deriving the AE probability estimates for the sunitinib arm, involving the Bucher indirect comparison analysis in section 4.2.5.2, and the duration for which AEs were measured in the model are described in the section on utilities (see section on Utility values; page 194). As described in that section, the AE probabilities were based on the assumption that the AE rates of individual types of AEs were constituted by single events per patient in each trial arm; this was a consequence of Novartis not having access to individual patient data from the A6181111 trial sponsored by Pfizer.

Moreover, as described in the utility section above, the Bucher IC produced sunitinib AE rates whose aggregate magnitude was smaller than the respective magnitude of the everolimus arm in RADIANT-3, whereas the opposite occurred when the count of different AEs was combined to derive an overall AE rate for sunitinib by the same Bucher method. This led Novartis to calculate the disutility and cost of a typical adverse event as a weighted average of the costs of the different AEs multiplied by the relative contribution to the overall sum of AEs rates for each treatment arm in the model. The inputs into this weighted average are presented in Table 83. In line with the weighted average disutility of AEs used in the Novartis model, the costs of a typical AE in the everolimus arm is more expensive, by 15%, than the average costs of an AE under sunitinib treatment. Novartis used this figures with an overall AE OR of sunitinib versus everolimus of 4.47, which used AE counts that differ from those reported by Pfizer in its submission to NICE; with the updated figures, the AG obtains a 1.37 OR estimate instead. Based on the monthly [redacted] probability of AEs with everolimus estimated by Novartis from RADIANT-3 individual-patient data, which the company applied for the first 25 cycles of the SD model phase under everolimus and changed to 0 for subsequent cycles, the Bucher OR estimated by Novartis led to the company's monthly probability of AEs with sunitinib in those cycles of 26%; with the OR calculated by the AG the sunitinib probability is instead 10%.

This means that the costs of the additional risks of an AE with sunitinib are partly offset by the lower severity of its AE, relative to everolimus. Moreover, updating Novartis's data on AEs with sunitinib with data submitted by Pfizer to NICE, reduces the additional costs of AEs with sunitinib. These additional costs decline over time as fewer people in both arms remain in stable disease. Further, in the base case they decline in the same proportion in both arms, since Novartis assume PFS are the same across the two arms, and until cycle 25 (at two years after treatment starts) after which no AEs costs are incurred.

Table 83: Grade 3 or 4 AE rates included in the model and associated costs

Grade 3 or 4 AE	Everolimus				Sunitinib		
	Unit cost (£)	AE rate[1]	Weighted frequency	AE cost (£)	AE rate from ITC*[1]	Weighted frequency	AE cost (£)
Neutropenia	127.70	0.002	0.007	0.83	0.055	0.224	28.60
Hypertension	736.89	0.002	0.007	4.81	0.044	0.179	131.56
Hand-foot syndrome	172.58	0.002	0.007	1.13	0.028	0.113	19.49
Leukopenia	1765.87	0.002	0.007	11.53	0.028	0.113	199.45
Diarrhoea	797.95	0.034	0.092	73.13	0.020	0.081	64.76
Stomatitis	431.84	0.071	0.189	81.78	0.017	0.071	30.58
Thrombocytopenia	643.48	0.042	0.111	71.43	0.017	0.071	45.57
Anaemia	777.82	0.061	0.163	126.98	0.002	0.010	7.70
Hyperglycaemia	1058.07	0.054	0.144	152.38	0.019	0.079	84.02
Fatigue	324.53	0.025	0.065	21.24	0.005	0.020	6.44
Infections	1080.69	0.025	0.065	70.74	0.005	0.020	21.45
Pneumonitis	1934.80	0.027	0.072	138.98	0.002	0.010	19.15
Nausea	79.47	0.027	0.072	5.71	0.002	0.010	0.79
Total				**760.68**			**659.58**

Key: AE: adverse event, ITC: indirect treatment comparison. [1] includes 0.5 correction due to cells with 0 counts.
Notes: *relative frequency calculated from ITC.
Source: Reproduced from Novartis submission, Table 6.11, with revised labels for clarity and correction; see footnotes

The use of symptomatic treatment, defined as SSA, in the SD phase was estimated from the 0.377 rate of use in the everolimus arm of RADIANT and the Bucher IC OR of 1.04 (95% CI: 95% CI: 0.478–2.262) estimated for everolimus vs. sunitinib (Novartis submission, section X, see section 6.1.1.2 above). This resulted in a SSA rate of use with sunitinib of 36.8, which was multiplied by the monthly costs of treatment with SSAs as described in Table 84 below. The costs used by Novartis were based on BNF drug acquisition prices. In contrast, average drug acquisition prices paid by hospitals, as recorded in the eMIT database[119], are 8%-26% lower for the symptomatic treatments considered by Novartis (last column of Table 84). As for symptomatic treatment in PD, a rate of SSA use of 25% was assumed based on the results of the healthcare resource survey of UK experts described above, and 1.9 administrations of octreotide per cycle, at mean daily dose of 30 mcg for the first 15 days and 450 mcg thereafter, and 90% RDI.

Table 84: Costing and dosing assumptions for SSA usage

SSA	Costing assumption	Administration Cost	Costing assumption based on eMIT price[119] (not considered by Novartis model submission)
Octreotide LAR (Sandostatin LAR®)	£799.33	£239.12	£632.40
Octreotide (Sandostatin®) - 500 mg	£14.12	£239.12	N/A
Lanreotide (Somatuline Autogel®) 500 micrograms/mL, 1-mL amp	£736.00	£239.12	N/A
	£27.09	£239.12	£25.10

Key: BNF: British National Formulary, LAR: long-acting repeatable, SSA: somatostatin analogue.
Notes: *Based on 50% of patients receiving octreotide LAR, and 50% lanreotide. In the model it was assumed 39.9% of patients received an SSA, thereby incurring this average total cost.
Source: Reproduced and extended from Novartis submission, Table 6.12 and BNF 2016[32]

Costs of subsequent treatments following disease progression were included for chemotherapy, radiotherapy and chemoembolisation. Information on subsequent therapy

used in the sunitinib arm A6181111 was not recorded in the trial (Pfizer, response to AG data request August 2016). Novartis states that the rates of subsequent treatments used in their model were obtained from those recorded in the RADIANT-3 trial of everolimus vs. placebo, and applied them to both the sunitinib and everolimus arms of the model. However the rates used in the model (reproduced in Table 85) and those observed in RADIANT-3 and reported in the Appendix of the Novartis submission (reproduced in Table 86) do not seem to correspond.

Table 85: Post-progression chemotherapy and procedures estimated utilisation and cost allocated to the initial post-progression tunnel state.

Treatment	Unit Cost (£)	Initial Drug Admin Cost	Subsequent Drug Admin Cost	Number of Cycles	Number of Units Adjusted by Number of Cycles	Proportion of Use	Total
Radiotherapy	2026.86	0.00	0.00	1.27	1.27	0.094	241.39
Chemoembolisation	3993.90	0.00	0.00	0.03	0.03	0.094	12.30
5-fluorouracil	11.20	239.12	326.46	2.50	13.57	0.219	983.32
Doxorubicin	129.78	239.12	326.46	1.66	1.80	0.281	206.87
Streptozocin	0.00	239.12	326.46	2.14	11.61	0.313	1156.84
Total							**2600.72**
Radiotherapy	2026.86	0.00	0.00	1.27	1.27	0.094	241.39

Key: Admin: administration.

Table 86: Subsequent treatments used in RADIANT-3 of pNETs by trial arm

Post-treatment therapy	Everolimus (N=204) N (%)	Placebo (N=203) N (%)
Any post-treatment therapy	[redacted]	[redacted]
Chemotherapy		
Targeted therapy		
Radiation therapy		
Other		
Hormonal therapy		
Immunotherapy		
Surgery		

Source: Reproduced from Appendix to Novartis submission to NICE

End of life care costs were included as a single fixed amount of £4,346 occurring at the time patients died in the model. This figure was obtained from a published study that estimates the per patient health care costs observed in the terminal phase of life of cancer patients in England and Wales, measured from the time when strong opioids are used, and included the costs of elective and non-elective inpatient hospitalisations, outpatient visits, AE attendances, and visits to district nurses and GPs (Round et al. 2015).[120]

Costs were expressed in 2015 prices.

6.1.1.4.2 Results

In the advanced pNETs patients with progressive disease, the base case analysis resulted in 4.17 life years life expectancy over a 20-year time horizon after the start of treatment with everolimus or sunitinib in patients with median age 58 years (as in the everolimus arm of RADIANT-3 trial); everolimus had more QALYs than sunitinib, 2.73 vs 2.71, a difference of 0.02 QALYs discounted at 3.5%. Since this analysis assumed equal PFS and OS outcomes between the two treatments, the QALY difference was purely due to the impact of treatment differences in AEs on health related quality of life.

Table 87: Main results of Novartis model submission in pNETs at current list prices

	Life years (undiscounted)	QALYs (discounted)	Costs	ICER
Everolimus	4.17	2.73	£36,933	Dominant
Sunitinib	4.17	2.71	£38,569	
Difference	0	0.02	£1,636	

Everolimus was associated with discounted healthcare costs of £36,933 per patient, that is, overall savings of £1,636 relative to sunitinib, which had total discounted healthcare costs of £38,569 per patient. With a [redacted] PAS discount applied to the list price of everolimus and reimbursement of the first cycle of sunitinib, the total costs to the NHS of choosing everolimus was reduced to [redacted] and of sunitinib to £36,247, that is, a saving of [redacted] per patient by using everolimus. Since PFS, OS and costs in PD state were the same across the two arms, the costs differences were due to differences of drug acquisition costs of targeted therapies in the stable disease period. As a result, everolimus was found to be dominant over sunitinib. See Confidential Appendix for details on PAS analyses.

Novartis report the total cumulative time spent per patient in SD health state to be 0.899 years under everolimus and 0.878 years under sunitinib (Table 6.18 Cumulative life years by health state, p. 112 Novartis submission). This must be in error since the base case model assumes equal PFS outcomes for both treatments and there is no account in the model for differences in Grade 5 AEs (deaths).

Probabilistic sensitivity analyses with drug acquisition prices unadjusted for PAS produced a mean cost saving estimate with everolimus of £2055 per patient, and a QALY gain of 0.002. With the PAS, the mean cost saving with everolimus was increased to [redacted]. This result suggests that the main determining factor is costs since the mean difference of 0.002 is not considered to be clinically significant.[121] However, these PSAs by Novartis are not adequately performed since the PFS and OS and SSA use (set at zero) parameter values are assumed to be the same rather than differ between the treatments according to their mean estimates in the trial data and their associated sampling uncertainty. Therefore, the claim by the company that "at the £30,000/QALY threshold, there is [redacted] probability of everolimus being cost-effective when compared to sunitinib at their respective PAS prices." should be considered with these reservations in mind.

Consequently, deterministic sensitivity analysis performed by Novartis showed that the most influential parameters are the relative treatment effects on PFS and OS, and the treatment duration, RDI and costs of AEs. However, the company states that the incremental difference is "so marginal, it does not materially affect the model results (Novartis submission, p. 116". Similarly, positive rates of SSAs use, use of PFS local expert assessed vs centrally assessed data, and choice of PFS distribution had marginal impact. The results of scenario analyses exploring the effects of changing clinical effectiveness, utility and cost parameter values as well as structural assumptions about OS and PFS outcomes, produced no changes to the results of everolimus being dominant, except for the case where the relative treatment effect on PFS was set to favour sunitinib according to estimates derived from the Bucher IC (HR PFS 0.93; OS 0.72), in this instance everolimus had lower costs and lower QALYs than sunitinib and the ICER was found to be £[redacted]. The interpretation of the ICER in this case reverses, i.e. the higher the value the more cost-effective everolimus is; it may be reasonable to consider [redacted] in this patient population. It must be noted

that this is the result of everolimus saving £5,963 [redacted] at the expense of having 0.685 fewer QALYs per patient (Novartis submission, Table 6.23 p. 117).

It is noticed that the scenarios explored by Novartis do not cover some major areas of uncertainty, such as variation in the relative probability of AEs, nor structural uncertainty associated with different functional forms for the different treatment arms in each of the PD and SD phases. Nevertheless, given the possibly clinically insignificant utility differences discussed before, or that Novartis may produce less QALYs than sunitinib in exchange for a small reduction in NHS costs, the dominance of everolimus over sunitinib in the Novartis base case analysis is not robust to the sources of uncertainty investigated by Novartis.

6.1.1.4.3 Strengths and Weaknesses in Novartis pNETs evaluation

The model by Novartis follows the NICE Reference case (see Appendix 8) except for one major aspect, which was the lack of inclusion of BSC as a comparator. This omission is at odds with the fact the two RCTs from which the effectiveness data were obtained for the model compared targeted therapy (everolimus or sunitinib) plus BSC with placebo plus BSC. There was no discussion by Novartis on the reasons for their omission of BSC only as a third arm in their cost-effectiveness analysis. However, in the opinion of our clinical experts, BSC is a relevant initial treatment option for patients with advanced, progressive pNETs and small or asymptomatic tumours, in whom active treatment may be considered upon disease progression.

This was a complex area to analyse due to limited data on advanced pNETs patients with progressive disease, which is a natural result of the small incidence of this disease. Evidence on resource use was particularly limited, especially for the progressive disease phase of the model where the quantities used in the model were based on expert opinion. Another major uncertainty in the evidence base is in the lack of HRQoL data measured for everolimus in the patient population of interest here. This ultimately led Novartis to base the comparison of HRQoL and, given the base case assumptions of equal OS and PFS outcomes between the treatments, QALY outcomes between the two treatments on their relative impact on AE incidence and severity. Thus the difference in QALYs was based on values derived from actual patient outcomes but clinical experts' views of the characteristics of quality of life attributes in stable disease with different adverse events.

A critical feature of the OS data used in the Novartis economic model was the adjustment for cross-over from placebo to active treatment in RCT data. In particular, the method used for such adjustment, the rank-preserving structural failure time model (RPSFTM) relied on the assumption that the benefit derived by patients from receiving targeted treatment was the same whether they were given it as initial treatment or subsequently on disease progression. This assumption may be questionable and it is therefore natural to expect that in the present case sensitivity analyses allowing for a reduction in the benefit conferred by targeted treatment received after disease progression should have been performed. Although other methods are available to adjust for treatment cross-over, such as Inverse Probability of Censoring Weight[122] and censoring at cross-over, they are clearly inferior as the majority of the cross-over in RADIANT-3 and A6181111 occurred following study termination, making the key assumption underlying these methods, i.e. that cross-over is either random or that patients who did not cross-over may be representative of those who did, unlikely to hold true.

The Bucher indirect comparison from which Novartis derived estimates of relative effectiveness and side-effects for populating its economic model was based on data that

appear outdated on three fronts. First, Novartis estimated relative OS effectiveness by an indirect comparison (Bucher method) of placebo adjusted hazard ratios that corrected for cross-over from the placebo to active treatment arms in the two RCTs used in the indirect comparison. The cross-over adjusted OS HR estimate used for sunitinib versus placebo in the indirect comparison by Novartis is lower than that in the recently published final OS results of the A6181111 trial. With this new data we obtained a cross-over adjusted OS HR for everolimus vs sunitinib of 0.51 instead of the 0.72 figure derived by Novartis. Second, our updated searches of the literature conducted in October 2016 produced a forthcoming publication,[48] currently only available online, providing Grade 3/4 AE counts that differ in some instances from those used for the everolimus and placebo arms in the Bucher Indirect Comparison submitted as evidence to NICE by Novartis. Third, some of the Grade 3/4 AE data used in the Novartis Bucher IC for the sunitinib and placebo arms were different from the corresponding data submitted by Pfizer to NICE. When the Pfizer data are used instead, the pooled AE OR estimated by Novartis to be 4.47 becomes 1.37, thus reducing the differences in costs and disutilities of AEs between sunitinib and everolimus.

The way Novartis synthesized the effectiveness and safety evidence in their cost-effectiveness model inadequately reflected the available information. The company's base case assumption was that the PFS and OS outcomes of sunitinib and everolimus were the same, on the basis of wide confidence intervals around the point estimate of relative effectiveness. This practice is clearly inadequate because it misrepresents the level of uncertainty on the data as evidence of lack of effect. This issue is made more serious in view of the direction and extent of possible bias due to the use of inadequate data discussed in the previous paragraph.

In terms of model implementation, the limitations of the Novartis model analysis include the assumption of same treatment duration for everolimus and sunitinib. As pointed out above, the mean number of treatment cycles of sunitinib use is likely to be lower than that of everolimus, based on the Pfizer data submitted to NICE and comparison of median treatment durations in the main publications of the A6181111 and RADIANT-3 trials. On the other hand, Novartis did not account for the fact that the mean PFS (area under K-M curve) in the placebo arm of the A6181111 trial of sunitinib was lower than the mean PFS of the placebo arm of the RADIANT-3 trial of everolimus. If treatment duration is proportional to PFS, a fair indirect comparison with everolimus would require an increase in sunitinib treatment duration in proportion to the magnitudes of PFS in the placebo arm of RADIANT-3 to PFS of placebo in A6181111.

Another limitation was the implementation of subsequent treatment costs. In the partitioned survival model used by Novartis the number of people who transitioned into progressive disease and was eligible to receive subsequent treatment was not obtainable from the model output, and had to be approximated using summary information reported in the trial about the number of people who was censored, died before progression, and experienced a PFS event. This approximation involved the strong assumption of a constant relative frequency of these events throughout the PFS horizon.

Despite its limitations, the evidence presented by Novartis suggests that with the current available information, the choice between sunitinib and everolimus hinges on their relative effects on PFS and OS and drug acquisition costs, and is subject to high levels of uncertainty related to clinical effectiveness. Disutility of adverse events is unlikely to be a significant

factor in that choice and determining its importance is hampered by lack of data of sufficient quality for meaningful assessment.

6.1.2 Economic evaluation of everolimus in GI/Lung NETs

6.1.2.1 Overview

The economic evaluation of everolimus plus BSC vs. BSC alone in advanced, progressive, nonfunctioning GI or lung NETs by Novartis was based on the effectiveness, safety and quality of life evidence reported from a phase III RCT, RADIANT-4 (Yao et al. 2016). As in their economic evaluation in pNETs discussed above, Novartis relied on data from a resource use survey, which was validated for the UK.

6.1.2.2 Efficacy, effectiveness and safety evidence

In RADIANT-4 205 patients were randomized to everolimus 10 mg daily and 97 to placebo, plus BSC in both groups. Randomisation was done by stratification on previous somatostatin analogue use (continuous SSA for ≥12 weeks), tumour origin (better prognosis stratum: Appendix, caecum, jejunum, ileum, duodenum, or NET of unknown primary origin; worse prognosis stratum: lung, stomach, colon (other than caecum) or rectum) and WHO performance status (0 vs. 1). The median follow-up period in the study was 21 months, and median treatment duration with everolimus was 40.4 weeks. Median PFS was 11·0 months (95% CI 9·2–13·3) in the everolimus group and 3·9 months (3·6–7·4) in the placebo arm. A 52% reduction in the estimated risk of progression or death was observed in the everolimus arm (HR 0·48; 95% CI: 0·35–0·67).

Patients in RADIANT-4 were not allowed treatment cross-over after disease progression. Interim overall survival analysis resulted in a reduction in the risk of death with everolimus of 36% (HR 0·64; 95% CI: 0·40–1·05), but data were not mature enough to estimate median OS in any arm. Grade 3/4 drug-related adverse events observed in the trial included stomatitis, diaorrhea, infections, anaemia, fatigue and hyperglycaemia (see section 4.2 for details).

6.1.2.3 Review of economic models and their results in the submission

A systematic literature review was conducted by Novartis with the aim of identifying economic evaluations related to the use of everolimus in the GI and Lung NETs patient population, and resource utilization or costing and utilities associated with health states or treatments in the GI/NETs patient population. No study was found.

6.1.2.4 Economic Evaluation by the company

Novartis evaluated the cost-effectiveness of everolimus 10 mg daily plus BSC relative to BSC alone in patients with advanced, progressive, well-differentiated, nonfunctional GI and Lung NETs. This evaluations assessed costs, life years and QALYs over a 30 year time horizon. For this purpose a three health state, semi-Markov model of monthly cycles was used, populated with data from a partitioned survival analysis of data from the RADIANT-4 phase III trial of everolimus plus BSC versus placebo plus BSC (Yao et al. 2014). The model represented the disease course experience of a cohort of patients from the start of treatment, starting from a stable disease phase, moving to a progressive disease phase at the time of disease progression and, at any time in the disease course facing the risk of death from any

cause. The structure is the same as that described in the Novartis pNETs model, and that used by Ayyagari in the GI locations.[101]

6.1.2.4.1 Data and Methods

Efficacy and effectiveness data used in the model

A partitioned survival analysis method was used to derive the distribution of the patient cohort between health states in each cycle, using the same methods as described above for the Novartis model of pNETs and involving PFS (cut-off date 28th November 2014) and OS (cut-off date 30th November 2015) data from RADIANT-4. For this purpose and to extrapolate the OS and PFS outcome distributions beyond the end of follow-up in RADIANT-4 a parametric survival curve was chosen from four parametric distributions of time to event: exponential, weibull, gamma, gompertz, log-normal and log-logistic. Two variants of each of these survival distributions were estimated. An unrestricted variant, where one distribution was estimated using data from both trial arms but different estimates of each parameter in the distribution were obtained for the two trial arms. Alternatively the data from both arms was analysed with the same distribution, but only all but one (i.e. the scale) parameter were restricted to be the same for the everolimus and placebo trial arms.

More broadly, Novartis assessed the empirical adequacy of three classes of treatment effect models in PFS and OS data. One was the Shifted Failure Time model, which assumes treatment effects take place by displacing the survival curve to the right by a constant amount at each percentile of the cumulative survival distribution. The second model class is the proportional hazards (PH), which assumes that the treatment proportionally alters the (instantaneous) *risk of the event* occurring; this model includes the exponential, Weibull, and Gompertz models. The third model class considered was the accelerated failure time (AFT), which assumes that treatment affects the *survival time* proportionally, and included the log logistic, log-normal and gamma models. By applying the counterfactual criteria of Bagust and Beale [123] to model section, Novartis was able to discriminate the AFT model class as providing valid PFS model candidates, whereas PH and AFT model classes were valid for modelling OS. The counterfactual criteria consists in obtaining for each candidate model the (predicted) survival curve of the placebo arm that would have occurred had the placebo patients been randomly allocated to the active treatment, and comparing it with the actual survival curve of the active treatment arm; valid models are those whose counterfactual placebo survival curves match the survival curve of the active treatment arm.

Additional criteria were used to select survival distributions within model classes, including having a low BIC statistic (goodness of fit), and plausibility of long-term extrapolation. The latter consisted of two requirements. One was having curves that were above the 15 year 5% survival rate, a criterion adopted by Novartis on the survival rate evidence from SEER database despite the caveats acknowledged by the company and discussed earlier on the Novartis pNETs model. The other requirement was that curves did not cross, which in the analysis of OS Novartis was justified on the basis that “there is no reason to believe that the OS for everolimus is BSC would be less than that for placebo plus BSC at any point in time” (Novartis submission, p. 137).

The PFS model selected for the base case was the (restricted) log-normal, whereas the (restricted) gamma, (restricted) log-logistic, and (unrestricted) log-normal were used for sensitivity analyses. The (restricted) log-logistic distribution was chosen to model the OS in the base case analysis, with the (restricted and unrestricted) log-normal used in sensitivity

analysis. Novartis considered unrestricted variants as more flexible options to the restricted forms of each survival distribution but in practice their added flexibility ended up ruling them out as candidate models of PFS and OS data because curve crossing between everolimus and placebo arms. Therefore, it is questionable whether the modelling approach adopted by Novartis may have imposed too straight a jacket by fitting a common survival distribution function to PFS and OS data from both arms of the RADIANT-4, given that the more flexible (although potentially less efficient) modelling approach of separately modelling the data from each trial arm was not considered.

Although patients in RADIANT-4 were not allowed to cross-over from placebo to open label everolimus after disease progression, data on subsequent treatments submitted to NICE as part of the economic model by Novartis, states that 9% of patients in the RADIANT-4 trial received everolimus as subsequent treatment after disease progression (Novartis Table 7.13, p. 154 and reference there in (Yao et al. 2016)). It may be argued that from the point of view of the NICE decision problem, the approach adopted by Novartis of modelling and extrapolating OS outcomes without adjustment for placebo cross-over to everolimus (in spite of including in the BSC arm of the model the costs of subsequent everolimus treatment used by placebo arm patients) in RADIANT-4 may be invalid.

Adverse events

The model included the costs of Grade 3/4 AEs reported in RADIANT-4 which had an incidence of at least 2%. This resulted in the inclusion of stomatitis, diarrhoea, fatigue, infections, peripheraloedema, anaemia, pyrexia, and hyperglycaemia. The proportions of patients experiencing these events were used to calculate a weighted average cost of AEs for each of the two model arms, which was then multiplied by the probability of any such AEs in each cycle. Using individual patient data from the trial, the average AE rate per cycle was calculated to be 0.0625 from the first to the 26th cycle in SD for everolimus, and 0.0147 from the first to the 30th cycle in BSC. Other cycles were assigned AEs probabilities of zero. Given that HRQoL outcomes that allowed derivation of health state utilities were measured in RADIANT-4, these AE probabilities were not used to calculate base case utility values but they were used to calculate alternative utility values in sensitivity analyses following the approach described for the Novartis pNETs above (see section 6.1.1.).

Model implementation

In order to incorporate the costs of subsequent treatment the model uses different costs in the first and in subsequent cycles after disease progression. Costs of drug administration are applied to both initial and subsequent treatments. Adverse event costs are only applied in the SD state. The costs of terminal care are also included as a single cost as patients die in the model. Costs and QALYs are discounted at a 3.5% annual rate.

Utility values

Health state utility values for SD and PD were obtained from FACT-G outcome data collected in RADIANT-4. This involved using the OLS mapping algorithm estimated by Young and colleagues.[124, 125] This served to meet the requirements of the NICE reference case of using patient reported HRQoL outcomes and valuing such outcomes using preferences from the general public.[126] The AG has been able to reproduce the utility estimates used in the base case analysis from publically available summary data on FACT-G domain scores reported by RADIANT investigators (Singh et al. 2016)[127] and a linearized version of the best fitting

nonlinear algorithm, based on domain responses (Longworth et al. 2014;[125] see section 7.1.5.5). The base case analysis used the value of 0.779 for SD and 0.725 for PD in both treatment arms, although the company also estimated treatment-specific SD utility values of 0.767 for everolimus plus BSC and 0.807 for placebo plus BSC and PD values of 0.714 and 0.747, respectively, and used these values in scenario analyses. The stated reason for this choice of base case values was that the differences in utilities between everolimus plus BSC and placebo plus BSC in RADIANT-4 "were not statistically significant or clinically meaningful" (Novartis submission, p. 159). As acknowledged by the company the utility values of PD are unlikely to be valid measures of the post progression period since they are based on HRQoL outcomes of a subgroup of people who had progressed by the time the study was ended and covered only the early phase of the PD state. This led the company to explore lower values in sensitivity analyses.

No adjustment was applied to utilities due to end of life or the effect of ageing on HRQoL of life.

Costs

Costs of drug acquisition, dispensation and administration associated with everolimus and BSC were included in the analysis. Analyses presenting costs using list prices and alternatively potential PAS discounts were presented.

The cost of drug acquisition of everolimus 10 mg daily, as given in RADIANT-4, was calculated using the 2016 BNF price of 2,673 for 30 tables of 10 mg. Alternatively, the PAS discount of [redacted] was applied to the list price of everolimus. This plus the cost of oral drug administration was multiplied by the proportion of patients remaining on everolimus at each cycle in the stable disease health state, which was derived from a time on treatment curve calculated from IPD from RADIANT-4. The K-M median treatment duration was [redacted] months and by month 38 [redacted] remained on treatment. A RDI obtained from RADIANT-4 data of 79.4 was applied to the everolimus treatment costs.

Costs of orally administered treatment were based on hospital pharmacy staff time at unit costs obtained from 2015 PSSRU figures. Costs of intravenously administered therapies as part of BSC were applied using unit costs from NHR Reference costs.

Included in BSC were analgesics, anti-emetics, anti-diarrhoeals, EBRT, and SSAs, based on the views of key opinion leaders consulted by Novartis to validate an earlier resource survey of UK clinicians. The rates used in the model for each of these categories of BSC were derived from RADIANT-4 data. Novartis selected the most commonly observed specific treatment as representative for each category, for the purposes of calculating the costs of BSC in the model. Frequencies of BSC used in the model are presented in Table 88 below:

Table 88: Usage rates of therapies constituting BSC in the model

BSC therapy	Usage rates (derived from RADIANT-4)	
	Everolimus plus BSC	Placebo plus BSC
Analgesics	12.7%	6.2%
Representative treatment: Lidocaine		
Other pain medication: corticosteroids and glucocorticoids	31.7%	10.3%
Representative treatments:	(corticosteroids)	(corticosteroids)
Dexamethasone (corticosteroids)	41.5%	11.3%
Prednisone (glucocorticoids)[a]	(glucocorticoids)	(glucocorticoids)
Anti-emetics	2.9%	3.1%
Representative treatment: Prochlorperazine		
Anti-diarrhoeals	5.8%	5.2%
Representative treatments:		
Biofermin		
Sacchromyces boulardii[b]		
EBRT	1% (radiotherapy)	0% (radiotherapy)
SSAs	2%	1%
Representative treatment: Octreotide LAR		

Key: BSC: best supportive care, BNF: British National Formulary, EBRT: external beam radiation therapy, LAR: long-acting repeatable, SSA: somatostatin analogue.

Notes: a, The two treatment categories above are included because they were the most frequently used concomitant medications in the trial that can be used to alleviate pain; b, 2 treatments were included because both were used equally as frequently in trial patients

Source: Yao *et al.* 2016 and reproduced from Table 7.8 in the Novartis submission.

Healthcare resource use was estimated from a survey conducted in 2016 to validate the results of an earlier 2011 survey of 32 UK clinicians in England, relative to current practice. The original survey findings have been published for the combined GI and Lung NETs location (Casciano et al. 2012).[95] The methods of the survey have been described above for the pNETs Novartis model. The validation exercise considered current management practice in non-functional GI and Lung NETs separately locations separately and involved 5 clinicians from four centres, two of which were ENETS European centres of Excellence. The results of the survey by averaging the responses of the five clinicians according to the annual number of GI and Lung patients they treated annually are presented in Table 89, weighted in proportion to the mix of GI and Lung patients in RADIANT-4.

The validation survey elicited the opinion from clinical experts that “patients on active treatment are more likely to receive follow-up care to monitor disease progression and toxicity” than patients receiving BSC alone (Novartis submission, p. 159). Further, patients in the PD state accrue costs depending on whether they are receiving active post-progression treatment or are under observation (32.7% of patients initially treated with everolimus and 33.3% of patients that started the model under BSC alone were under observation; see details in Table 90).

Table 89: List of resource use in stable disease and progressive disease and associated unit costs

Item	Resource use in stable disease health state		Resource use in PD health state		Unit cost
	Everolimus plus BSC	BSC alone	Everolimus plus BSC	BSC alone	
Physician visits					
Follow-Up (Medical Oncologist)	0.843	0.273	0.745	0.531	£158.54
Follow-Up (Surgeon)	0.046	0.048	0.021	0.013	£132.95
Follow-Up (Palliative Care)	0.000	0.230	0.000	0.313	£185.92
Follow-Up (Respirologist)	0.000	0.017	0.018	0.020	£156.29
Follow-Up (Nurse)	0.075	0.023	0.000	0.000	£37.26
Follow-Up (Dietitian)	0.044	0.046	0.000	0.039	£69.64
Procedures/tests					
Abdominal ultrasound	0.007	0.008	0.010	0.006	£55.17
Echocardiography	0.018	0.000	0.024	0.000	£81.48
Chest, abdominal, and pelvic CT scan (conventional)	0.117	0.057	0.048	0.039	£124.53
Chest, abdominal, and pelvic CT scan (helical/spiral)	0.201	0.057	0.251	0.020	£124.53
MRI	0.099	0.065	0.131	0.006	£181.76
Octreoscan/SRS	0.077	0.078	0.054	0.003	£806.32
NSE	0.056	0.055	0.106	0.000	£1.19
CgA	0.277	0.146	0.344	0.130	£1.19
5-HIAA	0.166	0.104	0.213	0.059	£1.19
CBC blood test	0.805	0.271	1.038	0.211	£3.01
BUN	0.655	0.136	0.748	0.158	£3.01
Serum glucose	0.805	0.271	1.038	0.211	£3.01
Serum creatinine	0.805	0.271	1.038	0.211	£3.01
Lipid profile	0.363	0.055	0.000	0.000	£3.01
Hospitalisations					
General hospitalisation	0.036	0.036	0.000	0.015	£586.93
Emergency room visit	0.036	0.036	0.045	0.015	£147.30

Key: 5-HIAA: 5-Hydroxyindoleacetic acid, BSC: best supportive care, BNP: B-type natriuretic peptide, BUN: blood urea nitrogen, CBC: complete blood count, CgA: chromogranin A, CT: computerised tomography, FDG-PET: 8-Fluoro-deoxyglucose positron emission tomography, mIBG: metaiodobenzylguanidine, MRI: magnetic resonance imaging, NSE: neuron-specific enolase, PP: pancreatic hormone, SRS: stereotactic radiosurgery, T4: thyroxine, VIP: vasoactive intestinal peptide.

Source: Reproduced and reduced from Novartis submission Table 7.10

To estimate the costs of adverse events, the probability of any AE derived from the pooled incidence of Grade 3/4 events with an incidence of 2% or more in either arm of RADIANT-4 (see section 4.2.5.3.4) was multiplied by a weighted average costs of those specific AEs, according to the relative magnitude of each AE type in the sum of all rates. The unit costs of specific AEs were obtained from NHS Reference costs for 2014-2015.

Novartis state that "Although the Key Opinion Leaders (KOLs) did not indicate that there would be a significant difference in how patients who had previously received everolimus plus BSC versus BSC alone would be treated, the relative use of these post-progression therapies was calculated using the RADIANT-4 trial data". The frequency of use of subsequent treatments is presented in Table 90 below. These treatments were applied costs for the number of treatment cycles they were observed to be given for in RADIANT-4, assuming standard dosages rounded to the nearest dose consistent with no wastage.

Table 90: Resource use of post-progression treatments

Post-progression treatment	Central review	
	Everolimus plus BSC	Placebo plus BSC
Octreotide LAR	0.298	0.227
Lanreotide	0.085	0.080
Everolimus	0.043	0.091
PRRT	0.050	0.034
IFN	0.014	0.000
Clinical trial	0.014	0.023
Hepatic artery embolization	0.050	0.068
Chemoembolization	0.007	0.034
Radiofrequency ablation	0.007	0.011
SIRT	0.000	0.023
Temozolomide	0.142	0.114
Capecitabine	0.142	0.114
Streptozocin	0.028	0.011
Fluorouracil	0.028	0.011
Observation	0.327	0.333

Key: BSC: best supportive care, IFN: interferon, LAR: long-acting repeatable, PRRT: peptide receptor radionuclide therapy, SIRT: selective internal radiation therapy.
Source: Yao *et al.* 2016; reproduced from Novartis submission, Table 7.13

We notice that Octreotide LAR was applied a unit cost of £998.41 per month from 2016 BNF prices. This price is 20% higher than the £806.42 average price available to hospitals according to the eMIT database (accessed October 2016). Another aspect to note is the 9.3% use of everolimus in the placebo arm vs. the 4.3% rate in the everolimus arm, both of which were given for a treatment duration of 6.18 cycles in the model. Clinical expert advice received by the AG suggests that there is currently no access to peptide receptor radionuclide therapy (PRRT) in England, although there was previously, and that chemotherapy would be used instead in most patients. The costs applied to subsequent treatments in the Novartis model are presented in Table 91.

A fixed cost of £4,346 was applied when patients died in the model to account for the costs of terminal care. This figure was derived from the literature.[120]

Table 91: Unit costs of post-progression treatments

Post-progression treatment			Treatment duration				Source
			Everolimus plus BSC		BSC alone		
Post-progression treatment	**Unit cost (unit)**	**Source**	**Number of units per cycle**	**Number of cycles**	**Number of units per cycle**	**Number of cycles**	
Octreotide LAR – 30 mg	£998.41 (per month)	BNF 2016	1.087	4.06	1.087	4.46	RADIANT-4
Lanreotide – 120 mg	£937.00 (per month)	BNF 2016	1.087	1.80	1.087	2.27	RADIANT-4
Everolimus – 10 mg	£89.10 (per day)	BNF 2016	30.438	6.18	30.438	6.18	RADIANT-4
PRRT	£2,247.10 (per procedure)	Reference Costs Year: 2014-15	0.400	5.74	0.400	0.03	RADIANT-4
IFN – 5 million IU	£28.37 (per day)	BNF 2016; IntronA Summary of Product Characteristics	13.045	3.84	13.045	3.84	RADIANT-4
Clinical trial	£0.00	N/A	0.000	0.00	0.000	0.00	N/A
Hepatic artery embolization	£3,993.90 (per procedure)	Reference Costs Year: 2014-15	1.000	1.00	1.000	1.00	RADIANT-4
Chemo-embolisation	£3,993.90 (per procedure)	Reference Costs Year: 2014-15	1.000	1.00	1.000	1.00	RADIANT-4
Radiofrequency ablation	£937.54 (per procedure)	Reference Costs Year: 2014-15	1.000	1.00	1.000	1.00	RADIANT-4
SIRT	£2,026.86 (per procedure)	Reference Costs Year: 2014-15	1.000	1.00	1.000	1.00	RADIANT-4
Temozolomide – 360 mg	£152.40 (per day)	BNF 2016; Strosberg JR *et al*. (2011)[128] Sacco JJ *et al*. (2010)[129]	5.435	2.34	5.435	3.08	RADIANT-4
Capecitabine – 2650 mg	£6.42 (per day)	BNF 2016; Strosberg JR *et al*. (2011)[128] Sacco JJ *et al*. (2010)[129]	15.219	2.34	15.219	3.08	RADIANT-4
Streptozocin – 895 mg	£0.00 (per day)	Assumption that cost is covered by Cancer Drugs Fund	2.174	1.23	2.174	1.45	RADIANT-4
Fluorouracil – 750 mg	£10.40 (per day)	BNF 2016 ; Sun W *et al*. (2005);[130]Sacco JJ *et al*. (2010)[129]	4.348	1.23	4.348	1.45	RADIANT-4
Observation	£0.00	N/A	0.000	0.00	0.000	0.00	N/A

Key: BNF: British National Formulary, HRG: Healthcare Resource Group, IFN: interferon, IU: international units, LAR: long-acting repeatable, N/A: not applicable, NHS: National Health Service, PRRT: peptide receptor radionuclide therapy, SIRT: selective internal radiation therapy, SmPC: summary of product characteristics.

6.1.2.4.2 Results

Novartis reports that the life expectancy over a 30-year period with everolimus 10mg daily plus BSC treatment for patients with advanced, well-differentiated, non-functional, progressive GI/Lung NETs, is 5.79 vs 4.77 with BSC alone (Table 92). The respective total discounted costs are expected to be £59,720 and £25,817, and the total QALYs, 4.28 vs. 3.51. This results in £43,642 cost per QALY gained with everolimus. Under the [redacted] PAS discount on the everolimus price, the cost per QALY gained with everolimus would be reduced to [redacted]. Seventy one percent of the QALY gained by everolimus over placebo takes place in the SD state, and the share of the cost falling during SD is 98% at list prices. The costs of active initial treatment with everolimus represents 79% and BSC costs account for 8% of the total incremental costs of everolimus. The mean PSA ICER of everolimus was £45,385 without PAS, and [redacted] with PAS.

Table 92: Main results of Novartis model submission in GI and Lung NETs at current list price

	Life years (undiscounted)	QALYs (discounted)	Costs	ICER
Everolimus	5.79	4.28	£59,720	£43,642
BSC	4.77	3.51	£25,817	
Difference	1.02	0.77	£33,903	

Univariate deterministic sensitivity analyses found that the ICER was most sensitive to the choice of distribution for extrapolating OS. The ICER varied in the £39,571 to £59,832 range with different OS distributions and [redacted] with PAS. When treatment specific utility values were applied the ICER became £56,385 and [redacted] under the PAS. Results were also sensitive to the RDI. Novartis also reports how extending the life time horizon and extrapolating outcomes beyond the trial period improves the cost effectiveness of everolimus.

From the results reported by Novartis it is evident that in the analysis of PAS, the [redacted] PAS discount was only applied to everolimus given as initial treatment, not as subsequent treatment. In principle, the discount should have been applied to subsequent treatment use too.

The company concluded that the ICER [redacted]. The company states that the results should be considered within the context of unmet medical need for effective treatment options in this heterogeneous and small patient population, which across the two indications (pNETs and GI/Lung) is constituted by approximately 936 patients in England (Novartis submission Table 3.1 Eligible patient population for everolimus in England, p. 27).

6.1.2.4.3 Strengths and Weaknesses of Novartis evaluation in GI/Lung NETs

The economic evaluation of everolimus in GI and Lung NETs patients by Novartis relies on the quality of the RADIANT-4 study, which provided the source of effectiveness, AEs and treatment duration and intensity data for the model and rates of subsequent treatment use. A major limitation is the omission of relevant active comparators, such as 177Lu-DOTATATE,

in the analysis. Another limitation of the study design is the lack of a separate analysis of Lung and GI patients.

In terms of data the main limitation is the lack of resource use data measured in a sample of patients. It is not clear how robust the estimated costs of subsequent treatment use are likely to be with issues such as administrative censoring (i.e. from termination of the study), and indeed whether the differences captured may have been an artefact of the length of follow up.

In terms of evidence synthesis, the decision analysis relied on applying the same parametric survival distributions for extrapolation to both arms, which may have unnecessarily restricted the modelling capabilities in this study. Another issue was that although cross-over from everolimus to placebo was not permitted in the trial, 10% (10/97) of patients in the placebo arm did cross over (4 before and 6 after unmasking). In spite of this, the analysis of OS data in RADIANT-4 did not adjust for such treatment cross-over. This limitation may slightly bias the results, if the analysis is intended to inform the evaluation of two alternative states of the world, one where everolimus is provided as initial treatment and another when it is not provided at all. If instead the NICE decision is between choosing everolimus as initial treatment or everolimus at the discretion of the physician as potential subsequent treatment, the lack of cross-over adjustment by Novartis may not need to be a source of bias per se.

Another minor limitation is the inaccuracy in estimating costs of subsequent treatments in the GI/Lung Novartis model. This issue is the same as discussed above for the Novartis model in pNETs (section 6.1.1.4.3) and is not repeated here.

On the other hand, data on BSC treatment use, everolimus treatment duration and intensity, and incidence of Grade 3/4 AEs in RADIANT-4 are detailed and Novartis describes important sources of uncertainty in the evidence base.

6.2 AAA submission

6.2.1 Overview

In anticipation of European market authorisation the company's submission considers the use of the radiolabelled somatostatin analogue 177Lu-DOTATATE (7.4 GBq, equivalent to 200 mCi) for people with inoperable progressive somatostatin receptor positive GEP-NETS. The company separate the GEP-NETs population into two sub-populations in the model:

[redacted]

Separation into these sub-populations from the wider GEP-NETs population was seen by AAA as appropriate since pNETs and GI-NETs have different clinical profiles and management. Also it is important to note that with the selection of these trials the populations considered in the economic evaluations were further restricted to the sub-population of somatostatin subtype receptor positive (SSTR+) patients.

The comparators in the pNETs 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. Best supportive care was not offered as a comparative strategy.

In the base case analysis of pNETs the reported ICERs favoured 177Lu-DOTATATE over both included comparators. The estimated cost per QALY gained versus everolimus was

[redacted]. In the comparison with sunitinib, 177Lu-DOTATATE was estimated to be less costly and produce more QALYs and therefore dominated sunitinib.

In the base case analysis of GI-NETs the reported ICER also favoured 177Lu-DOTATATE. The cost per QALY gained versus everolimus was estimated to be [redacted].

Supportive arguments for these findings are not discussed except that the result is driven by superior survival with 177Lu-DOTATATE. The company did not draw comparisons with existing published economic evidence since this is the first cost-effectiveness analysis of 177Lu-DOTATATE.

6.2.1.1 Efficacy and effectiveness evidence

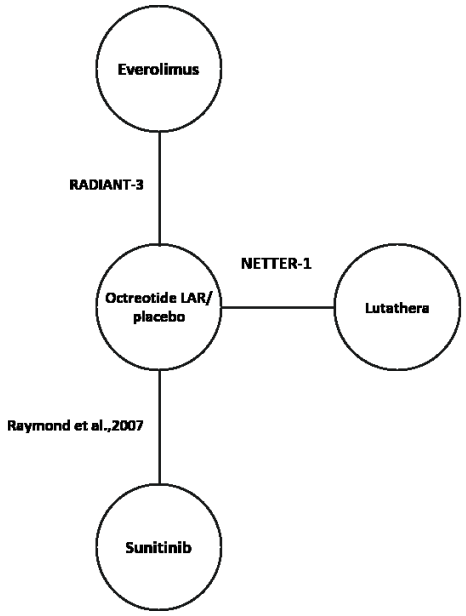
AAA conducted a systematic review for studies providing evidence on the clinical efficacy and safety of 177Lu-DOTATATE in patients with GEP-NETs. Randomised and non-randomised studies were included. Only one RCT was included, NETTER-1, which compared 177Lu-DOTATATE + Octreotide 30mg with Octreotide 60mg in individuals with GI NETs.

AAA conducted two MTCs for the outcomes of PFS and OS: one for GI NETs to compare 177Lu-DOTATATE with everolimus and one for pNETs comparing 177Lu-DOTATATE with everolimus and sunitinib. AAA considered the study and participant characteristics in all studies in the two networks to be comparable, including RADIANT-2 which was excluded since all participants have functioning tumours which is outside of the license for everolimus. These are illustrated in Figure 35 and Figure 36

AAA make three major assumptions to perform their MTCs:

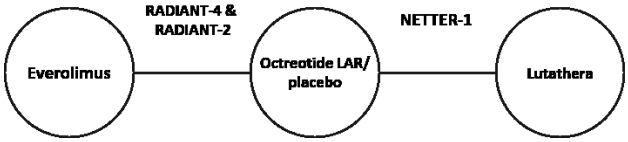
1. that octreotide 60mg can be assumed to be equivalent to placebo and placebo + octreotide 30mg (in order to connect NETTER-1 to the other trials) in the GI NETs network,
2. that octreotide 60mg is equivalent to placebo and placebo + BSC to connect NETTER-1 to the other trials for the pNETs network, and
3. that data from the NETTER-1 trial can be used to inform the network for pNETs even though no participants within NETTER-1 had pNETs.

Figure 35: Indirect comparison networks for PFS and OS in pNETs



Source: Reproduced from AAA submission Chapter 4 Figures 12, pages 71-72.

Figure 36: Indirect comparison networks for PFS and OS in GI-NETs



Source: Reproduced from AAA submission Chapter 4 Figures 13, pages 71-72.

AAA undertook a Bayesian analysis with MCMC simulation in R. They ran fixed and random effects models with hazard ratios as response variables with hazard ratios as response variables, using the poisson/log model and the binomial/cloglog model. AAA report assessing convergence using trace plots, autocorrelations and "other standard convergence diagnostics" (p210 of AAA submission), but do not state explicitly whether convergence was achieved in the models.

The results of the MTCs are shown in Table 93 and Table 94.

Table 93: GI-NETs HRs synthesised from MTC (95%CrIs)

Intervention	PFS		OS	
177Lu-DOTATATE vs octreotide/placebo *everolimus vs octreotide/placebo* *177Lu-DOTATATE vs everolimus*	[redacted]			[redacted]

Table 94: pNETs HRs synthesised from MTC (95%CrIs)

Intervention	PFS		OS	
177Lu-DOTATATE vs octreotide/placebo *everolimus vs octreotide/placebo* *sunitinib vs octreotide/placebo* *177Lu-DoTATATE vs everolimus* *177Lu-DOTATATE vs sunitinib* *everolimus vs sunitinib*	[redacted]			[redacted]

We have a number of reservations regarding the MTCs conducted by AAA.

- RADIANT-2 should be excluded from this MTC as the population all have functioning tumours which is outside of the marketing license for everolimus for GI NETs,
- NETTER-1 should be excluded from the pNETs network as it does not contain any patients with pNETs,
- for the evaluation of GI NETs the populations for OS differ across the three studies (midgut NETs in NETTER-1, all NETs in RADIANT-2, GI and lung-NETs in RADIANT-4),
- there is no justification for the assumption that octreotide LAR 60mg is equivalent to placebo, placebo + octreotide 30mg and placebo + BSC,
- there is no consideration of the extent of treatment switching within RADIANT-2 (58% switched to active treatment), RADIANT-3 (73% switched to active treatment) and A6181111 (69% switched to active treatment) which limits the interpretation of results for OS,
- the 95%CrIs are very wide indicating a great deal of uncertainty,
- results from the random effects Poisson model, and the fixed and random effects Binomial model, are not reported in the submission and so no comparison of any differences in point estimates or 95% CrIs between these models can be made.

For the non-randomised evidence, AAA identify 4 single arm non-RCTs: Kwekkeboom et al 2003/2005/2008 (ERASMUS);[66-68] Delpassand et al. 2014;[58] Paganelli et al. 2014[69] and Sansovini et al 2013,[74] yet focus on the Dutch subset of the ERASMUS study. This is a single centre phase I/II open-label study of Dutch participants with GI NETs and pNETs (n=810) administered 177Lu-DOTATATE. The primary outcomes of ORR, median PFS and OS by location are shown in Table 95.

Table 95: Primary outcomes from the ERASMUS non-randomised open label study

	Midgut	Hindgut	Foregut	Pancreatic
ORR (%)	34 (28, 41)	46 (19, 73)	50 (22, 78)	56 (48, 65)
Median PFS (months)	29.6 (24.8, 34.4)	29.3 (22.3, 39.0)	NR	30.5 (24.9, 36.2)
Median OS (months)	55.4 (49.8, 70.1)	NR	NR	70.8 (63.2, ND)

NR, not reached; ND, not determined.

6.2.1.2 Review of economic models and their results in the submission

The submission details a systematic review of the economic literature which identifies 11 cost-effectiveness studies relevant to the decision problem.

- Individual search strategies were developed for the following included databases:
  - MEDLINE (OvidSP)
  - MEDLINE In-Process Citations & Daily Update (OvidSP)
  - Embase (OvidSP)
  - Cochrane library (Wiley): CDSR, CENTRAL, DARE, HTA, NHS EED.
  - EconLit (internet-American Economic Association)

- The electronic database search was supplemented by hand searching the CEA Registry, NICE HTA, PBAC and CADTH submissions, and conference proceedings.
- 597 records were retrieved and after deduplication 533 individual titles and abstracts were screened. 16 records were retrieved for full review and 11 of these met the criteria for final inclusion. Three were from the UK, ten were CEA studies, and one was a budget impact study. All 11 were assessed as good quality.
- 7 CEAs compared sunitinib and BSC with BSC; two compared octreotide and BSC with BSC; one compared everolimus with chemotherapy; and one compared everolimus with sunitinib.
- Nine papers evaluated people with pNETs; one with carcinoid syndrome and VIPoma; and one GI (midgut) NETs.

The methodology of the company's systematic review of the economic literature was sound and comprehensive. However, the company did not include a description of results or conclude any strengths or limitations of their review, nor were the findings of the included studies discussed alongside the findings of the company's original economic evaluations.

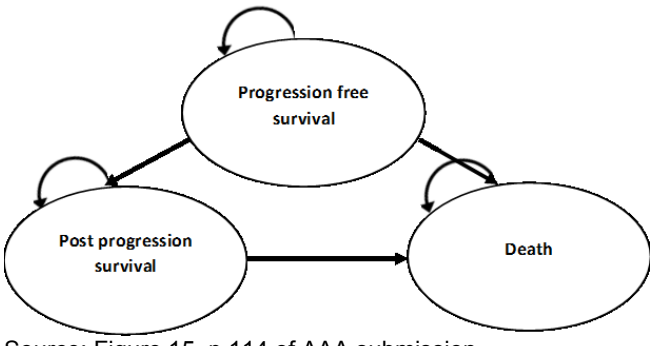
6.2.1.3 Economic Evaluation by the company

The decision analytic model is structured using a partitioned survival ('area under the curve') approach based on a parametric extrapolation of Kaplan-Meier curves for baseline PFS and OS and hazard ratios applied proportionally through a 20 year time. It utilises a three-health state cohort transition model to simulate survival and progression. The selected cycle length is one month, costs and benefits were discounted at 3.5% in future years, and are reported from the NHS/PSS, and patient's perspective, respectively.

AAA conducted two MTCs for the outcomes of PFS and OS: one for pNETs comparing 177Lu-DOTATATE with everolimus and sunitinib, and one for GI NETs to compare 177Lu-DOTATATE with everolimus (See section 6.2.1.1)

The sources of evidence of health effect in the pNETs evaluation were the NETTER-1 study (unpublished) for octreotide LAR (baseline reference) and 177Lu-DOTATATE; the RADIANT-3 study for everolimus; and Clinical trial A6181111 for sunitinib. The sources of evidence of health effect in the GI-NETs evaluation were the ERASMUS study for 177Lu-DOTATATE (Dutch pNETs subgroup), and RADIANT-4 for everolimus.

Figure 37: Decision analytic model structure



Source: Figure 15, p 114 of AAA submission

6.2.1.3.1 Data and Methods

Efficacy and effectiveness data used in the model

- Baseline rates of progression and overall survival were estimated using Weibull parametric extrapolations of Kaplan Meier curves from individual patient data, fitted using ordinary least squares regression methods. The Weibull function was selected based on goodness of fit using the Akaike information criterion and Bayesian information criterion, combined with clinical plausibility on visual inspection.
- A partitioned survival model was implemented in MS Excel with Weibull coefficients for PFS and OS generated in STATA for each comparator.
    - The pNETs evaluation used the progressive pNETs subgroup of the Dutch population of patients treated with 177Lu-DOTATATE in the ERASMUS study for baseline risk (Number at risk: PFS n=80; OS n=87; Median PFS=35.6 months; Median OS=80.7 months).
    - The GI-NETs evaluation used patients treated with octreotide LAR in the NETTER-1 study for baseline risk (Number at risk: PFS n=106; OS n=113; Median PFS=8.4 months; Median OS=not reached).
- Under an assumption of proportional hazards, hazard ratios generated from the MTC were applied to the baseline survival curves (Table 96)
- Background mortality was not included in the base case analysis but included as a scenario analysis.

Table 96: Hazard ratios from MTC comparison of interventions (deterministic median) applied to baseline risk

Intervention	PFS (95% CI)	OS (95% CI)
Everolimus pNETs v PBO	[redacted]	[redacted]
Sunitinib pNETs v PBO		
177Lu-DOTATATE GI-NETs v PBO		
Everolimus GI-NETs v PBO		

Key: PBO = Placebo; PFS = Progression-free survival; OS = Overall survival

Adverse events

- Serious adverse events (grade 3 and 4) were incorporated into the model using incidence data form clinical trials (Table 97). For each treatment an adverse event profile was developed whereby each event, where appropriate, carried a cost of management and an associated utility decrement.
- Treatment specific adjustments to the baseline PFS utility were calculated using decrements weighted according to event incidence in trials (Table 98).
- Decrements for adverse events were applied to every cycle patients remained progression free, including the post-treatment progression-free for those patients administered 177Lu-DOTATATE.
- The utility decrement weightings for serious adverse events followed the trend advised by the AG expert clinicians:
    - BSC > 177Lu-DOTATATE > everolimus > sunitinib

- 177Lu-DOTATATE dose adjustment due to adverse events or missed-treatments in NETTER-1 was incorporated into the costing of 177Lu-DOTATATE in the base case by applying a relative dose intensity reduction in mean drug acquisition cost. No such adjustment was made for everolimus or sunitinib.
- Adverse event utility decrements were applied to all treatment strategies whilst patients were progression-free. Since these decrements should be applied to the treatment period only, this approach overestimates the period of disutility from adverse events. Whilst the disutility penalty is greatest for everolimus and sunitinib, the mean duration of treatment of 177Lu-DOTATAE is in practice less than everolimus and sunitinib. In any case, the ICERs are insensitive to this limitation.

Table 97: Incidence of serious adverse events in respective clinical trails

SAE (%)	177Lu-DOTATATE (NETTER-1)	Everolimus pNETs (RADIANT-3)	Sunitinib pNETs	Everolimus GI-NETs (RADIANT-4)
Nausea	4	2	1	2
Vomiting	7			
Diarrhoea	3	3	5	7
Abdominal pain	3		5	
Thrombocytopenia	2	4	4	
Lymphopenia	9			
Leukopenia	1			
Stomatitis		7	4	9
Flushing	1			
Fatigue	2	2	5	3
Infections		2		9
Asthenia		1	5	2
Anaemia		6		4
Pyrexia				2
Hyperglycaemia		5		3
Neutropenia			12	
Hypertension			10	
Musculoskeletal pain	2			

Key: SEA = Serious adverse event

Table 98: Adverse event utility decrements to PFS

Intervention	Utility decrement weighting for PFS
177Lu-DOTATATE pNETs	0.9725
Everolimus pNETs	0.9649
Sunitinib pNETs	0.9432
Everolimus GI-NETs	0.9560

Utility values

- A systematic literature search was conducted for relevant published HRQoL papers. Pragmatic searches were conducted for HRQoL mapping algorithms and utility decrements for serious adverse events.
- HRQoL scores are collected for stable and progressive disease in the base case from pNET/GI-NET patients administered 177Lu-DOTATATE in the ERASMUS study

(Table 99). However, the exception is the base case estimate of stable disease in GI-NETs, for which the estimate is sourced from a UK registry. The company have not made it clear why this approach was adopted.

- Patients in the ERAMUS trial were Dutch not UK, and their number and characteristics are not stated. Responses were collected every 12 weeks from first treatment to 72 weeks. HRQoL scores from EROTC-QLQ-C30 questionnaire used in ERASMUS were mapped to EQ-5D scores (Longworth et al. 2014).
- HRQoL scores from registry patients at Guy's and St Thomas' NHS Foundation Trust (UK) were attained directly using the EQ-5D questionnaire (58 patients; 57% male; 94% Caucasian; mean age 60 years).
- Overall the synthesis of health state utility estimates is potentially weak due to the use of multiple sources, the use of multiple quality of life assessment tools, and the use of cohorts from single arm studies/registries rather than RCTs.

Table 99: Utilities used in the base case by primary NET site and health state

Site of NET / Health state	PFS	PPS
pNETs	0.80 [a] (95% CI: 0.79, 0.81)	0.79 [a] (95% CI: 0.76 0.82)
GI-NETs	0.79 [b] (95% CI: 0.77, 0.82)	0.74 [a] (95% CI: 0.72, 0.76)

Notes: a, Sourced from the ERASMUS clinical trial of 177Lu-DOTATATE; b, Sourced from GI-NETs patient database at Guy's and Thomas' NHS Foundation Trust, UK.

- Adverse events were not modelled using an additional health state, instead dis-utilities were applied to the baseline PFS estimates according to the incidence of adverse events in trial of each treatment (See section titled 'Adverse events').
- Utility decrements were estimated for 19 event types, although 12 of these were assumptions based on the remaining seven for which sources were found. In nine cases the decrement was assumed equal to the worst value, which was incorrectly selected as 0.11 (thrombocytopenia) rather than 0.2 (fatigue).
- No adjustment were applied to utility accrual in the base case for end-of-life wellbeing, but is included in a univariate deterministic sensitivity analysis.

Costs

- The included cost categories were drug acquisition, drug administration, disease monitoring, and adverse event management. No provision was made for any hospitalisation of patients owing to deterioration of condition.
- Patients with stable disease received continual drug treatment until the point of progression, except for the 177Lu-DOTATATE strategy whereby therapy was limited to four treatment cycles.
- All patients received and incurred the cost of octreotide (30mg) drug following progression and until death.
- Drug acquisition prices and posology were sourced from The British National Formulary (everolimus, sunitinib, octreotide), except for 177Lu-DOTATATE, for which information was supplied by AAA (Table 100).
- Drug prices were incorporated into the base case at NHS list price, no discount or patient access scheme prices were explored in sensitivity analyses.

- A relative dose intensity adjustment to reflect downward dose modifications or skipped doses observed in the NETTER-1 (0.864) was applied to the acquisition cost of 177Lu-DOTATATE. No equivalent adjustments were made for everolimus or sunitinib. This reduces the cost of the 177Lu-DOTATATE strategy which decreases the ICERs versus everolimus/sunitinib.
- The cost of 177Lu-DOTATATE administration was based on 15 minutes of pharmacist time, 1 hour of day ward nursing time, and a 4 hour (one-third) day case attendance. This is inconsistent with the company's statement in Chapter 2 of their submission in which the involvement of nuclear medicine department resources are anticipated. It is also inconsistent with expert clinical opinion we have received which indicates specialist involvement and admission with overnight stay is routine.
- Everolimus and sunitinib are self-administered orally and therefore attracted zero administration cost.

Table 100: Drug posology and acquisition price

Treatment	Dose and frequency	Unit cost in base case
177Lu-DOTATATE	4 administrations of 7.4GBq (200mCi), administered once every 8 weeks	29.6 GBq (800 mCi) = [redacted]
Everolimus	10mg administered once daily	30 tab, 10mg packs £2,673
Sunitinib	37.5mg administered once daily	30 tab, 12.5mg packs £784.70
*Granisetron**	3mg To be administered before administering 177Lu-DOTATATE	10 tab, 1mg packs = £32.89
*Vamin 18-18%**	To be administered before while administering 177Lu-DOTATATE	Vamin 18 (electrolyte-free) = Net price 1 litre = £23.38

Notes: *Supportive treatments administered alongside 177Lu-DOTATATE

- The resource utilisation for monitoring of disease was assumed the same for all treatment strategies. Unit costs are shown in Table 101.

Table 101: Resource utilisation rates and unit costs

Resource use	Frequency	Unit cost in base case
CT/MRI	Every 12 weeks	£124.10
ECG	Every 8 weeks	£83.94
CBC with differential	Every 4 weeks	£3.00
Blood chemistry	Every 4 weeks	£3.00
Urinalysis	Every 4 weeks	£1.19

Key: CT = Computerised tomography; MRI = Magnetic resonance imaging; CBC = Complete blood count; ECG = Electrocardiogram

- Monitoring costs at baseline (screening) were not included because these costs are not influenced by choice of treatment and apply to all patients.
- The unit costs of treatment were included for 18 separate serious adverse event types. Seven were attributed dedicated estimates taken from standard literature sources; eight were arbitrarily assigned a cost of £1, based on the presumption that the event would have little impact on NHS resources; and three were assumed equal to the cost of the highest cost event (Stomatitis, £385.17).

- The cost of managing adverse events was included for every cycle in stable disease, rather than whilst on treatment. Note earlier assumption that everolimus and sunitinib treatment is continued until progression in all cases.
- Additional costs relating to end-of-life care, or palliative care, were not included in the base case analysis but provided as an option in a univariate deterministic sensitivity analysis.
- The price year used in the analysis was not stated but may reasonably be assumed to be 2015.

6.2.1.3.2 Result

- Over a time horizon of 20 years, for people with inoperable progressive SSTR+ pNETs the use of 177Lu-DOTATATE is found to be cost-effective versus both everolimus and sunitinib at threshold of £20,000 per QALY gained (Table 102).

Table 102: Incremental costs and effects of deterministic evaluation in pNETs

Outcome	177Lu-DOTATATE	Everolimus	Sunitinib
PFS at 5 years (%)			
OS at 5 years (%)			
Life-years (discounted)			
QALYs PFS (discounted)			
QALYs PPS (discounted)			
Total QALYs			
Drug cost			
Drug administration			
Disease monitoring			
AE management			
Total costs			
Incremental cost versus 177Lu-DOTATATE		£21,489	-£6,648
LYs gained by 177Lu-DOTATATE		2.75	0.07
QALYs gained by 177Lu-DOTATATE		2.18	0.10
ICER, £ (177Lu-DOTATATE versus)		£9,847	Dominant (-£68,916)

- Over a time horizon of 20 years, for people with inoperable progressive SSTR+ functional and non-functional carcinoid midgut NETs (GI-NETs) the use of 177Lu-DOTATATE is found to be cost-effective versus everolimus at a threshold of £20,000 per QALY gained (Table 103).

Table 103: Incremental costs and effects of deterministic evaluation in GI-NETs

Outcome	177Lu-DOTATATE	Everolimus
PFS at 5 years (%)		
OS at 5 years (%)		
Life-years (discounted)		
QALYs PFS (discounted)		
QALYs PPS (discounted)		
Total QALYs		
Drug cost		
Drug administration		
Disease monitoring		
AE management		
Total costs		
Incremental cost versus 177Lu-DOTATATE		£28,099
LYs gained by 177Lu-DOTATATE		1.77
QALYs gained by 177Lu-DOTATATE		1.42
ICER, £ (177Lu-DOTATATE versus)		£19,816

- In a one-way deterministic sensitivity analysis whereby individual parameter point estimates were varied to their upper and lower 95% confidence interval, or interquartile range boundaries (or where not available ±20% of the mean):
    - 177Lu-DOTATATE acquisition cost and RDI adjustment were identified as highly sensitive model input parameters,
    - PFS and PPS utility scores were identified as moderately sensitive input parameters.
- Uncertainty around the point estimates of input parameters in the deterministic analysis was explored in a probabilistic sensitivity analysis (PSA). In 5,000 iterations selected parameters were varied using conventional distributions. Parameters not included in the PSA were relative treatment effect (PFS, OS), drug acquisition, and drug administration. Results revealed that PSA ICERs were consistently lower than deterministic ICERs. AAA offered no explanation for this discrepancy, which in theory may be due to an error in the PSA build or the inclusion of one or more non-linear parameter in the model.

Table 104: Incremental cost effectiveness ratios in deterministic and probabilistic analyses

ICER (Cost per QALY gained, £)	Deterministic result	Probabilistic result
pNETS: 177Lu-DOTATATE v everolimus	£9,847	[redacted]
pNETS: 177Lu-DOTATATE v sunitinib	-£68,916 (Dominant)	[redacted]
GI-NETS: 177Lu-DOTATATE v everolimus	£19,816	[redacted]

- Summary results of scenario analyses:
    - Shortening the time horizon to 5 or 10 years reduced ICERs, except the 5-year comparison with everolimus in GI-NETs where the ICER increased to £23,334.
    - Discounting of costs and benefits to 6% and 1% respectively decreased all ICERs.
    - Increasing 177Lu-DOTATATE dose intensity to 100% increased all ICERs (pNETs, vs everolimus = £14,206 per QALY gained; pNETs, vs sunitinib = £29,686; GI-NETs, vs everolimus = £26,386).
    - •Alternative source of utility in pre-progression in the GI-NETs
        - NETTER-1 (mean all patients, 0.750) instead of Guy's and St Thomas' NHS Foundation Trust (0.793), the ICER 177Lu-DOTATATE vs everolimus = £21,295.
        - ERASMUS (GI-NETs subgroup, 0.773) instead of Guy's and St Thomas' NHS Foundation Trust (0.793), the ICER 177Lu-DOTATATE vs everolimus = £20,931 (not £20,136 as reported by AAA).
    - Including palliative care costs and an end-of-life utility decrement in the last four weeks of life has a negligible effect on ICERS in both pNET and GI-NET evaluations.
    - The inclusion of background mortality has a negligible effect on findings.

6.2.1.3.3 Strengths and Weaknesses of AAA's evaluation

Strengths

- The analysis separated the evaluation of pNETs from GI-NETs.
- The structural methodology followed recommended approaches and was implemented correctly. The model was well presented, transparent and generally straight-forward to understand.
- Serious adverse events were incorporated, albeit poorly.
- The model was found to contain only minor errors in wiring which could effectively be overlooked.

Weaknesses

- No comparison was made with a strategy of best supportive care.
- The MTCs used to inform the relative treatment effect in each of the evaluations were premised on crucial yet unjustified assumptions:
    - that octreotide 60mg can be assumed to be equivalent to placebo and placebo + octreotide 30mg in the GI NETs network,
    - that octreotide 60mg is equivalent to placebo and placebo + BSC in the pNETs network, and
    - that data from the NETTER-1 trial can be used to inform the network for pNETs even though no participants within NETTER-1 had pNETs.
- The MTCs used to inform the relative treatment effect in each of the evaluations were premised on weak methodology:
    - RADIANT-2 should be not have been included from the GI NETs MTC as the population all have functioning tumours which is outside of the marketing license for everolimus for GI NETs.
    - NETTER-1 should not have been included in the pNETs MTC as it does not contain any patients with pNETs, making AAA's pNETs evaluation is tenuous.
    - there is no consideration of the extent of treatment switching within RADIANT-2 (58% switched to active treatment), RADIANT-3 (73% switched to active treatment) and A6181111 (69% switched to active treatment) which limits the interpretation of results for OS,
- Treatment after progression was over-simplified to octreotide for across all strategies, continued until death.
- Everolimus and sunitinib treatment was assumed to continue until disease progression. This is an overestimate of usage and therefore cost since the average duration of treatment in trials is a fraction of this period.
- The pNETs evaluation relied on non-randomised evidence for baseline estimates of PFS and OS.

- The resource requirement for the administration of 177Lu-DOTATATE is underestimated given that current practice as described by AG clinical experts is for overnight stay rather than day case administration, and there is a greater time requirement from clinical specialists. No alternative estimates of drug administration cost were tested. Exploratory univariate variations in 177Lu-DOTATATE administration cost carried out by the AG revealed that this may be an important area for scrutiny.
- The costing of serious adverse events is implemented poorly. On the one hand they are underestimated due to overly low unit costing of serious adverse events, most of which require attention in the hospital setting; on the other hand they are over-estimated by their application well beyond the expected mean duration of treatment.

Table 105: Characteristics of submitted models by Novartis

Company	Population	Comparators	Horizon	Model structure	Health states/events modelled	Utilities	Costs	Key individual parameters (sensitivity analysis)	Source of effectiveness parameters	Comments
Novartis	Advanced, progressive, well or moderately-differentiated pNETs	Everolimus vs Sunitinib	20 years	Semi-Markov – partitioned survival with monthly cycles Proportional hazards model PFS and OS with baseline Weibull form	-SD -PD -Death	SD with no AE SD with AE: Everolimus SD with AE: Sunitinib PD Death (0) Source: Vignettes (Swinburn 2012)	drug administration, drug acquisition, AEs, resource use (physician visits, procedures/ tests and hospitalisations) and post-progression therapy costs Source: Novartis data on file NHS Ref Costs & PCTs combined	-PFS HR -OS HR -relative dose intensity - treatment duration (use of PFS for treatment costs)	HR: IC of HRs of (updated) A6181111 RCT (Sunitinib) vs. RADIANT-3 (Everolimus) outcome data [Bucher method] Parametric baseline function from RADIANT3 company data on file	The model adjusted OS outcomes for treatment crossover in the placebo arm using RPSFT method. Were PFS, OS and treatment duration estimated from publicly available data? – OS: Everolimus, company data from RADIANT3; Sunitinib, aggregated data (KM curve) from internal SMC submission. PFS : yes, data from RADIANT3 and A6181111 (updated) Were the mean treatment cycles provided? No – Assumptions based on PFS were used Resource use was obtained from a UK resource utilisation survey with 32 expert clinicians Weibull baseline (Everolimus) OS curve selected by comparison with SEER data. PFS Weibull curve selected for consistency with OS curve.
Novartis	Advanced progressive, non-functional, GI/Lung NETs From phase III RADIANT-4 trial	Everolimus + BSC vs BSC	30 years	Partitioned survival with monthly cycles (3 states) Restricted lognormal distribution for PFS and OS (base case)	-Stable disease -Disease progression -Death	SD PD Death	Active-anti-tumour treatment, BSC, Procedures/tests, Physician visits, Therapy Administration Costs and Dispensing Fees, Hospitalisations, AEs, Post-progression treatments, End-of-life care.	Not presented in the submission (including Appendices)	The most mature data from RADIANT-4 were used in the modelling of PFS (by central review) and OS. For PFS, the primary analysis data cut-off (28th November 2014) was used and for OS, data from the	Did the model adjust for treatment crossover in all arms? In the trial crossover was not allowed. Were PFS, OS and treatment duration estimated from publicly available data? RADIANT-4 Were the mean treatment cycles provided? "The proportion of patients remaining on everolimus at each cycle in the stable disease health state was derived from the time-on-treatment curve which was

								second OS interim analysis data cut-off (30th November 2015) were used	calculated using patient-level data from RADIANT-4" (Novartis' submission).	

Table 106: Characteristics of submitted models by AA

Company/ Indication	Population	Comparators	Horizon	Model structure	Health states/events modelled	Utilities	Costs	Key individual parameters (sensitivity analysis)	Source of effectiveness parameters	Comments
AAA, pNETs within GEP-NETs	pNETs Effectiveness evidence from only the Dutch population of the progressive pNET subgroup of patients in the ERASMUS study - patients with inoperable somatostatin receptor-GEP-NETs.	177Lu DOTATATE Versus: Everolimus Sunitinib Also: Octreotide LAR – out of scope	20 years (lifetime)	CUA, QALYs Three state Markov with Partitioned-survival. 4-week corrected cycles Proportional hazards model PFS and OS with baseline Weibull form	Pre-progression (PFS) Post-progression (PPS) Death	EORTC-CQC- C30 mapped to EQ-5D. PFS: 0.80 PPS: 0.79 AE disutility from various literature sources. G3/4 only. Applied per cycle.	Drug acquisition; drug administration; monitoring; adverse events. Resource utilisation rates from the NETTER-1 CSR Base case includes 177Lu DOTATATE drug acquisition cost reduction for real world dose intensity (86.4%) BSC = Octreotide LAR 30mg	PFS HRs OS HRs PFS and PPS health state utilities 177Lu DOTATATE dose intensity 177Lu DOTATATE drug cost	ERASMUS clinical study report (v1) for baseline PFS and OS risk curves (direct extraction). PFS and OS adjusted for an extreme value. Mixed-treatment comparison for adjusted proportional hazards. RADIANT-3 RCT for Everolimus outcome data [Yao 2011]: Raymond 2011 for Sunitinib data. NETTER-1, RADIANT-3 and Raymond 2011 RCTs for AE proportions.	No comparison to BSC. No reported crossover between arms in NETTER-1. Crossover was not allowed in RADIANT-4. PFS and OS of 177Lu DOTATATE was not drawn from publicly available source (NETTER-1 CSR). To link MTC network the treatment effect of octreotide LAR was assumed equivalent to placebo. Everolimus and sunitinib treatment is continued until progression, not for their mean treatment duration. No nuclear scientists involved in administration of lutetium- cost underestimated?

									PFS utility sourced from ERASMUS study.	
AAA, GI NETs within GEP-NETs	Patients with inoperable, somatostatin receptor-positive mid-gut carcinoid tumours (NETTER-1 study)	177Lu-DOTATATE versus Everolimus (also Octreotide LAR – out of scope)	20 years (lifetime)	CUA, QALYs Three state Markov with Partitioned-survival. 4-week corrected cycles Proportional hazards model PFS and OS with baseline Weibull form	Pre-progression (PFS) Post-progression (PPS) Death	EORTC-CQC- C30 mapped to EQ-5D. PFS: 0.79 PPS: 0.74 AE disutility from various literature sources. G3/4 only. Applied per cycle.	Drug acquisition; drug administration; monitoring; adverse events. Resource utilisation rates from the NETTER-1 CSR Base case includes 177Lu-DOTATATE drug acquisition cost reduction for real world dose intensity (86.4%) BSC = Octreotide LAR 30mg	PFS HRs OS HRs PFS and PPS health state utilities 177Lu-DOTATATE dose intensity 177Lu-DOTATATE drug cost (no PAS) Drug costs not included in SA	NETTER-1 clinical study report (v1) for baseline PFS and OS risk curves (direct extraction). Mixed-treatment comparison for adjusted proportional hazards. RADIANT-2 and 4 RCTs for Everolimus outcome data [Pavel 2011, Yao 2016] NETTER-1 and RADIANT-4 RCTs for AE proportions. PFS utility sourced from UK Trust registry; PPS from ERASMUS study.	No comparison to BSC. No reported crossover between arms in NETTER-1. Crossover was not allowed in RADIANT-4. PFS and OS of 177Lu-DOTATATE was not drawn from publicly available source (NETTER-1 CSR). To link MTC network the treatment effect of Octreotide LAR =was assumed equivalent to placebo. Everolimus and sunitinib treatment is continued until progression, not for their mean treatment duration. No nuclear scientists involved in administration of lutetium- cost underestimated?

Table 107: Results of industry model submissions

Study	Regiments compared	Patient characteristics	Time horizon	PFS years	Life years (un-discounted) unless otherwise stated	Discounted (3.5%) Incremental QALYs	Discounted (3.5%) Incremental costs (£)	ICER Incremental cost per QALY	Notes on ICER
Novartis pNETs	Everolimus Sunitinib	pNETs As in RADIANT-3 (Everolimus) A6181111 (Sunitinib)	20 yrs	Eve: 14.348 Sun: 12.512	Eve: 3.298 Sun:2.85	0.021	-£1,635.86 [redacted] (PAS)	Dominant Dominant (PAS)	Costs & and QALYs 3.5% discounting PAS with [redacted] discount on Everolimus
Novartis GI-NETs	Everolimus+BSC BSC	Mean age 61.7 yrs (RADIANT-4)	30 yrs	Eve: 11.01 BSC: 5.50	Eve: 5.793 BSC:4.775	0.777	£33,902	£43,642 (list price) [redacted] (PAS price)	Costs & QALYs adjusted to 3.5%/ year, and are in 2014-2015 prices
AAA, GI NETs within GEP-NETs	177Lu-DOTATATE Everolimus	From NETTER-1 CSR: Mean age 63.7 years; weight 74.05 kg. Population: Unresectable or metastatic GI-NETs with disease progression	20 yrs	LUT: 1 yr: 80.84% 5yrs: 11.58% 10yrs: 0.34% EVE: 61.99% 5yrs: 0.79% 10yrs: 0.00%	Discounted: LUT: 4.26 EVE: 2.49	1.42	[redacted]	[redacted]	Base case excludes cost of palliative care; includes concomitant drugs; includes a dose intensity adjustment for lutetium.
AAA, P NETs within GEP-NETs	177Lu-DOTATATE Everolimus Sunitinib (SUN)	From NETTER-1 CSR: Mean age 63.7 years; weight 74.05 kg. Population: Unresectable or metastatic pNETs with disease progression	20 yrs	LUT: 1 yr: 90.06% 5yrs:19.53% 10yrs:0.58% EVE: 83.97% 5yrs: 6.56% 10yrs:0.02% SUN: 78.53% 5yrs: 3.80% 10yrs:0.00%	Discounted: LUT: 6.91 EVE: 4.16 SUN: 6.84	2.18	LUT v EVE [redacted] LUT v SUN [redacted]	LUT v EVE [redacted] LUT v SUN [redacted]	Base case excludes cost of palliative care; includes concomitant drugs; includes a dose intensity adjustment for lutetium.

Key: EVE, everolimus LUT, 177Lu-DOTATATE; pNETs, pancreatic NETs; SUN, sunitinib; yrs, years

7 Independent economic assessment

7.1 Methods

7.1.1 Model structure

7.1.1.1 Structure of relevant published models

In Table 108 we present the key aspects of published models from the studies included in our systematic review of the cost-effectiveness of drugs for treating NETs. For comparison, we include characteristics of the PenTAG model.

Table 108: Structure of relevant published cost-effectiveness models compared to PenTAG model

	Casciano et al. (2012)	Ortega et al. (2012)	Johns et al. (2012)	Walczak et al. (2012)	PenTAG
Model type	Partitioned survival	Markov	Markov	Markov	Partitioned survival
Patient population	Advanced progressive pNETs	Non-resectable pNETs	Advanced or metastatic pNETs	Patients with unresectable or metastatic well-differentiated pNETs with disease progression	People with progressed unresectable or metastatic neuroendocrine tumours of pancreatic, gastrointestinal or lung origin
Initial treatments	Everolimus vs. Sunitinib (including somatostatin analogs)	Sunitinib + BSC vs. Placebo + BSC	Sunitinib+BSC vs. Placebo + BSC	Sunitinib and BSC vs. placebo and BSC (including somatostatin analogs)	For pNETs, everolimus vs. BSC; everolimus vs. sunitinib; sunitinib vs. BSC For GI NETs: everolimus vs. BSC; everolimus vs. 177Lu-DOTATATE; 177Lu-DOTATATE vs. BSC; For GI and lung NETs: everolimus vs. BSC
Health states	"Stable disease with no adverse events", "Stable disease with adverse events", "Disease progression" and "Death"	"Pre-progression", "Post-progression" and "Death"	"Progression-free", "Post-progression" and "Death"	"Initial state", "Disease progression" and "Death"	"Pre-progression", "Post-progression" and "Death"
PFS & drug costs	PFS estimates were obtained from the indirect analysis [Signorovich] based on data from RADIANT-3 trial and the A6181111 study. Initial treatment assumed up to progression.	PFS data used in this analysis was from A6181111 study. Costs included the costs of drug acquisition, medical management, including specialist consultations, laboratory and imaging tests, pain management, and palliative care.	PFS data are from the phase III A6181111 trial. Cost components were not reported.	PFS data from the A6181111 RCT (2011) was extrapolated using Weibull method and RPSFT method (to allow for crossover between the arms of the clinical trial). Not stated	Initial treatment assumed up to progression
Subsequent treatments	BSC	BSC		BSC	BSC
Method of estimating overall survival					
	OS estimates were obtained from the indirect analysis [Signorovich] based on data from RADIANT-3 trial and the A6181111 study. []	OS data used in the analysis was from A6181111 study.	OS data from the phase III A6181111 trial was adjusted for crossover using RPSFT method.	OS data from A6181111 RCT (2011) was extrapolated using Weibull and RPSFT method (to allow for crossover between the arms of the clinical trial).	Extrapolation of OS from RCTs

Patient age at model entry (years)	Not reported	Not reported	Not reported	Not reported	60
Cycle length	30.4 days	2 weeks	Not reported	4 weeks	28 days
Time horizon	20 years	20 years	Lifetime	Lifetime	40 years

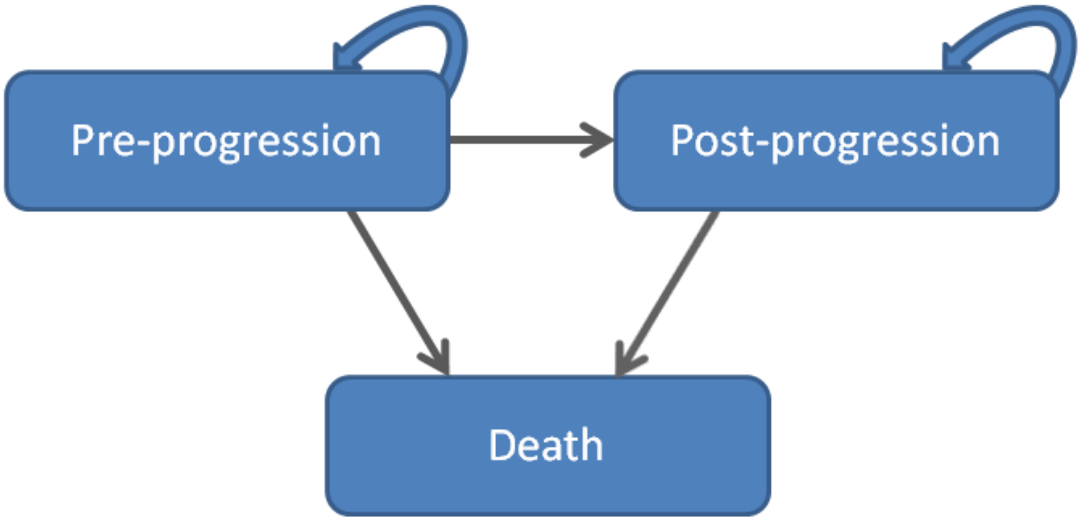
Key: BSC = best supportive care; OS = overall survival; PFS = progression free survival; PD = progressive disease; pNETs – pancreatic neuroendocrine tumours; RCT = randomised control trial

7.1.1.2 Structure of PenTAG model

The majority of the studies, selected during systematic review of cost-effectiveness (see section 5.1), reported models with 3 health states. The study by Casciano et al. (2012)[95] reported a 4 states model distinguishing patients with and without symptoms in the stable disease state. However, in this publication there is inconsistency between the graphical representation of the model and the model description. We believe that the reported model had only 3 states: stable disease, disease progression and death.

In our analysis, we adopt the 3 states model structure shown on Figure 38.

Figure 38: Structure of PenTAG cost-effectiveness model



The model health states are defined as follows:

- Pre-progression
- Post-progression
- Death

A description of the health states is provided in Table 109.

Table 109: Model states

Health state	Description	Possible transitions
Pre-progression	This health state captures the period of time from the start of treatment to disease progression.	Post-progression, Death
Post-progression	This health state captures time from disease progression to death.	Death
Death	This is an absorbing state in the model.	N/A

The PenTAG cost-effectiveness model, implemented in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), simulates a hypothetical cohort of 1,000 patients with progressed unresectable or metastatic neuroendocrine tumours. At the beginning of simulation, all patients start in the pre-progression state and then transition to post-progression and death states according to PFS and OS estimates. At the end of each cycle, they can either remain in their current health states (which is denoted by bent arrows) or

move to other states (which is depicted by straight arrows). Death is the absorbing state in this model. Health state membership is defined using partitioned survival approach which estimates the mean time spent in each health state from the area under the relevant survival curve. Therefore, the transitions in Figure 38 are not modelled explicitly. Costs and utilities are estimated for each health state and model cycle, and aggregated over the modelled time horizon to estimate the total per patient costs and QALYs for each treatment. The economic outcome in the model is the ICER. A model half-cycle correction has been applied.

The structure of the PenTAG model, informed by a cost-effectiveness systematic review and the opinions of our clinical experts, is very similar to the structures of the models submitted by the companies (see Table 74 for a detailed description of submitted models).

In the model, we assume that:

- Patients receive active treatment until disease progression or earlier treatment discontinuation due to onset of serious adverse events or other reasons as observed in the RCT sources of effectiveness data.
- On progression of disease, patients are treated with BSC.

See section 7.1.3 for further details on treatments and comparators considered in our analysis.

7.1.2 Population

In line with the NICE Scope, we considered people with progressed unresectable or metastatic neuroendocrine tumours from 3 different patient populations according to tumour location:

- Patients with NETs of pancreatic origin
- Patients with GI and lung NETs
- Patients with GI midgut NETs

The choice of these particular patient populations was determined by the available clinical effectiveness RCT data. We did not consider any other subgroups in our analysis since no relevant clinical evidence was identified during the clinical effectiveness systematic review (see sections 4.2.5.1.6 and 4.2.5.3.6 further details).

7.1.3 Interventions and comparators

Clinical data identified during the systematic literature review allowed the analyses shown in Table 110. The treatments included in the model were:

- Everolimus
- Sunitinib
- 177Lu-DOTATATE (in scenario analyses only)
- BSC

All treatments are in the NICE Scope.

Table 110: Comparative analyses of treatments

Tumour location	Treatment	Treatment or Comparator	Type of data	Source of data
pNETs	Everolimus	BSC	Head-to-head RCT	RADIANT-3
	Everolimus	Sunitinib	Indirect comparison	RADIANT-3, A6181111
	Sunitinib	BSC	Head-to-head RCT	A6181111
GI NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4
	Everolimus	177Lu-DOTATATE	Indirect comparison	RADIANT-4, NETTER-1
	177Lu-DOTATATE	BSC	Head-to-head RCT	NETTER-1
GI and lung NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4

Key: BSC = best supportive care; GI = gastrointestinal; pNETs = pancreatic neuroendocrine tumours

All treatments included in the model are used in NHS clinical practice in England and Wales. Chemotherapy and interferon alpha were both considered as comparators in the NICE Scope. However, no evidence on the clinical effectiveness of chemotherapies listed in the Scope has been identified during clinical effectiveness systematic literature review (Section 4.2). Therefore, chemotherapy was not included in our analysis. Following the advice from our clinical experts, the AG did not consider interferon alpha in their economic analysis since it is not commonly used in UK clinical practice.

No evidence on the clinical effectiveness of chemotherapies listed in the NICE scope has been identified during clinical effectiveness systematic literature review (Section 4.2). Therefore, chemotherapy was not included in our analysis. We did not include interferon in the analysis given the opinion of our clinicians that it is rarely used in this country.

7.1.4 Perspective, time horizon and discounting

The model perspective was that of the NHS and Personal Social Services, in accordance with the NICE Reference Case.[131] In the base-case analysis, the model time horizon was 40 years which reflects the lifetime horizon of patients with advanced neuroendocrine tumours; costs and benefits were discounted at 3.5% per annum. The model used a 4-weekly cycle length, in order to facilitate the implementation of the costs of 177Lu-DOTATATE drug acquisition and administration as these were incurred every 4 weeks.

A number of scenario analyses were performed to estimate the effect on outcome of different survival model structures and data, assumptions on discount rate and model time horizon (see scenario analysis section 7.2.20 for further details).

7.1.5 Model parameters

7.1.5.1 Population characteristics

7.1.5.1.1 Mean age

We assume that all patients are aged 60 at the start of treatment. The estimate of the mean age of patients in the model population was based on the patient characteristics from clinical trials used in our analysis. In the model, this affects only age-related utilities and background mortality. Mean age estimates from the companies' models are shown in Table 111 alongside the value used in PenTAG's base-case analysis.

Table 111: Mean age in the PenTAG and companies' models

Model	Parameter value	Source
PenTAG	60	Average age in the trials identified during cost-effectiveness systematic review
AAA: GI-NET	63.7	Netter-1
AAA: pNET	63.7	Erasmus
GEPNETs	61.7	Netter-1 CSR
GETNETs	Not reported	

7.1.5.1.2 Gender composition

All analyses were performed assuming the proportion of male patients is 53% (as in RADIANT-3), which only affects background mortality (Scenario analysis section 0). Relevant assumptions from the models in the company submissions are shown in Table 112.

Table 112: Gender composition

Model	% male	Source
PenTAG	53%	RADIANT-3
AAA	50%	Not reported
GEPNETs	Assuming 105 male births for every 100 female births (Excel model)	Not reported
GETNETs	Not reported	Not reported

7.1.5.2 Background mortality

In the base case, we did not incorporate background mortality in all analyses; we accounted for this in scenario analyses related to 177Lu-DOTATATE. This was because the PFS and OS curves on which the partitioned survival in the model was based was expected to account for background mortality. However, background mortality rises as the modelled cohort ages, and since in some analyses OS data were immature, in those cases the effect of background mortality was taken into account using data for the years 2012-2014 from the Office for National Statistics (Table 113).

Models submitted by AAA for GEPNETs allow estimation of ICER with and without general mortality. When it was taken into account, it was modelled in the subpopulation of patients with stable disease, while in the subpopulation of patients whose disease has progressed background mortality was not modelled. Therefore, death events are double-counted during stable disease stage and may be underestimated in progressive disease subpopulation.

In contrast, none of the model-based analyses submitted by Novartis', which considered pancreatic and GI/Lung locations, separately models background mortality.

Table 113: Background mortality

Model	Probability of death	Source
AAA	Yearly probability of death was averaged across genders	Not reported
GEPNETs	Not considered	N/A
GETNETs	Not considered	N/A
PenTAG	Background mortality was not modelled in the base-case analysis. In scenario analyses related to 177Lu-DOTATATE, background mortality was applied in pre- and post-progression states.	Office of National Statistics for the years 2012-2014.

7.1.5.3 Treatment effectiveness and extrapolation

7.1.5.3.1 Baseline RCTs

For pNETs population, the RADIANT-3 RCT was chosen as the baseline trial, while RADIANT-4 was the baseline RCT for GI (midgut), and GI lung NETs analyses. The size of the study population in these trials was larger, and the data was more mature compared with A6181111 and NETTER-1. In addition, the control arm in NETTER-1 was octreotide 60mg daily plus BSC, which is out of NICE Scope for this review.

7.1.5.3.2 Modelled PFS and OS

A partitioned survival approach was used to populate the parameters of the semi-Markov model. PFS Kaplan-Meier curves of trial arms from the main RCTs informing the company submissions on pNETs (including the A6181111 and the RADIANT-3 trials), GI/Lung location (RADIANT-4), and GI midgut (RADIANT-4 midgut subgroup and NETTER-1) were extracted from graphs in the latest available source (peer reviewed publications for A6181111[45], RADIANT-3,[31] and RADIANT-4,[44] a published conference abstract for RADIANT-4 midgut [127], and industry submission (NETTER-1)) using digitizing software and the extracted data used to recreate the associated original individual patient data using the Guyot algorithm implemented in R.[133]

A range of parametric curves from the

- proportional hazards (Weibull, exponential, and Gompertz),
- piecewise proportional hazards (restricted cubic splines with 5 pieces or knots), and
- accelerated failure time (log normal, log-logistic, and generalised gamma)

families were fit to the recreated individual patient data of each arm separately and evaluated for use in the base case analysis according to goodness of fit criteria (Akaike's and Bayesian Information Criteria), visual fit to the empirical data (i.e. the instantaneous probability of event occurrence and Kaplan-Meier curve), plausibility of long term extrapolation, and consistency between PFS and OS (i.e. no crossing of PFS and OS curves of the same trial arm). We also consulted our clinical experts for their opinion about the plausibility of the long term extrapolations associated with candidate functions. Finally, for our base case analysis we adopted the recommended practice that the same parametric function be used to extrapolate trial data for all arms in a comparison, to avoid introducing subjective assumptions in the long term effectiveness estimates.[134] We relax this restriction in scenario analyses. The following is a summary of the main results of the two time to event outcomes in each of the three locations analysed.

In the RCT sources of effectiveness data for the pNETs model, treatment switching from the placebo arm to the active treatment arm was observed after disease progression (89% in RADIANT-3 and 65% in A6181111). Therefore the following analyses for pNETs are based on Kaplan-Meier OS curves adjusted for cross-over, using the rank-preserving structural failure time method (Robbins and Tsiatis 2002). This approach only affects the placebo arm of each trial, and produces a counterfactual placebo Kaplan-Meier curve, that is, the curve that would have occurred had no patient switched to the active arm.

In contrast, the analysis for GI or Lung NETs is based on the RADIANT-4 trial, where 6% of placebo patients switched to the active arm after disease progression (Yao et al. 2016).

Since no evidence has been identified on RADIANT-4 OS data that adjusts for treatment switching in the placebo arm, the following analyses are based on the most recent ITT OS curves reported for RADIANT-4 (cut-off date November 20 2015; Yao et al. 2016). As for the PFS Kaplan-Meier curves used in our analysis, switching to new active antineoplastic therapy before disease progression occurred in [redacted] of patients in the everolimus arm and [redacted] in placebo (central radiological review), and these cases were censored from the analysis at the time of switch (RADIANT-4 Final CSR, p. 71).

Pancreatic NETs

In general, accelerated failure time models had better fit than other models to the observed progression free survival data from the RADIANT-3 treatment arms, but their advantage was not significant (i.e. BIC difference < 5 between Weibull and Loglogistic) in the everolimus arm. The fact that the best model for the placebo arm of RADIANT-3 was the restricted cubic spline (with 6 segments), suggests that the other models may not be valid representations of the trial data for that arm. The exponential was the model with best (i.e. lowest) goodness of fit statistic for sunitinib in A6181111 (Table 114), although no significant differences were found between models. On the basis of this and the available evidence discussed below and for consistency across arms, the model adopted the Weibull function for the everolimus plus BSC and BSC only arms, and the exponential (i.e. Weibull with shape parameter set to the value of 1) for sunitinib plus BSC, in the base case analysis.

In contrast, proportional hazard models had better fit to the overall survival data, with the exception of OS in the placebo arm of RADIANT-3, which was best represented by the lognormal according to the BIC statistic (Table 114). The model adopted the Weibull function for the everolimus arm, and exponential functions for sunitinib and BSC only model arms in the base case analysis.

Table 114: Akaike's and Bayesian information criteria of parametric models of OS in pNETs

	Everolimus plus BSC[1] N=207			**Sunitinib plus BSC[2] N=86**			**Placebo plus BSC[1] N=203**		
	Progression Free Survival								
	No. of para-meters	AIC	BIC	No. of para-meters	AIC	BIC	No. of para-meters	AIC	BIC
Weibull	2	416	422	2	178	183	2	465	472
Exponent	1	424	428	1	176	**179**	1	488	492
Gompertz	2	422	429	2	177	182	2	485	491
Lognorm	2	413	420	2	174	179	2	440	447
Loglogit	2	**412**	**419**	2	176	181	2	443	450
Gamma	3	414	424	3	172	180	3	440	450
Spline	6	419	439	6	**169**	183	6	**374**	**394**
	Overall Survival								
weibull	2	554	561	86	237	242	203	396	403
Expon	1	555	558	86	235	**238**	203	399	402
gompertz	2	555	561	86	237	242	203	401	407
lognonrm	2	560	567	86	**233**	238	203	387	**394**
Loglogit	2	557	563	86	234	239	203	393	399
Gamma	3	556	566	86	235	242	203	**385**	395
Spline	6	560	580	86	238	252	203	390	410

Notes: [1] Source: recreated data from ITT PFS (central review) Kaplan-Meier curves in RADIANT-3 (Yao et al. 2011) and RPSFT model-adjusted OS Kaplan-Meier curves in RADIANT-3 (Yao et al. 201X, Novartis submission to NICE). [2] Source: recreated data from ITT PFS Kaplan-Meier curves in A6181111 (Raymond et al. 2011) and PFSFT model-adjusted OS Kaplan-Meier curves in A6181111 (Raymond et al. 2016, Pfizer submission to NICE).

Progression free survival

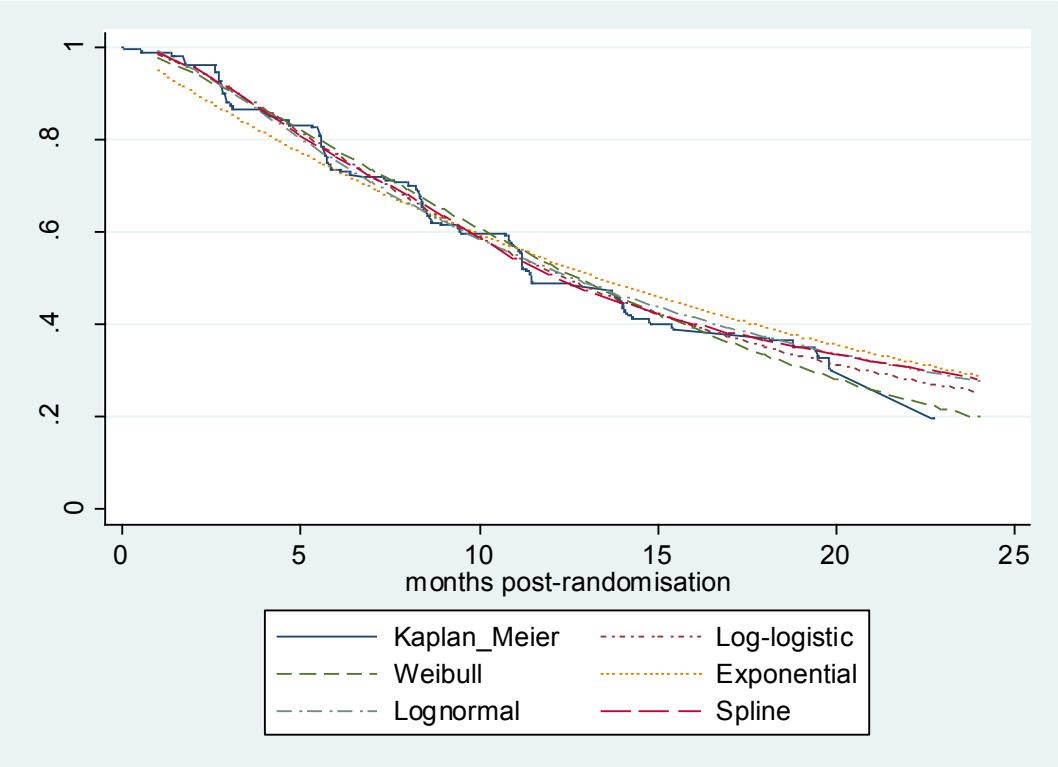
Our base case analysis adopted the Weibull function for PFS outcomes with everolimus and the BSC only arm, and the exponential for the sunitinib arm in the model. Scenario analyses adopted instead the log-logistic, exponential and log normal, for everolimus plus BSC, sunitinib plus BSC, and BSC only, respectively.

Everolimus plus BSC

The loglogistic model has the most favourable goodness of fit results (i.e. lowest value of information criteria) to the data form the everolimus arm of RADIANT-3 , although its advantage over the lognormal and weibull is not statistically significant (Table 114). The log logistic model also follows the shape of the instantaneous risk (hazard) of progression or death (see Figure 64 in Appendix 7).

The log-logistic and lognormal models perform similarly to each other in fitting the Kaplan-Meier PFS, with the Weibull model fitting the data almost as well as the log-logistic and lognormal models. However, by the end of the observed follow up period the risk of progression or death with the latter model is increasing while risk with the log normal and log-logistic are declining (see Figure 64 in Appendix 7 and Figure 39).

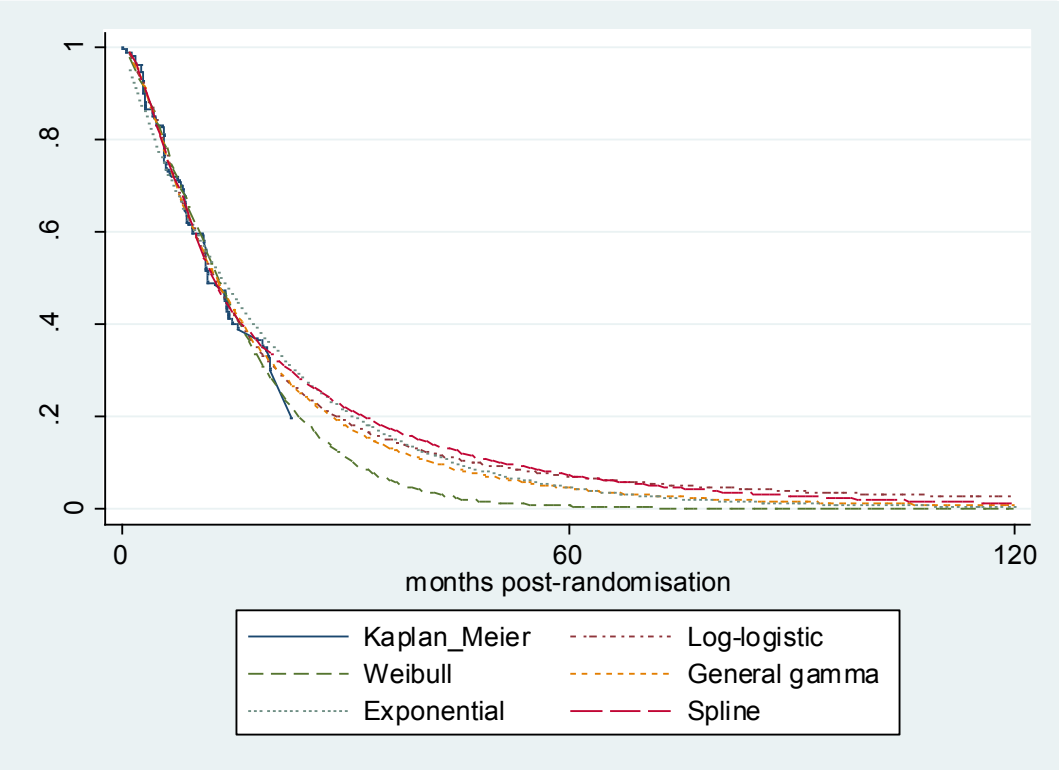
Figure 39: Everolimus arm in RADIANT-3: Kaplan-Meier and best fitting parametric PFS curves



By the end of the observation period, almost two years after randomisation, 20% of patients in the everolimus arm are alive and their disease has not progressed (Figure 40). Thus, adopting the log-logistic or log normal model has noticeable implications for the long term modelling of life free of disease progression. By the end of a 10-year follow-up 3.5% of patients would be alive and progression-free with the log logistic or log normal (not shown)

models whereas according to the Weibull, all patients would have progressed or died by 6 years after randomisation.

Figure 40: PFS of everolimus arm in RADIANT-3: Extrapolation to 10 years



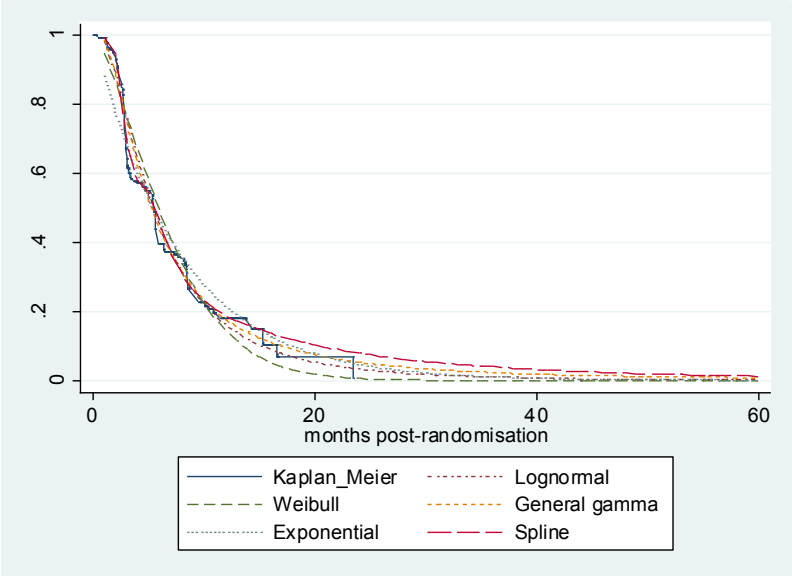
BSC alone

The BSC only arm was modelled from data from the placebo arm in RADIANT-3 (Yao et al. 2011). The information criteria in Table 114 favour the lognormal, log-logistic and generalised gamma models over the rest. The AIC and BIC statistics, however, do not discriminate between those favoured models (their magnitudes differ by less than 5 points.

The hazard function is non-constant and non-monotonic, which suggests Weibull and exponential are inappropriate models of these data (see Figure 65 in Appendix 7). The information criteria statistics are consistent with this observation and suggest that the log-normal or gamma models fit the data best.

Consistent with the model diagnostics of Table 114, the generalised gamma model is a closer match to the hazard function (see Figure 65 in Appendix 7). The log-normal approximates the smoothed hazard in Figure 65 (in Appendix 7), except for the drop between weeks 20 and 40.

Figure 41: Placebo arm in RADIANT-3: Kaplan-Meier and best fitting parametric PFS curves



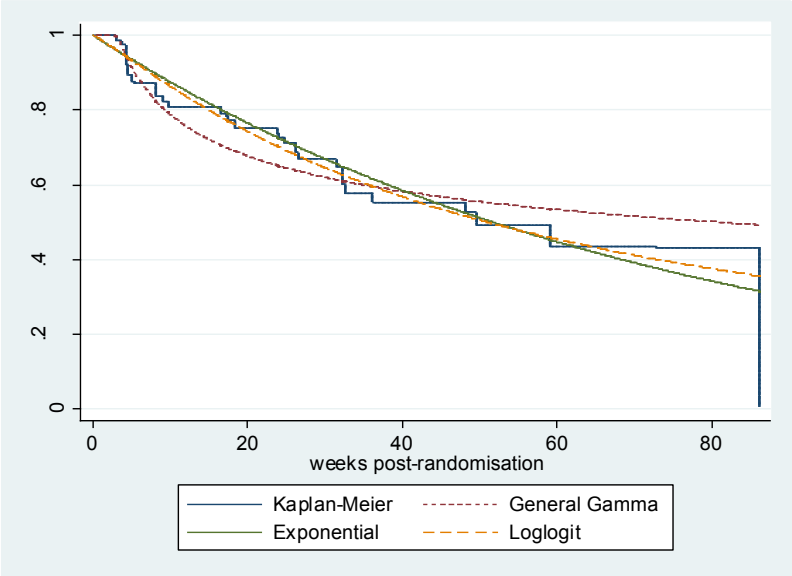
As illustrated in Figure 41, the Weibull model underestimates PFS early on, overestimates it in the medium term and underestimates it in the latter part of the analytical horizon. The log normal and generalised gamma models differ only in the latter part, which appears consistent with the log normal form. Nevertheless, the choice of curve has little impact on mean PFS in this case.

Sunitinib plus BSC

As presented in Table 114, for the PFS data of the sunitinib arm of A6181111 (Raymond et al. 2011), the gamma function has the best diagnostic results, although the differences with the exponential and lognormal models are not significant.

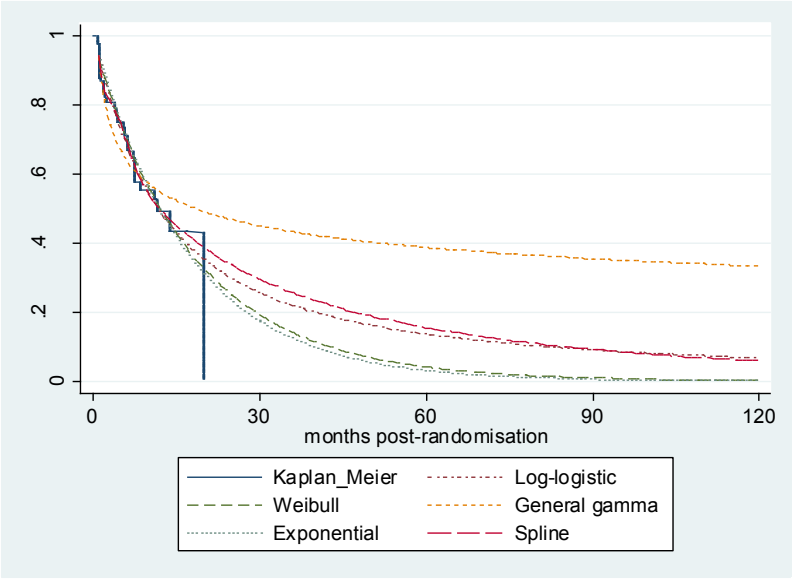
As depicted in see Figure 66 in Appendix 7 and Figure 42, the generalised gamma model consistently underestimates the risk of progression, whereas the exponential, with its constant risk fits the pattern of risk up to approximately week 30 and underestimates it thereafter. The log logistic form seems to follow the shape of the hazard function for longer periods than the other forms.

Figure 42: Sunitinib arm in A6181111: Kaplan-Meier and best fitting parametric PFS curves



The implications of adopting one of these curves to extrapolate outcomes for cost-effectiveness analysis is illustrated in Figure 43. The generalised gamma model's parametric flexibility appears to produce an overly optimistic forecast of approximately 35% of patients still alive and without experiencing disease progression after 10 years. The exponential model in contrast predicts that by 5 years 95% of people have experienced progression or died. The predictions of the log logistic model fall in between the other two, much closer to the exponential than the generalised gamma forecast.

Figure 43: PFS in sunitinib arm: Extrapolation to 10 years



t

The apparent contradictory results between the diagnostic results in Table 114, which suggests the generalised gamma function fitting the data best, and the hazard and survival function fits, suggesting that the log logit form is superior, appears to be determined by the ability of the gamma form to fit the data better in the early follow-up period, when more observations are available (e.g. number at risk 85 at baseline vs 39 at 22 weeks). Its poor

ability to match the risk (hazard) profile and the latter part of the survival curve suggests, however, that it overfitted the data. The exponential curve was thus selected for the base case analysis.

Adjustment for indirect comparisons

In order to derive estimates of PFS time for the sunitinib arm that were comparable to the PFS estimates in RADIANT-3, the sunitinib parametric PFS distribution was adjusted by the ratio of the area under the nonparametric Kaplan-Meier curves of the placebo arm in A6181111 and the placebo arm in RADIANT-3 at the shortest of the maximum follow up times across the two placebo arms. This method was preferred to the common alternative approach of using the extrapolated means, which by definition are affected by the choice of parametric function as opposed to be determined solely by the observed data, as in our 'restricted means' approach. Thus, in the base case, where the sunitinib PFS parametric distribution was the exponential, it was adjusted according to the equation:

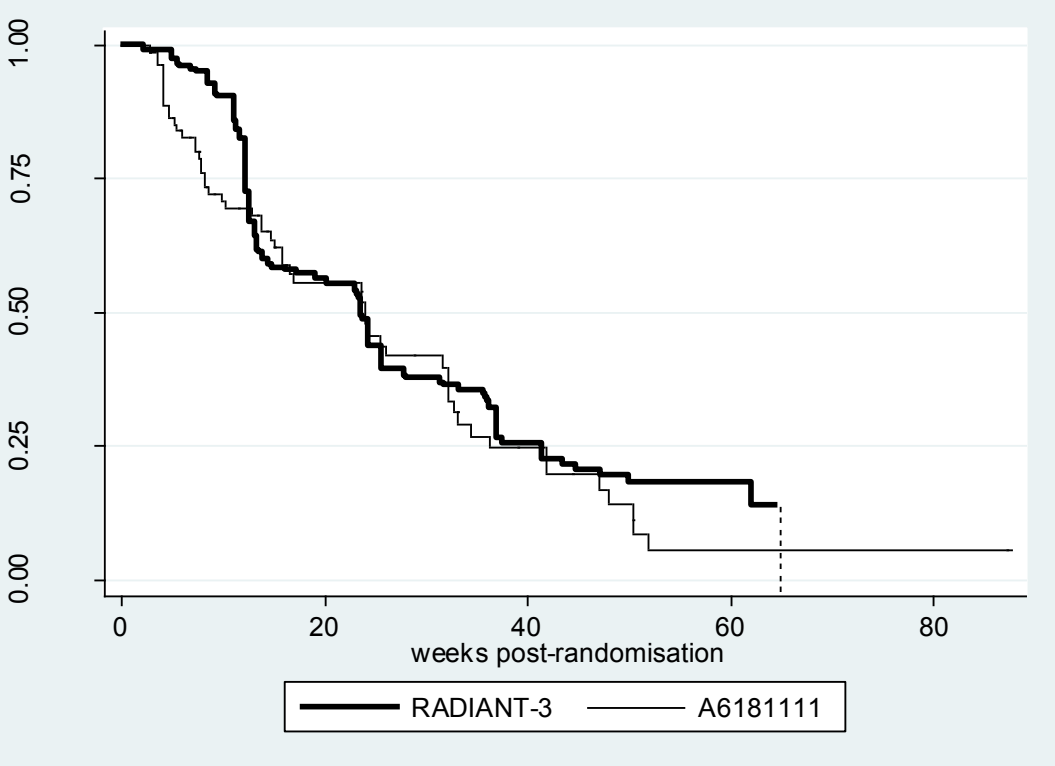
$$\widehat{\lambda_S} = \{\frac{1}{\lambda_S} * \frac{AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Ap}}{AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Rp}}\}^{-1} = (\frac{1}{0.01345} * \frac{28.85}{25.68})^{-1} \qquad \text{(Eq. 1)}$$

Where $\widehat{\lambda_S}$ is the adjusted hazard function of the exponential time-to-disease progression or death distribution, the λ_S is the hazard function of the exponential distribution estimated from the sunitinib arm of A6181111, the $AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Ap}$ and $AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Rp}$ functions are respectively the area under the K-M curves of the placebo arms of A6181111 and RADIANT-3 trials evaluated at the shortest of the maximum observation times of the placebo arms of the two trials, respectively (i.e. 65 weeks). This is illustrated in Figure 44, where the vertical discontinuous line denotes the 65th week time point. At such point the mean PFS with placebo is 25.69 weeks in A6181111 and 28.85 weeks in RADIANT-3. Thus, the PFS distribution of the sunitinib arm in the base case is $(t) = \exp(-\hat{\lambda}t) = \exp(-0.01197 * t)$. The same approach was applied for OS.

Individual patient data provided by Pfizer to the AG for this assessment allowed to investigate the robustness of indirect comparisons of PFS outcomes between the sunitinib arm in A6181111 and everolimus and placebo arms in RADIANT-3. We conducted a matched adjusted indirect comparison following the methods described in a previous study by Signorovitch and colleagues (Signorovitch et al. 2009).

[redacted]

Figure 44: PFS in the placebo+BSC arms of pNETs trials



Overall Survival

Using similar criteria to that in the analysis of PFS above, the diagnostics information in Table 114 and visual fit in Figure 67, Figure 68 and Figure 69 (from Appendix 7) and extrapolated survival rates in Figure 45, Figure 46, Figure 47 and Figure 48 resulted in the exponential model being chosen for the everolimus arm, the exponential for the sunitinib and the exponential for the BSC only arm of RADIANT-3. The resulting equation for sunitinib was then matched to the RADIANT-3 arms using the same scaling method as described for the PFS time to event analysis above. For scenario analyses, the OS function for the BSC only arm was changed to the log-normal, while keeping the exponential function for the active treatment arms.

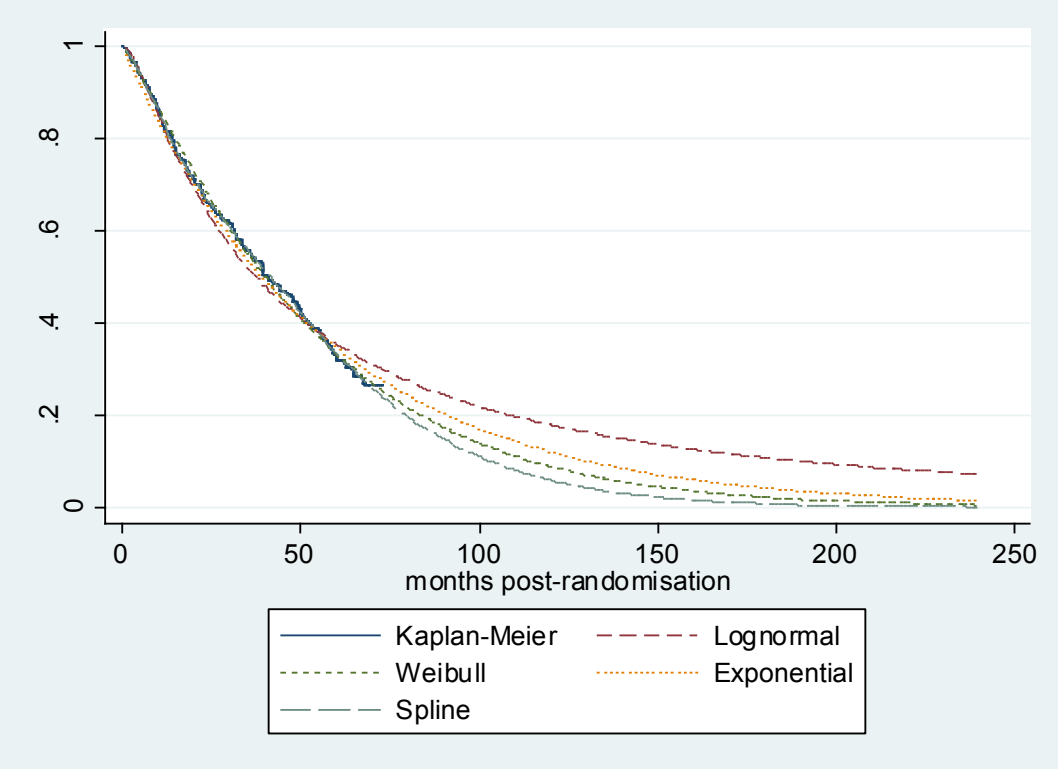
Everolimus plus BSC

As illustrated in Figure 45, according to the exponential function by 15 years (180 months) 4% of patients initially treated with everolimus remain alive, whereas according to the lognormal survival curve 10% of patients would be alive at that time point. In its submission, Novartis cites an estimated 15-year survival rate of 6% paatients with advanced pNETs from the SEER database, to narrow the candidate set of curves to those predicting survival rates above that level. However, there is the caveat that “the RADIANT-3 trial only included patients with well- or moderately-differentiated tumours with radiologic progression within the 12 months prior to entry in the study.

[redacted] In contrast, patients in the SEER registry are followed from diagnosis, and are therefore likely to be treatment-naïve. Also SEER includes all advanced patients regardless of tumour grade and SEER data were derived over a relatively long period

beginning in 1973 whereas follow-up in RADIANT-3 began in 2009." (In English life tables, the 15-year survival rate in the general population aged 60 increased from 56% in males and 74% in females in 1980-1982, to 75% and 83%, respectively, in 2006-2008 (ONS 2016)). The company states that the net impact of these differences in patient characteristics is unknown. It concludes that "it is reasonable to assume that survival in the everolimus arm of the RADIANT-3 trial would not be substantially less than that for patients with advanced pNETs in the SEER registry." (Novartis submission, p. 93).

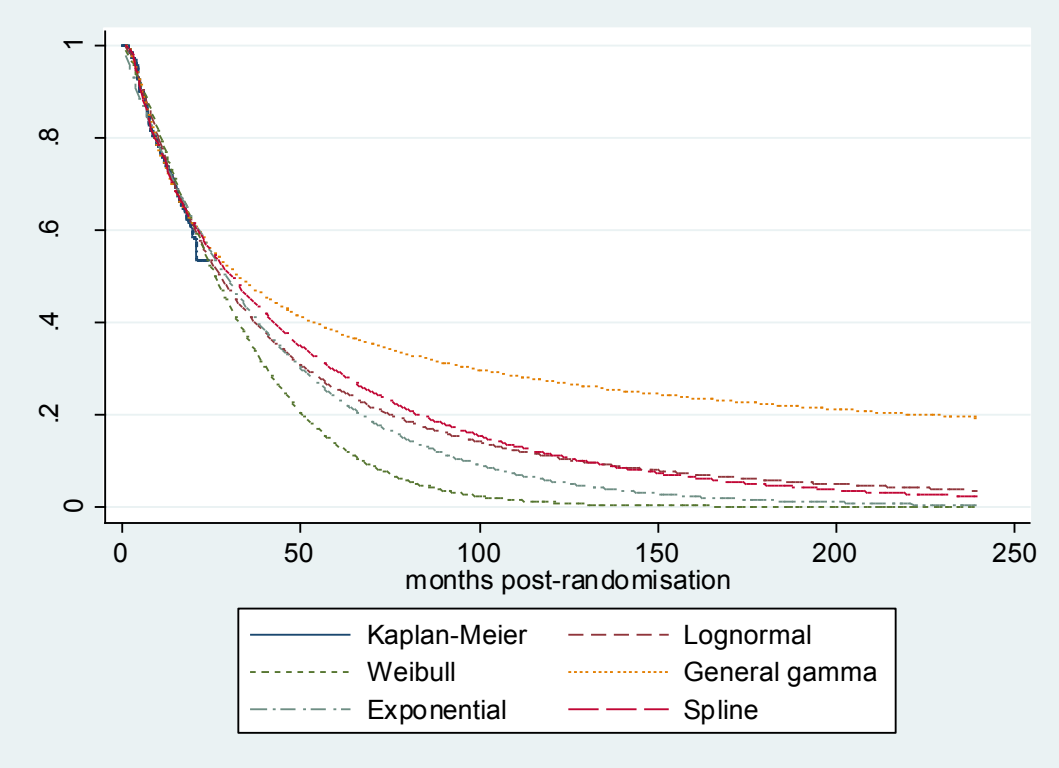
Figure 45: OS in everolimus arm of RADIANT-3: Extrapolation to 20 years



BSC alone

The lognormal function had the best fit to the data of the placebo plus BSC arm in RADIANT-3 (Yao et al. 2016). The generalised gamma had a good visual fit to the risk of disease progression or death observed in the trial (Figure 69 in Appendix 7) but an overly optimistic 20-year PFS rate of 20% (Figure 46). The exponential function underestimated the hazard risk throught the trial period (Figure 69 in Appendix 7), but had a 20 year PFS in the middle of those depicted in Figure 45.

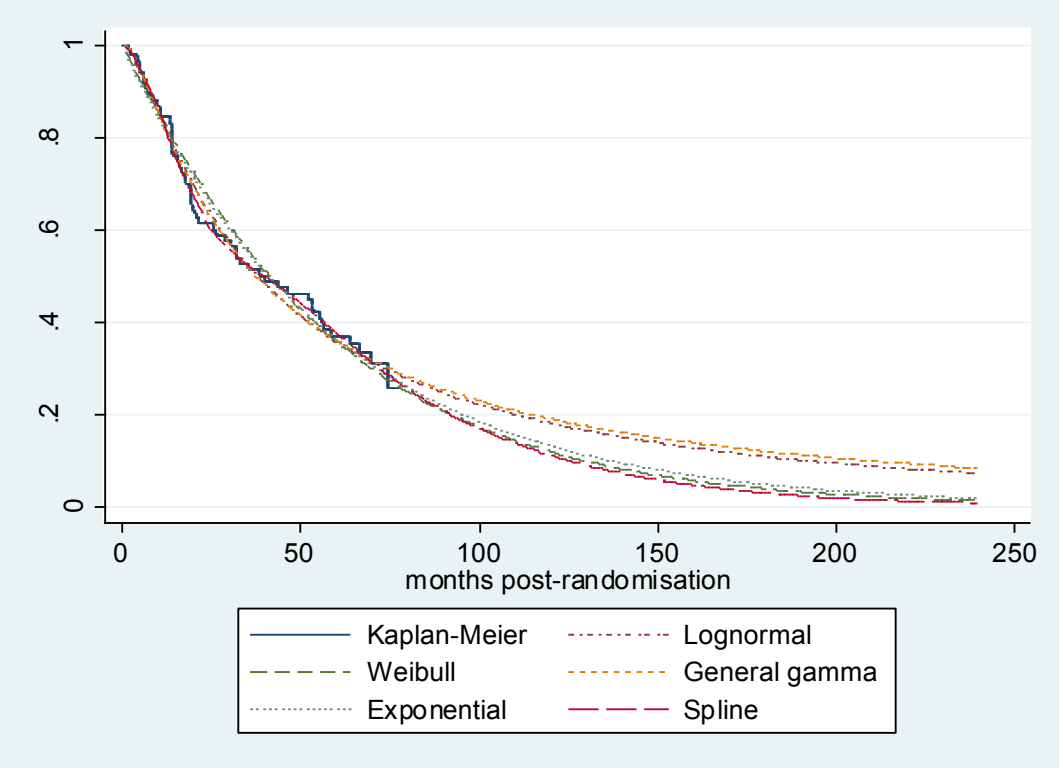
Figure 46: OS in placebo arm of RADIANT-3: Extrapolation to 20 years



Sunitinib plus BSC

The log normal and exponential functions had the best fit to the OS data from sunitinib in the A6181111 trial (Raymond et al. 2016) (Table 114), although the log normal tracked the risk of death (hazard) observed in the trial better than the exponential function (Figure 70 in Appendix 7). The projected 15-year survival rates with the log normal function are above 10% whereas with the exponential it is 4.7% (Figure 47). However, the 15-year overall survival rate used in the model, was higher than that since, after adjusting the exponential function for the difference in the placebo arms of the A6181111 and RADIANT-3 trials (see Adjustment for indirect comparisons below), it became 9.7%.

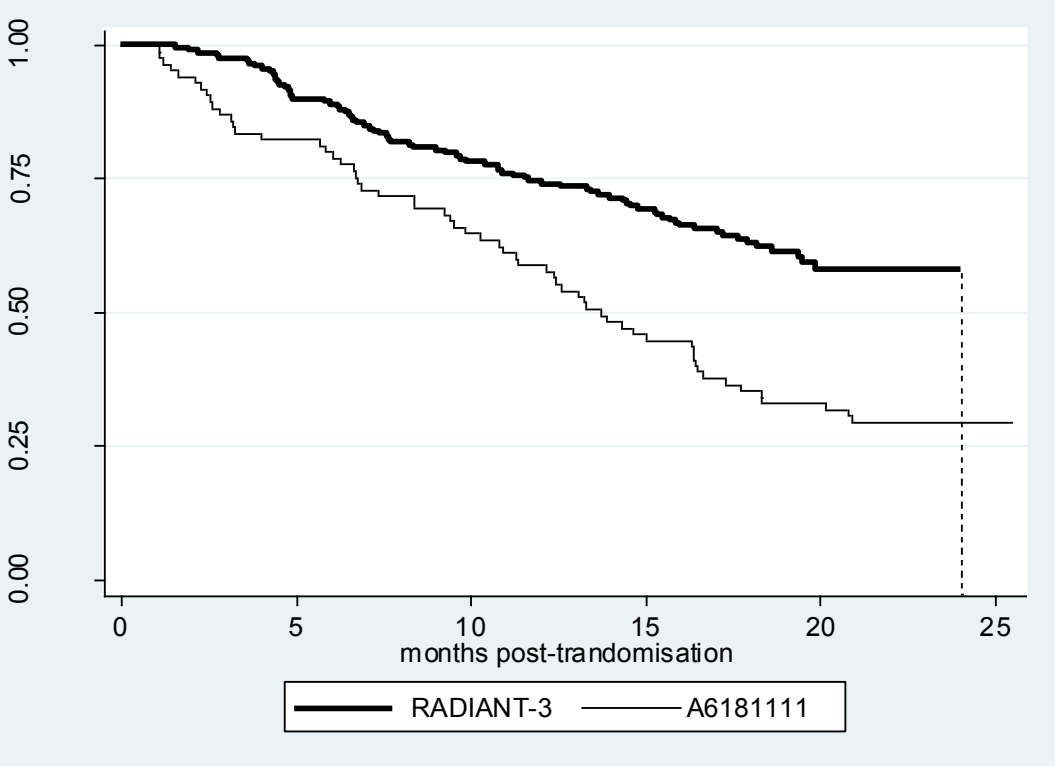
Figure 47: OS in sunitinib arm of A6181111: Extrapolation to 20 year



Adjustment for indirect comparison

As before, in order to derive comparable OS estimates with the treatments in RADIANT-3, the OS exponential curve for sunitinib was adjusted to reflect the differences in OS between the placebo arms of A6181111 and RADIANT-3. Figure 48 illustrates the difference and the vertical discontinuous line marks the point at which the AUC calculation was restricted for both arms (24 months).

Figure 48: Kaplan-Meier OS in the placebo+BSC arms of pNETs trials



GI and Lung NETs

The model diagnostics suggested that the log normal model had the best fit to the PFS data in the everolimus arm of RADIANT-4, whereas none of the 2-parameter models fitted the PFS data in the placebo arm of RADIANT-4 as well as the 3-parameter gamma or 6-parameter spline model (Table 115). In contrast, the exponential, Gompertz and Weibull models fitted the OS data as well or better than other models.

Table 115: Akaike's and Bayesian information criteria of parametric models of PFS and OS in GI/Lung NETs

	Everolimus plus BSC[1] N=205			Placebo plus BSC[1] N=97		
	Progression Free Survival					
	No. of parame-ters	**AIC**	**BIC**	**No. of para-meters**	**AIC**	**BIC**
Weibull	2	456	463	2	258	263
Exponential	1	461	465	1	256	259
Gompertz	2	462	469	2	253	258
Lognormal	2	**446**	**453**	2	237	242
Loglogit	2	450	456	2	240	246
Gamma	3	447	457	3	211	218
Spline	6	449	469	6	**198**	**213**
	Overall Survival					
Weibull	2	340	347	2	194	199
Exponential	1	346	350	1	**192**	**195**
Gompertz	2	**338**	**345**	2	194	199
Lognonrm	2	348	355	2	193	198
Loglogit	2	342	349	2	193	198
Gamma	3	341	351	3	195	202
Spline	6	344	364	5	198	210

Source: Recreated data from ITT PFS (central review; Yao et al. 2016) and ITT OS Kaplan-Meier curves in RADIANT-4 (CSR and Novartis submission to NICE).

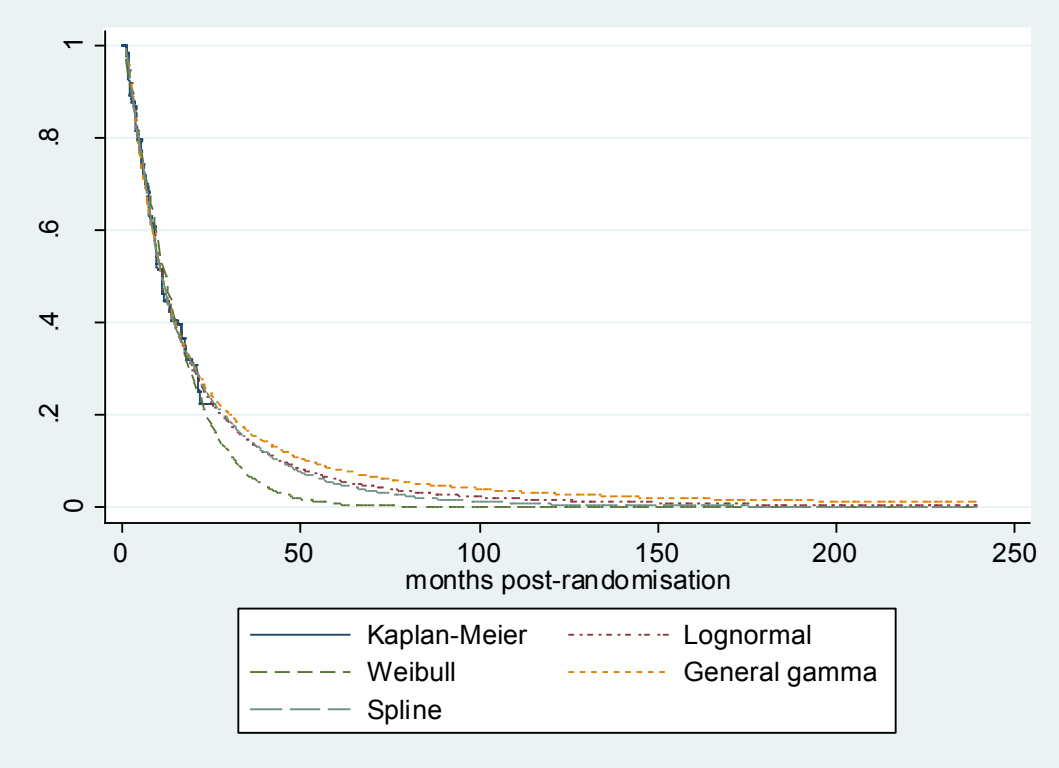
Progression Free Survival

In the base case analysis the Weibull function was chosen for everolimus plus BSC arm and the Weibull function for BSC only arm based on data from RADIANT-4. In scenario analyses, the generalised gamma function was used instead for both model arms.

Everolimus plus BSC

The log normal had the best diagnostic results (Table 115), and followed the pattern of the risk of death or disease progression (central review) in the everolimus arm of RADIANT-4 (Yao et al. 2016) (Figure 70 in Appendix 7), but it resulted in a predicted long term progression free survival rate that was smaller than that of the placebo arm (presented below). In contrast the gamma distribution had a goodness-of-fit performance equivalent to that of the lognormal and extrapolated PFS rates that were never below those for the chosen distribution of the placebo arm in RADIANT-4. In contrast, the Weibull distribution resulted in the lowest extrapolated PFS rates (Figure 49).

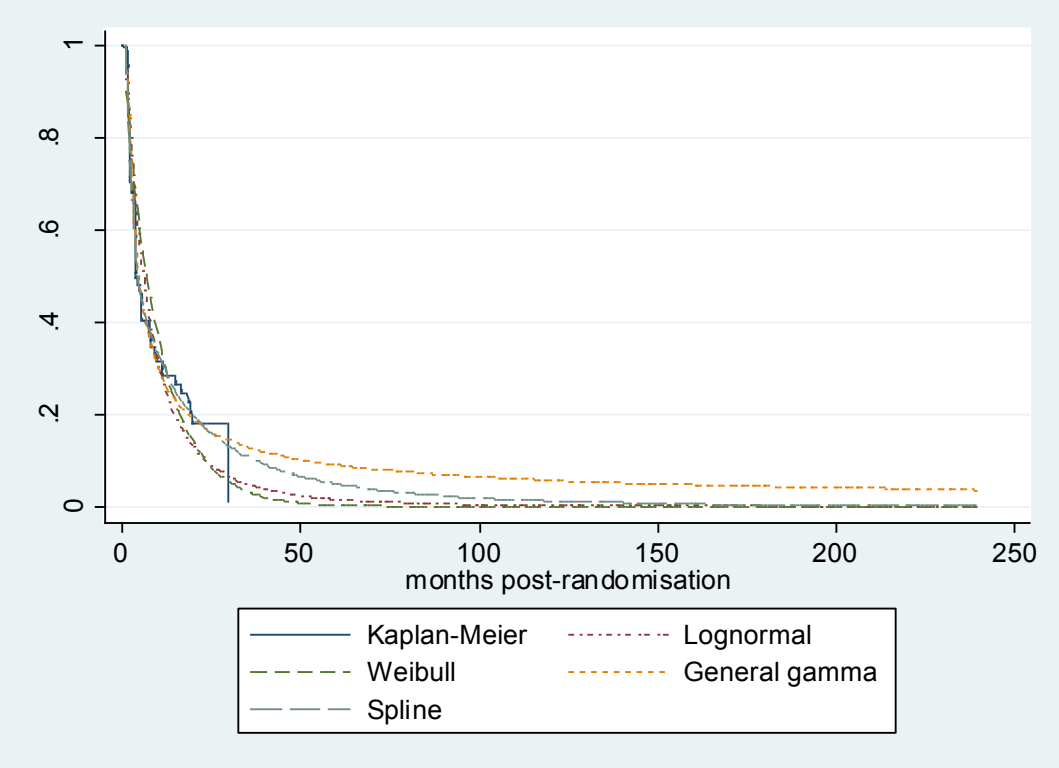
Figure 49: PFS in everolimus arm of RADIANT-4: Extrapolation to 20 years



BSC alone

The cubic spline function had the best fit (Figure 71 in Appendix 7) to the PFS data (central review) of the placebo arm in RADIANT-4 (Yao et al. 2016), and extrapolated rates in the middle of the range produced by the candidate curves (Figure 50). As before the Weibull function produces the shortest tails and the generalised gamma the longest.

Figure 50: PFS in placebo arm of RADIANT-4: Extrapolation to 20 years



Overall Survival

The base case analysis adopted exponential distributions separately fitted to OS data in the everolimus arm and placebo arm of RADIANT-4. The Gompertz and Weibull distributions had the best goodness of fit statistics and seemed to provide the best fit to the everolimus hazard rates (Figure 72 in Appendix 7) and K-M curves (Figure 51) , while the exponential seemed to be the best fit to the placebo data (Table 115 and Figure 51). However only the extrapolations of the exponential and log-logistic distributions seemed plausible as discussed below. In scenario analyses log-logistic distributions separately estimated to the two trial arms, were adopted.

Everolimus plus BSC

To reflect the uncertainty due to immature data, Figure 51 presents the OS extrapolations for all available parametric curves. The exponential appears underestimate the risk of death (Table 115) and the K-M OS curve in the early part of the trial observation period (Yao et al. 2016, data cut-off 30th November 2015), although the discrepancy is within the sampling error (95% CI, not presented). The exponential curve crosses the log-logistic curve twice, once during the interpolation (within trial) period and another in the late extrapolation (beyond trial) period. In their submission to NICE Novartis turns to external data to inform their choice of survival curves. In particular, it states that “Analysis of distant NET cases diagnosed between 1997 and 2012 in the SEER database (a large population-based registry in the USA) suggests that survival for patients with distant disease at diagnosis at 15 years is approximately 10% (Data unpublished). Although it is difficult to make comparisons between the RADIANT-4 trial population and the available SEER data (see Appendix 9 of Novartis submission for further details), it is reasonable to assume that survival in the placebo plus BSC arm of the RADIANT-4 trial is likely to be no less than that of patients with

distant disease in the SEER database given improvements in survival over time in patients with NET." (Novartis submission, p. 137). In Appendix 9 of Novartis submission, Novartis reports the data and methods used to obtain their 10% survival benchmark at 15 years; Kaplan-Meier survival curves by location from SEER, reproduced in Figure 52 below, were weighted according to the distribution of patients by location in RADIANT-4, also reproduced below in Table 115. Novartis also acknowledges the limitations of these SEER data as discussed above for pNETs.

Figure 51: OS in everolimus arm of RADIANT-4: Extrapolation to 20 years

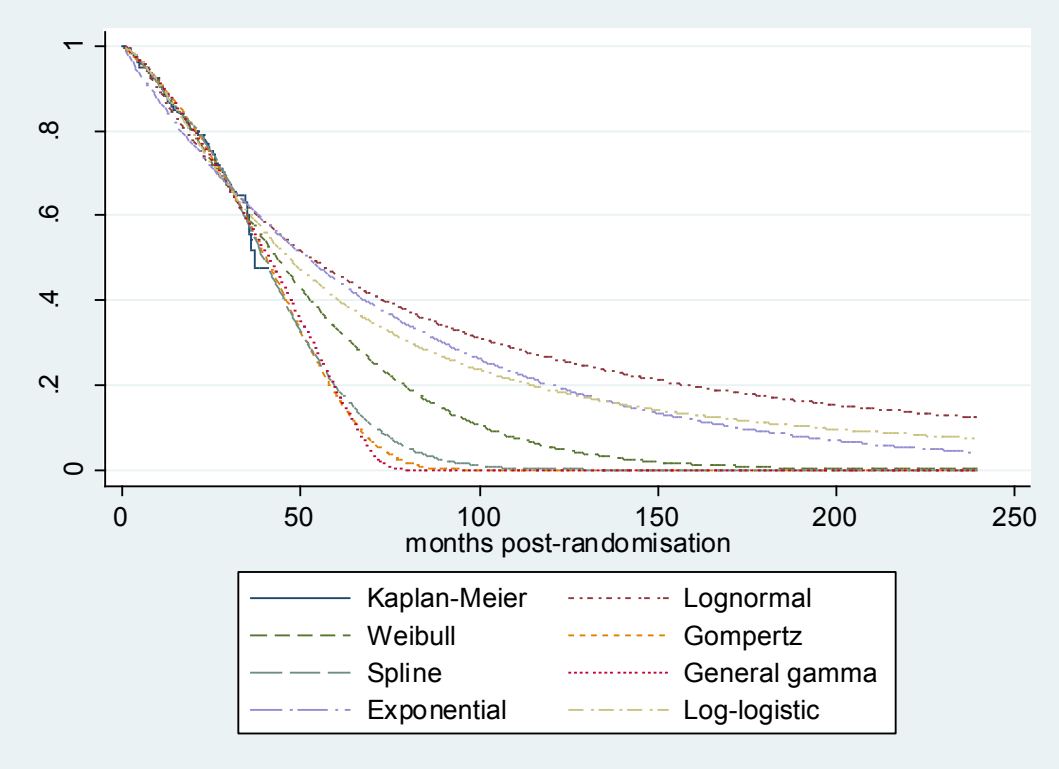
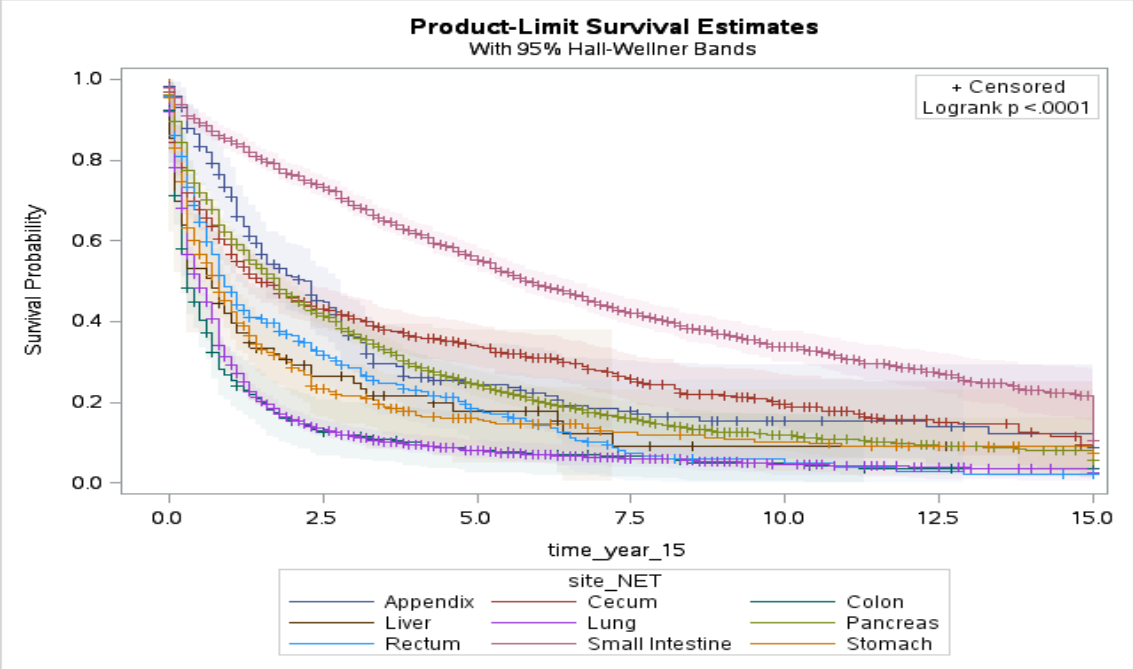


Figure 52: Survival of advanced NETs (1997 – 2012) in SEER by Site



Key: NETs: neuroendocrine tumours, SEER: Surveillance, Epidemiology and End Results.
Source: Reproduced from Novartis submission Appendix 9, Figure 9.9

Table 116: Distribution of patients by site of primary cancer in RADIANT-4 and weights used to calculate pooled Kaplan-Meier curves from SEER

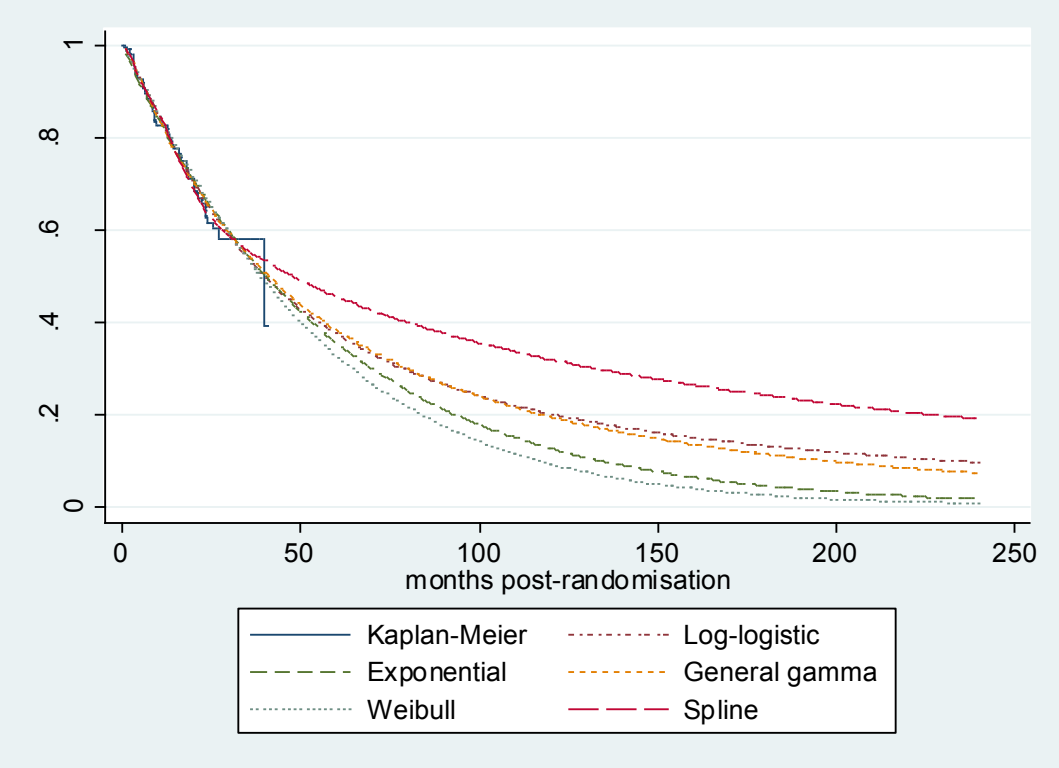
Primary site of cancer (SEER)	Percent of patients in RADIANT-4	Weights used to calculate pooled Kaplan-Meier curves from SEER
Small Intestine	34.1%	39.9%
Appendix	0.3%	0.4%
Cecum	1.7%	1.9%
Pancreas	0.0%	0.0%
Rectum	13.2%	15.5%
Stomach	3.6%	4.3%
Liver	0.0%	0.0%
Lung	29.8%	34.9%
Colon	2.6%	3.1%
Total	85.4%	100.0%

Key: CUP: carcinoma of unknown primary origin, SEER: Surveillance, Epidemiology, and End Results.
Note: Small intestine includes duodenum, jejunum, ileum. In SEER, 14.6% of patients had site equal to CUP or other site. These patients were assumed to have survival similar to average of the other sites.
Source: Reproduced from Novartis submission Appendix 9, Table 9.1

BSC alone

High degrees of uncertainty are similarly present in the latter parts of the follow-up period of patients in the placebo arm of RADIANT-4 (Yao et al. 2016), as evidenced by the large steps observed after approximately two years of follow up (Figure 53).

Figure 53: OS in placebo arm of RADIANT-4: Extrapolation to 20 years



GI (midgut)

The base case analysis of the GI (midgut) location was populated with data from the head to head comparison of everolimus plus BSC and placebo plus BSC investigated in RADIANT-4 among the subgroup of GI midgut population (Singh et al. 2016).

Table 117: Akaike's and Bayesian information criteria of parametric models of PFS and OS in GI (midgut)

	Everolimus plus BSC[a] N=80			177Lu-DOTATATE plus BSC[b] N=116			Placebo plus BSC[a] N=35		
	Progression Free Survival								
	N	AIC	BIC	N	AIC	BIC	N	AIC	BIC
Weibull	2	149	154	2	139	145	2	87	90
Expon	1	151	**153**	1	140	**143**	1	85	87
gompertz	2	150	155	2	141	146	2	87	90
lognonrm	2	**149**	154	2	**138**	143	2	83	**86**
Loglogit	2	150	154	2	139	144	2	85	88
Gamma	3	151	158	3	139	148	3	**82**	87
Spline	6	151	158	6	140	149	6	87	96
	Overall Survival								
Weibull	2	N/A	N/A	2	99	105	2	N/A	N/A
expon	1	N/A	N/A	1	**98**	**101**	1	N/A	N/A
gompertz	2	N/A	N/A	2	99	105	2	N/A	N/A
lognonrm	2	N/A	N/A	2	99	105	2	N/A	N/A
loglogit	2	N/A	N/A	2	99	105	2	N/A	N/A
gamma	3	N/A	N/A	3	101	109	3	N/A	N/A
spline	6	N/A	N/A	6	102	119	6	N/A	N/A

Notes: a, RADIANT-4 (Singh et al. 2016). b, AAA submission to NICE.

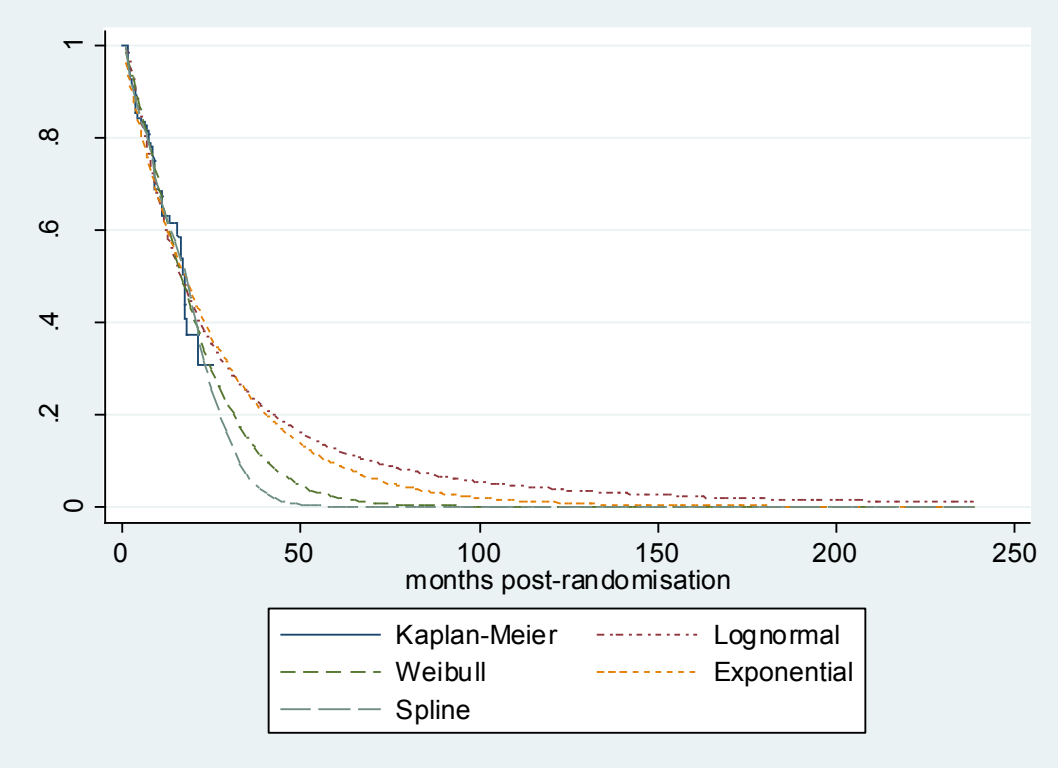
Progression Free Survival

The exponential distribution was adopted in the base case analysis to model PFS outcomes of the everolimus arm in RADIANT-4, and the exponential distribution was used to model PFS in the placebo arm of RADIANT-4. The PFS in the 177Lu-DOTATATE arm of NETTER-1 was modelled with an exponential distribution (for scenario analyses; see Appendix 6).

Everolimus plus BSC

The exponential function, which was the one with best statistical fit (Table 117), appeared to have poor fits to the hazard rates with everolimus in RADIANT-4 (Singh et al. 2016) (Figure 74 in Appendix 7). However, this is caused by the small sample available in the latter part of the RADIANT-4 follow-up period. Of the candidate functions, the lognormal has the longest PFS durations, followed by the exponential and the Weibull (Figure 54).

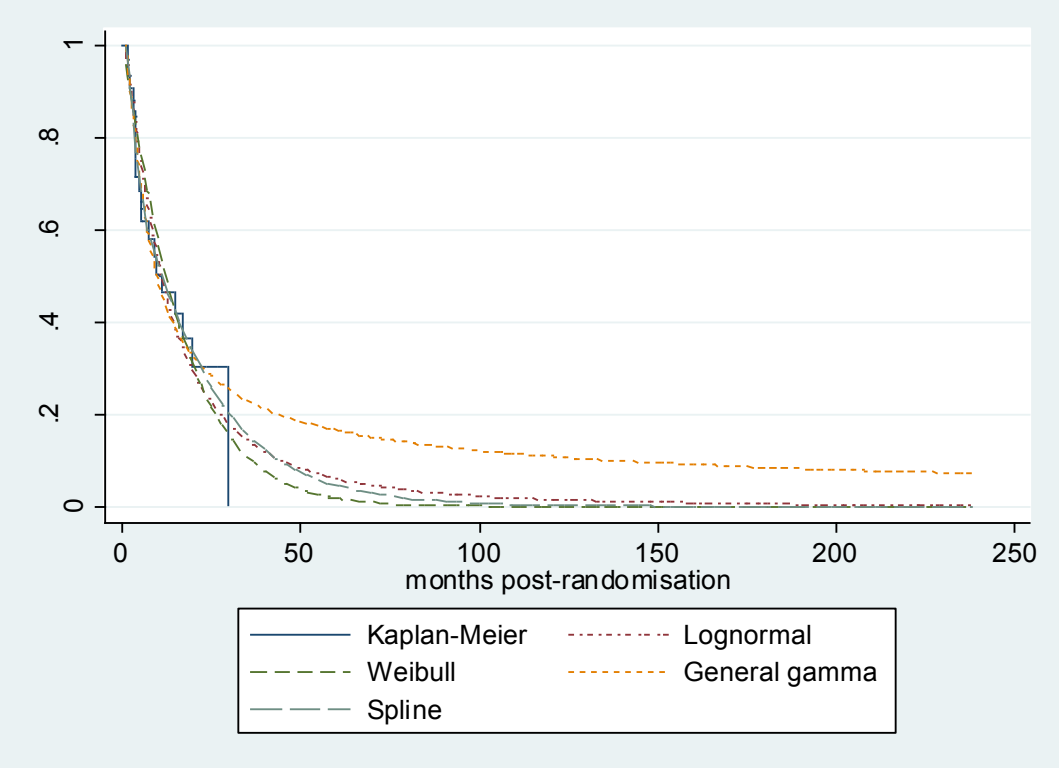
Figure 54: PFS in everolimus arm of RADIANT-4 (midgut): Extrapolation to 20 years



BSC alone

The diagnostic statistics (Table 117) did not discriminate between the (AFT or PH) models available to represent the PFS data in the placebo arm of RADIANT-4 (Singh et al. 2016), although the generalised gamma and log normal forms displayed hazard PFS hazard rates that were similar to those observed during the trial (Figure 75 in Appendix 7). When turning to the extrapolation of PFS, the generalised gamma seems to result in overly optimistic disease progression-free survival rates (Figure 55).

Figure 55: PFS in placebo arm of RADIANT-4 (midgut): Extrapolation to 20 years



Overall Survival

In the absence of data, the base case analysis currently assumes the OS curve for everolimus in the midgut only location is the exponential OS curve estimated in the GI or Lung patient population in the everolimus arm of RADIANT-4 discussed above, adjusted by the proportional difference in mean PFS in the everolimus arm of RADIANT-4 between the overall GI/Lung patient population and the subgroup of GI (midgut) patients. Likewise, the OS curve for the BSC only arm of RADIANT-4 in GI midgut only population is derived from adjusting the exponential function fitted to the OS data from the everolimus arm of RADIANT-4 in the GI/Lung population considered above by the proportional difference in the mean PFS between the overall GI/Lung and GI (midgut) patient groups. These derivations following the same steps as in Eq. 1 before. At the time of writing, Novartis is in the process of providing OS data for the GI midgut only location.

7.1.5.3.3 Adverse events

The probabilities of AEs were used to estimate costs in the stable disease state. For the economic evaluation of treatments for pNETs they were derived from rates estimated from our indirect comparison of treatment related Grade 3/4 AEs of ≥2% incidence in any active treatment arm (see section 4.2.5.2 and Appendix 9). We updated these analyses with data provided in the Pfizer submission to NICE. For the GI/Lung analysis, the AG model adopted the probabilities in the Novartis model submitted to NICE, since these were calculated with individual patient data not available to the AG. For everolimus plus BSC and BSC only option in the GI (midgut) evaluation, we adopted the Grade 3/4 AEs rates for the everolimus and placebo arm reported in a recent conference poster by RADIANT-4 investigators (Singh et al. 2016), and for the 177Lu-DOTATATE option we used the grade 3/4 AE rates reported in the AAA submission to NICE.

The AE probabilities for the pNETs model were obtained by assuming that patients had no multiple instances of the same AE type and lasted only for 1 cycle. This seems a reasonable assumption in the light of the evidence in the CSR of A6181111, which reports the actual duration of the Grade 3/4 recorded in the trial (Tables 5, 27, 29 & 32 in Full CSR of A618111). For GI/Lung and GI midgut the same assumption was adopted.

Based on calculations by the AG the measured differences in Grade 3/4 AE between everolimus and sunitinib in pNETs considered by Novartis in their submission and for which disutility values are available (see section 6.1.1.4.1 for details), are associated with negligible differences in utility, equal to a 0.002 quality adjusted month, and were therefore not used in calculating utility values of SD in the pNET model. For GI/Lung and GI midgut analyses the available utility values, which were derived from patient reported outcomes in RADIANT-4 and evidence from the Erasmus study submitted to NICE by AAA, were assumed to capture the impact of adverse events.

7.1.5.3.4 Modelled post-progression

Based on data from RADIANT-3, for pNETs, and RADIANT4, for GI and Lung NETs, which we assumed applied to GI (midgut) NETs, in the base-case analysis we assumed that all patients have best supportive care after progression on initial treatment. This consists of palliative care and octreotide 30mg for symptomatic treatment, with no active drug treatment.

Subsequent treatments were allowed in the post progression phase and applied as a fixed cost on the first cycle after disease progression. The frequency of subsequent treatment use was assumed to be zero in the base case analysis, and scenario analyses considered applying the same costs of subsequent treatments as in the pNETs and GI and lung models by Novartis. This choice of base case reflected the fact that a) the A6181111 trial of sunitinib did not collect information on subsequent treatments, which led Novartis to apply the same costs of subsequent treatments to both arms, and b) the way Novartis implemented subsequent treatment costs in their models is unreliable (see discussion in Chapter 6 Critique of industry models). In the GI and Lung and GI (midgut) only analyses we adopted the same costs and implementation of subsequent treatments as in the GI and Lung model of Novartis, where Novartis used detailed information on frequency of treatment use post-progression in RADIANT-4 that differ between treatment arms. Since we had no information for 177Lu-DOTATATE we assumed it had the same subsequent treatment costs as applied to everolimus.

Costs of disease monitoring in our model were obtained from the pNETs and GI and lung models by Novartis. Based on the opinion of our clinical experts, we adopted a smaller number of visits for the GI and lung evaluation than that used Novartis in their model of the same location (see below).

7.1.5.4 Health related quality of life

7.1.5.5 Systematic review of utilities

7.1.5.5.1 Methods for reviewing HRQoL data

A systematic review was conducted to identify, appraise and synthesise all available data on HRQoL of NETs patients, with the objective of estimating utility values for populating the `de novo' PenTAG cost-effectiveness model.

Identification of studies

The systematic searches were conducted on MEDLINE (Ovid), EMBASE (Ovid), ScHARRHUD (www.scharrhud.org), the HERC Database, the EQ-5D web-site, the 'patient-reported outcome and quality of life instruments' database and Cochrane HTA and NHS EEDs. These searches were not limited by study designs and language. A complete list of search strategies can be found in Appendix 1.

All references were exported into Endnote X7 (Thomson Reuters) where automatic and manual de-duplication was performed.

Inclusion/exclusion criteria

Studies identified by the searches were screened for inclusion according to the criteria listed below. Abstracts were included conditional on their good reporting of the methods used and the outcomes obtained.

The population of interest consisted of patients with progressive, unresectable or metastatic neuroendocrine tumours irrespective of the tumour location. The following outcome was considered: HRQL of health states relating to patients with progressive, unresectable and/or metastatic NETs. No exclusion criteria relating to the intervention, comparator or study design were used.

Screening

First, one researcher screened for inclusion titles and abstracts returned by the search strategy. All included records were then independently screened by a second researcher. Disagreements were resolved by discussion. Full texts of identified studies were obtained and screened in the same way.

Data extraction

Data extraction from included studies was: details of the study's design and methodology, characteristics of the study population, the measure used to capture HRQoL outcomes, details on the outcomes measured, the time horizon of the study and the type of statistical analysis undertaken by the authors. Data were extracted by one reviewer (SL) and checked independently by a second reviewer (RMM). Disagreements were resolved by discussion.

Critical appraisal strategy

The quality of all studies included in the review was assessed by one reviewer. Due to the lack of a standardised checklist for the quality appraisal of HRQoL studies, a set of criteria was laid out to critically appraise the studies included in the systematic review. The checklist used (Appendix 4A) heavily relies on the 14-item checklist designed by Mols et al. (2005) for the appraisal of quality-of-life studies in the area of breast cancer, and later used by Cornish et al. (2009) in the area of cutaneous melanoma. Compared to the original version outlined in Mols et al. (2005), three items were added and one was deleted in order to adapt the checklist to this specific disease area and type of studies. This version better captures the quality of HRQoL studies included in this review. Some changes in the formulation of a number of items were also made to clarify ambiguous language. Finally, the quality of reporting of two published economic evaluations included in this review was assessed using the CHEERS checklist.[135, 136]

7.1.5.5.2 Mapping

Mapping was performed to obtain utility values from the EORTC QLQ-C30 and FACT-G data identified in the literature review.

Mapping EORTC QLQ-C30 to EQ-5D

Doble and Lorgelly (2016)[137] conducted a comprehensive external validation study on the algorithms developed to map EORTC QLQ-C30 scores to EQ-5D-3L. The dataset they used consisted of EORTC QLQ-C30 and EQ-5D values from a sample of 988 patients enrolled in the Cancer 2015 longitudinal study [138]. The patients involved were treatment-naïve and had been diagnosed with a variety of cancers. Different stages of disease were accounted for by dividing the patient sample into three groups according to disease severity and time to first follow-up.

Most mapping algorithms, particularly those relying on the Ordinary Least Squares (OLS) model and dummy variables, were found to perform inadequately (Doble and Lorgelly, 2016)[137]. Specifically, when tested using different tumour-specific samples, predictive accuracy was found to be higher, on average, in healthier patient samples and lower in patient samples with poorer health, corresponding to lower EQ-5D utility values. In general, the analysis concluded that most algorithms seemed to be insensitive to tumour location but very sensitive to the disease severity. The algorithm by Versteegh et al. (2012)[139] and that by Longworth et al. (2014)[125] proved to perform particularly well on a range of different validation criteria, including the ability to predict extreme EORTC QLQ-C30 health states and make predictions consistent with the country-specific EQ-5D tariff range. Moreover, such algorithms showed relatively small mean squared error (MSE) when predicting EQ-5D values and corresponding QALYs.[137] While the algorithm in Versteegh et al. (2012)[139] cannot be generalised easily as it can only provide utilities drawn from the Dutch value set, the algorithm developed by Longworth and colleagues (Appendix 6), although being computationally intensive, had the advantage of providing utility values for any country-specific tariff, making it more generalizable.

The algorithm developed by McKenzie and van der Pol (2009)[104], although not found to provide the highest accuracy in the review of algorithms by Doble and Lorgelly (2016))[137], has been widely used and cited in studies of cancer. The validation process showed that the McKenzie algorithm performs well in terms of predictive power, as all the actual EQ-5D values were found to be in the 95% confidence interval of the mapped values. Even more importantly, the difference in QALYs between treatment arms calculated using mapped utilities was almost identical to the difference in QALYs calculated with the original EQ-5D utilities (-0.019 vs -0.017 QALYs). Nonetheless, questions relating to the generalizability of such results remain unanswered, particularly in relation to the application of this algorithm to patient groups with widely different age range and health status to the esophageal cancer patient group used to validate the algorithm.

As the impact of using different algorithms in cost-utility analysis could not be measured by Doble and Lorgelly (2016) and a number of limitations in their analysis prevented the identification of a preferred algorithm beyond doubt, the authors recommend conducting sensitivity and scenario analysis to illustrate the impact of choosing different algorithms and corresponding sets of mapped utilities.

Mapping FACT-G to EQ-5D

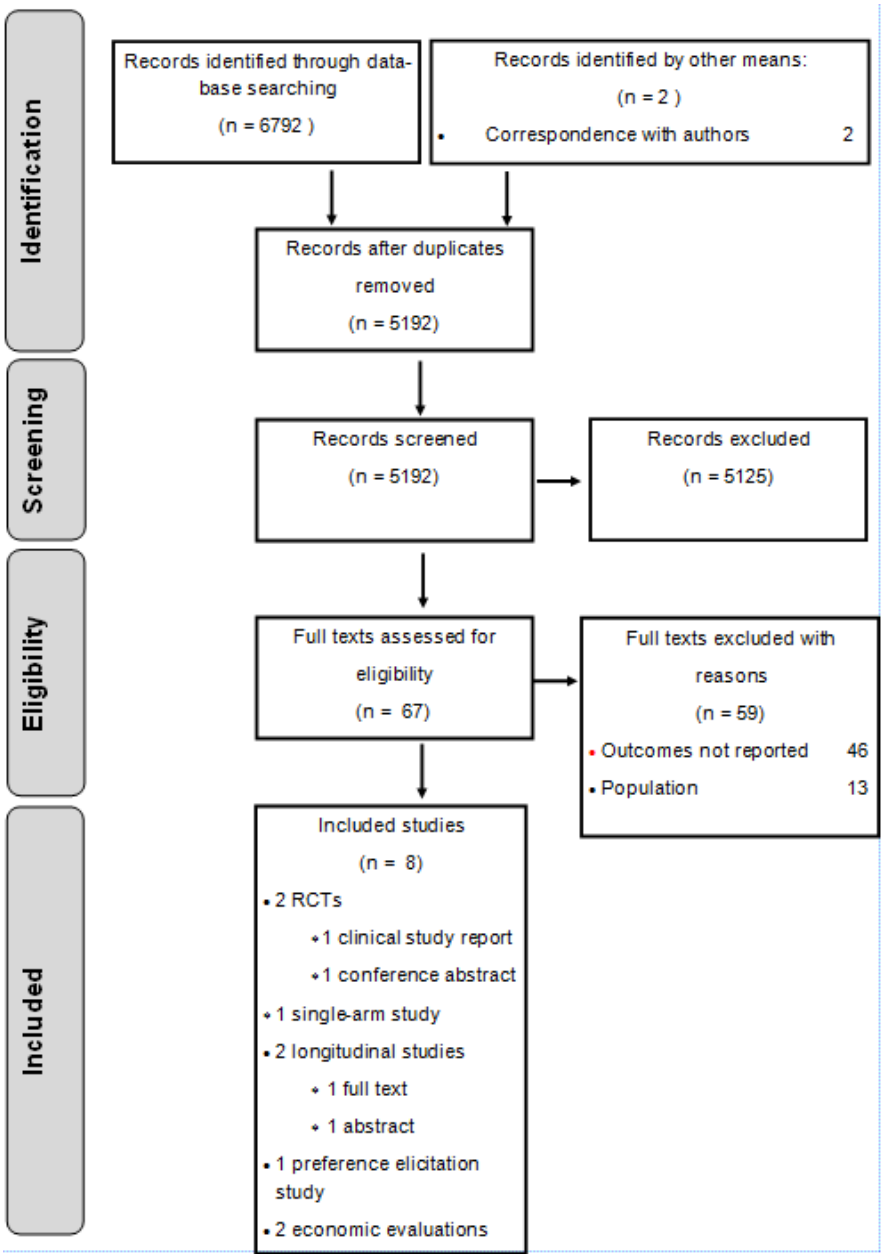
The mapping of FACT-G scores to EQ-5D utilities was performed relying on the work by Longworth et al. (2014) that considered a wide range of models and tested their ability to predict EQ-5D utilities based on FACT-G values. In particular, models that employed item-level data were found to perform better than those using significant domain and total score models. The methods used to evaluate the algorithms presented in Longworth et al. (2014) show that the best fitting algorithm (Appendix 8A) used in this analysis achieves a high degree of accuracy in predicting EQ-5D values. Nevertheless, Young et al. (2015) raise concerns regarding the generalizability of such results on the grounds that the patient sample used to test the algorithms in Longworth et al. (2014) included a surprisingly low number of patients in poor health.

In this analysis, the best fitting algorithm by Longworth and colleagues (Appendix 8B) was linearised and used to map published FACT-G summary domain scores (Yao et al. 2016) into EQ-5D values for stable disease and disease progression health states for patients in RADIANT-4. These utility values were the only empirical data available on EQ-5D health state utility values in patients treated with everolimus, and since we did not have access to the original individual patient data from the RADIANT-4 trial to replicate the analyses by Novartis, we validated their analyses by mapping published mean scores for FACT-G domains with linear Taylor series approximations to Longworth's best fitting algorithm. FACT-G scores mapped using the linearised algorithm were then compared with published EQ-5D utilities obtained from the corresponding FACT-G individual patient data mapped with Longworth's nonlinear, best fitting algorithm (Appendix 10).

7.1.5.5.3 Results

A total of 6792 records were identified. After de-duplication, 5192 records were manually screened by two reviewers. After the screening process, eight studies were ultimately included in this review. See the modified PRISMA figure (Figure 56) below.

Figure 56: PRISMA



The main characteristics of the studies identified through the systematic search of utilities are summarised in Table 118.

Table 118: Studies identified through the systematic search of utilities - Description

Author, year	Study design [1]	N	Population	Intervention	Measure (Type[2] & name[3])	Outcomes[4]	Time period	Statistical method of analysis
Cramer et al. (2014)	U	30	U.S. NET pts with hepatic metastases	Y-90 radioembolization	G, SF-36	A	24 months	
Pavel et al. (2016)	E	246	Pts with advanced NETs (pNETs vs non-pNETS separately). Non-pNETs include small intestine, lung, colon, and other.	Everolimus	G, EQ-VAS, EQ-5D, EORTC QLQ-C30, EORTC QLQ-GINET21	A	12 months	Last HRQoL value before treatment discontinuation was used
Teunissen et al. (2004)	U	50	Dutch metastatic GEP NETs	Lu-octreotide	D, EORTC QLQ-C30	A	Until 6 weeks after last treatment	Variance analysis to compare before and after QoL
Swinburn et al. (2012)	U	100	Bespoke health states were designed based on the literature and clinicians. States were valued by a sample of the English population	Unspecified	Vignettes	HS	One off	N/A
Walczak et al. (2012)	EE	/	Adults with unresectable or metastatic well-differentiated pNETs with disease progression	Sunitinib + BSC vs Placebo + BSC	G, mapped EORTC QLQ C-30 onto EQ-5D	HS	Patients' lifetime	Markov model
Mucino Ortega et al., (2012)	EE	/	Mexican non-resectable pNETs pts	Sunitinib +BSC vs Placebo + BSC	G, mapped EORTC QLQ C-30 onto EQ-5D	HS	10 years	Markov model

Key: EE: Economic evaluation, E: Experimental, Q:Quasi-experimental, U: uncontrolled; 2. G: Generic, D:Disease specific. 3 EORTC-QLQ-C30; FACT-G, FACIT. 4: HS: health state, AE: Adverse events, C: Comorbidity, A: Average at fixed time point (e.g. 6 months after treatment start, or at beginning of cycle 1, 3, etc.), pNETs: pancreatic NETs.

Evidence identified through the systematic search of utilities

Six studies were included and data extraction was undertaken. Of the six studies, one is a conference abstract on a longitudinal study (Cramer et al., 2014); one is a phase-3 expanded access study (Pavel et al., 2016), one is a prospective cohort study (Teunissen et al., 2004), one is a preference elicitation study (Swinburn et al. 2012) and two are economic evaluations (Walczak et al, 2012; Mucino Ortega et al., 2012).

Evidence obtained by contacting the authors or the sponsor of the study

A second set of studies were identified in the systematic search of utility values as abstracts only, while the study outcomes were not available to the public. In order to obtain such data, the authors or the sponsor of the studies had to be contacted directly. Table 119 summarises the main characteristics of the studies included: a conference poster reporting HRQoL outcomes and some details on the methods used in a major clinical trial [140] and a

clinical study report (Cohen and Allred, 2009) provided by the sponsor of the study as part of the NICE appraisal process.

Table 119: Evidence obtained by contacting the authors - Description

Author, year	Study design[1]	N	Population	Intervention	Measure (Type[2] & name[3])	Outcomes[4]	Time period	Statistical method of analysis
Singh et al., (2016)	E	284	Adults with advanced, progressive, non-functional GI or lung NETs	Everolimus	G, mapped FACT-G onto EQ-5D	HS	Unclear	Linear mixed models
Cohen and Allred (2009)	E	144	Adults with progressive, well differentiated pNETs	Sunitinib	D, EORTC QLQ C-30	A	21 months	Repeated measures mixed effects model

Key: E: Experimental, Q:Quasi-experimental, U: uncontrolled; 2. G: Generic, D:Disease specific. 3 EORTC-QLQ-C30; FACT-G, FACIT. 4: HS: health state, AE: Adverse events, C: Comorbidity, A: Average at fixed time point (e.g. 6 months after treatment start, or at beginning of cycle 1, 3, etc.). pNETs: pancreatic NETs.

7.1.5.5.4 Utility values for the PenTAG model

Of the eight independent sources of data identified through the systematic search of utility studies, only a limited proportion of evidence was suitable to populate the PenTAG cost-effectiveness model. This was mainly due to the differences in the treatments being evaluated and the discrepancies between the definition of HRQoL outcome measures in the studies and the model's health states.

The utility values used in the PenTAG cost-effectiveness model and their sources are presented per tumour location, in accordance with the NICE Scope (Appendix 11; Appendix 8). No utility values for HRQoL outcomes measured in pNETs patients under treatment with everolimus were found (Table 120). The only available estimates for everolimus in pNETs were those reported by the preference elicitation study of Swinburn and colleagues(Swinburn et al. 2012), who asked ~100 members of the general public to assess descriptors (vignettes) of pre-progression and post-progression health states of patients with gastrointestinal and pNETs, using the Time-Trade-Off method. The study also elicited utility decrements resulting from the occurrence of some of the most common adverse events associated with treatment therapies (see section 5.1.2.2 above for details)[1]. In the base case analysis submitted to NICE, Novartis used the utility value reported by this source for the pre-progression health state, adjusted for the disutility associated with the incidence of the common types of grade 3 or 4 AEs in the RADIANT-3 trial (Novartis submission). Since these values do not meet the NICE reference case we only considered them in scenario analyses.

In the absence of HRQoL outcomes measured in patients treated with everolimus in pNETs, the base case value is assumed to be the same as for sunitinib discussed below. This assumption was adopted after calculating the net difference in disutility from Grade 3/4 AEs

[1] Adverse events considered include: neutropenia, hypertension, hand-foot syndrome, leukopenia, diarrhoea, stomatitis, thrombocytopenia, anaemia, hyperglycaemia, fatigue, infections, pneumonitis and nausea

between Everolimus and Sunitinib according to the disutility values reported by Swinburn and colleagues and finding them equal to 0.002 quality adjusted month. Giving the uncertainty associated with other parameters in the model, including the limited quality in AE data available for economic evaluation purposes, we considered such difference insignificant.

Estimates on the utility of pNETs patients undergoing treatment with Sunitinib in both pre- and post-progression health states (Table 120) were obtained by mapping individual patient data on responses to the EORTC-QLQ-C30 from the A6181111 trial provided by the manufacturer (Pfizer, data request through NICE) using the algorithm by McKenzie and van der Pol (2009).[104] Using these data the utility values that the company used in the model-based cost-effectiveness evidence submitted to NICE were validated. Although the methods used by the company were not properly described in the submission itself, the values used and their methods had been reported in the study by Mucino Ortega et al. (2012).[96] The validation exercise therefore sought to replicate the utility values submitted to NICE by following the methods described by Mucino and colleagues.[96] This consisted in fitting a linear mixed model equation to the EORTC QLQ-C30 data mapped to EQ-5D using the algorithm developed by McKenzie and van der Pol, (2009) to estimate the effect of random group allocation (sunitinib vs. placebo) on EQ-5D utilities adjusting for baseline EQ-5D score and treatment cycle (information available from the authors).

[redacted]. Nonetheless, the estimate obtained employing the model is an approximation, as the estimate of utility in progressive disease was based only on data for the end of treatment follow-up time point relating to the placebo arm. This approximation relies on the fact that over 90% of patients in the placebo arm had progressed by the end of the study.

[redacted]. This difference is due to the incorrect use of the data in the analysis conducted by Sunitinib's manufacturer (Pfizer Inc.) in their submission to the Scottish Medicines Consortium and used by Novartis in their sensitivity analysis of the economic evaluation submitted to NICE. The company incorrectly used baseline utility as the utility for the pre-progression health state, thus omitting the effects of treatment on patients' utility during stable disease. In contrast, our replication of the utility values in Mucino-Ortega and colleagues' study led us to the following estimated linear mixed model equation for SD:

[redacted]

where EQ-5Dm is the mapped utility score from EORTC-QOLQ-C30 in the A6181111 (Raymond et al. 2011), using the algorithm by McKenzie et al. 2009. In order to estimate utilities for the two trial arms in the stable disease state, this model was fitted on data excluding the last follow-up, i.e. the end of treatment follow-up observations, when some patients may have experienced disease progression resulting in their withdrawal from treatment.

For gastrointestinal and lung NETs patients under treatment with Everolimus (Table 121) we used unpublished treatment-specific utility values, which were presented by Novartis as part of the evidence submitted to NICE and used by the company in sensitivity analyses of their economic evaluation. These data were preferred to published estimates[127] from pooled analysis (i.e. utilities by health state regardless of treatment arm) used by the company in their base case economic model submission, as they incorporate the impact of treatment-specific adverse events and comorbidities on HRQoL. The treatment-specific utilities in the company's submission were based on unpublished individual patient data from the RADIANT-4 trial that were not available to us for review. In order to validate such estimates, we mapped mean FACT-G scores in the RADIANT-4 trial, reported by Singh and colleagues [127] in a poster also reporting pooled utilities by health state, using a linearised version of the algorithm by Longworth et al. (2014)[125] (Appendix 10). The values we obtained were approximately equal to those produced by the company from individual patient data in the pooled analysis with the original, nonlinear mapping algorithm (Appendix 10).

In the absence of data specific to Lung or to GI only patients for Everolimus plus BSC and BSC only, we assumed the same utility values for these subgroups as for the overall RADIANT-4 population.

No data on HRQoL for patients treated with 177Lu-DOTATATE was identified through the systematic review. For this reason, we had to rely on unpublished data submitted by the company (AAA Ltd., 2016). The utility values in the PenTAG base-case model are based on a Dutch single-arm, uncontrolled study which has not been published at the time of writing. Utility values for pre-progression GI-NETs patients (Table 121) were measured in the Erasmus study, a single centre non-controlled phase I/II open-label study, conducted in 810 Dutch patients with different somatostatin receptor positive tumour types. These data were used to estimate the utility of GI-NET patients in pre- and post-progression health states the base-case cost-effectiveness model. Empirical data on HRQoL associated with 177Lu-DOTATATE in GI-NET patients obtained from the Guy's and St Thomas (UK) hospital registry was used by the company to estimate the utility of pre-progression patients. As no justification for this inconsistency in the choice of sources between the two health states was provided, the evidence from the Erasmus study was preferred.

The utilities adopted for the de novo model by the AG, presented in Table 120 and Table 121, were further adjusted for the effect of ageing in the model using the following linear equation, which was estimated by the AG from EQ-5D data in the HSE 2012 following the approach of Ara and Brazier (2010):

Health state (HS) utility in cycle x = HS utility in cycle 0 * (1- 0.0018 × cycle x – 2 * 0.00001 × Square of cycle x*).*

This adjustment was applied to all utilities irrespective of health state or treatment arm.

Table 120: Utilities in pancreatic NETs - Interventions: Everolimus, Sunitinib; Comparator: BSC only

Health state	Pre-progression			Post-progression		
Treatment	**Everolimus+BSC**	**Sunitinib+BSC**	**Placebo**	**Everolimus**	**Sunitinib**	**Placebo**
N	N/A	86	85	N/A	86	85
Mean utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE						
Source	Assumed equal to Sunitinib+BSC	Analysis by the AG from individual patient data of A6181111 provided by manufacturer	Analysis by the AG from individual patient data of A6181111 provided by manufacturer	Assumed the same as Sunitinib+BSC	Analysis by the AG from individual patient data of A6181111 provided by manufacturer	Analysis by the AG from individual patient data of A6181111 provided by manufacturer
*Alternative values**	0.749	0.749	0.771	0.612	0.612	0.612
Source	Swinburn et al. (2012) times ratio of sunitiniv to BSC in A6181111	Assumed the same as everolimus	Swinburn et al. (2012) - AE adjusted	Swinburn et al. (2012)	Assumed the same as everolimus	Swinburn et al. (2012)

Table 121: Utilities in gastrointestinal NETs - Interventions: Everolimus and 177Lu-DOTATATE

Health state	Pre-progression			Post-progression		
Treatment	**Everolimus + BSC**	**Placebo + BSC**	**177Lu-DOTATATE**	**Everolimus + BSC**	**Placebo + BSC**	**177Lu-DOTATATE**
N	837	281	227	238	143	111
Mean utility	0.767	0.807	0.77	0.725	0.725	0.725
SE	0.010	0.015	0.005	0.010	0.010	0.010
Source	Treatment arm analysis using individual patient data from RADIANT-4 (Novartis, 2016).		Erasmus study (AAA Ltd., 2016)	Pooled analysis of individual patient data from RADIANT-4 (Novartis, 2016)		Assumed the same as everolimus
Alternative values	0.779		0.79	0.714	0.747	0.740
Source	(Novartis, 2016) – Pooled analysis		Guy's and St Thomas registry (AAA Ltd., 2016)	Treatment arm specific analysis Novartis, (2016)		Erasmus study (AAA Ltd., 2016)

7.1.5.5.5 Summary

There is a lack of published evidence on HRQoL especially for PD in pNETs. In addition, for one of the comparators evaluated in this location, everolimus, there is no evidence available on the HRQoL outcomes in actual patients. In contrast, the present review benefited from access to individual patient data on HRQoL outcomes in patients from one of the main trials in the assessment, A6181111, provided by Pfizer through a NICE request.

The AG was able to validate the utilities derived by Novartis for the PD and SD states in GI location from RADIANT-4 trial data, without having access to the individual patient data but only aggregate HRQoL domain score, by a linear approximation to the best-fitting algorithm by Longworth et al. (2014) used by Novartis to map individual FACT-G scores onto EQ-5D. Linearising the best fitting non-linear algorithm using first order approximations was shown to enable the successful validation of published mapped utilities.

In the absence of data specific to Lung or to GI only patients for Everolimus plus BSC and BSC only, we assumed the same utility values for these subgroups as for the overall RADIANT-4 population.

The analyses of individual patient data conducted highlighted the importance of requesting such data from the trial sponsors. This allowed the identification of fundamental errors in the interpretation of the data contained in the submissions to the three bodies responsible for making resource allocation decisions for England, Wales and Scotland.

7.1.5.6 Resources and costs

7.1.5.6.1 Cost parameters and assumptions

The unit cost of treatments and resources were sourced according to the NICE Guide to the methods of technology appraisal 2013.[131] Only costs that relate to the included interventions for the treatment of neuroendocrine tumours, and to resources under the control of the NHS and personal and social services, are included. Value added tax is excluded. Costs common and equal in all treatment strategies over the time horizon of the analysis are excluded. Cost-effectiveness results reflect the present value of costs and benefits accruing over the time horizon of the analysis.

We model the following costs, which were inflated to the cost year 2016. The annual discount rate is 3.5%.

- Drug acquisition
- Drug administration
- Medical management and disease monitoring
- Serious adverse event management
- End-of-life

7.1.5.6.2 Cost of drug acquisition

Comparator treatments

Table 122 presents the unit costs of comparator treatments. The unit costs of everolimus and sunitinib were the list prices sourced from the British National Formulary in September 2016. [32] In the absence of market authorisation (anticipated January 2017) the cost per unit of 177Lu-DOTATATE was provided by AAA as commercial in confidence information.

Table 122 Unit cost of comparator treatments by unit size

Comparator	Unit size	Unit cost (list price)*	PAS agreement*
Everolimus	5mg tablet, 30-tab pack	£2,250.00	[redacted]
	10mg tablet, 30-tab pack	£2,673.00	
Sunitinib	12.5mg capsule, 28-cap pack	£784.70	[redacted]
	25mg capsule, 28-cap pack	£1,569.40	
	50mg capsule, 28-cap pack	£3,138.80	
177Lu-DOTATATE	7.4 GBq single cycle	[redacted]	N/a

Source * information provided in the text

The base case analyses used list prices. The results were also run using PAS prices, which can be found in the Confidential Appendix.

Table 123 presents the recommended dosing of everolimus and sunitinib sourced from their 'Summary of Product Characteristics', and the dose and administration schedule of 177Lu-DOTATATE, provided by AAA.

Table 123 Drug posology of comparator treatments

Comparator	Dose	Frequency
Everolimus	10 mg	Daily
Sunitinib	37.5 mg	Daily
177Lu-DOTATATE	7.4 GBq	4 administrations at intervals of 8±1 week

The base case used recommended dosing adjusted for treatment interruptions and dose modifications as observed during clinical trial. These relative dose intensities are presented in (Table 124)

Table 124 Relative dose intensity observed in clinical trials

Comparator	Trial	Evaluation	RDI
Everolimus	RADIANT-3	P NETs	85.9%
	RADIANT-4	GI and Lung NETs	79.4%
Sunitinib	A6181111	P NETs	91.3%
177Lu-DOTATATE	NETTER-1	GI (midgut) NETs	86.4%

Table 125 presents the median unadjusted durations of treatment observed in the trial. We used median values to create exponential distributions for sunitinib to estimate the proportion of patients with stable disease remaining on treatment, and thereby estimate the average cost of a course of treatment. As a conservative approach, for everolimus we adopted the mean values used by Novartis in its pNETs and GI/Lung economic evaluations. Had we used exponential extrapolations fitted to the median treatment durations, the mean value for everolimus would have been 12.68 and 13.40 months, instead of the base case values of 9.41 and 11.54 months, respectively used for pNETs and GI/Lung. Time on treatment in the AG model is then assumed to follow and exponential distribution using the mean values in Table 131.

Table 125 Median durations of treatment observed in trial & mean values in AG model

Comparator	Trial	Evaluation	Median duration of treatment in trial	Mean duration in AG model
Everolimus	RADIANT-3	P NETs	[redacted]	[redacted] months[b]
	RADIANT-4	GI and Lung NETs	9.29 months	11.54 months[c]
	RADIANT-4	GI midgut	N/A	13.99 months[d]
Sunitinib	A6181111	P NETs	4.64 months	7.51 months[e]
177Lu-DOTATATE	NETTER-1	GI (midgut) NETs	N/A[a]	

Notes: a: 177Lu-DOTATATE is administered over a fixed number of cycles. b: Provided in Novartis submission, p. 101. c: Calculated by AG from time on treatment Kapln-Meier curve provided by Novartis submission, Figure 7.14. d: Calculated by AG from a and ratio of PFS durations between everolimus arm and GI midgut subgroup of everolimus arm in RADIANT-4 (Singh et al, 2016). e: calculated by AG from exponential extrapolation fitted to the median sunitinib duration in A6181111 and Bucher type adjustment using ratio of PFS between placebo arms of A6181111 ad RADIANT-3.

Table 126 presents the acquisition cost of comparator treatments per 28-day Markov cycle. These are calculated by multiplying unit cost for 28-days treatment by relative dose intensity.

Table 126 Base case acquisition cost of comparator treatments per 28-day Markov cycle

Comparator	Evaluation	Cycle cost without PAS
Everolimus	P NETs	£2,143.03
	GI and Lung NETs	£1,980.87
Sunitinib	P NETs	£2,148.93
177Lu-DOTATATE	GI (midgut) NETs	[redacted]

Other treatments

The unit cost of SSAs, drugs administered adjunct to 177Lu-DOTATATE, chemotherapies, and supportive treatments are presented in Table 127.

Table 127 Cost of other treatments

Treatment	Unit size	Unit cost	Cost per 28-days	Source
Octreotide	20mg depot preparation	£632.40	£632.40	eMIT[141]
	30mg depot preparation	£806.42	£806.42	eMIT[141]
	500mcg SC PFS	£5.02	£140.56	eMIT[141]
Lanreotide	90mg pre-filled syringe	£736.00	£736.00	BNF[32]
Granisetron	1mg tablet, 10-tab pack	£50.38	£50.38	BNF[32]
Vamin 18	1l pre-mixed	£26.70	£26.70	BNF[32]
5-flouro uracil[1]	250mg vial	£4.00	£52.00	BNF[32]
	500mg vial	£6.40		
Capecitabine[2]	500mg tablet, 120-tab pack	£225.72	£158.00	BNF[32]
Doxorubicin[3]	50mg vial	£100.12	£200.24	BNF[32]
Streptozocyn	n/a	Nil*	Nil	
Interferon A[4]	5 million units	£28.37	£397.32	BNF[32]
Temozolomide[5]	180mg capsule, 5-cap pack	£296.48	£762.38	BNF[32]
Lidocaine[6]	50mg per gram plasters, 30	£72.40	£67.57	BNF[32]
Dexamethasone[7]	2mg tablets, 100-tab pack	£78.00	£131.04	BNF[32]
Prednisone[8]	5mg tablets, 100-tab pack	£89.00	£74.76	BNF[32]
Prochlorperazine[8]	5mg tablets, 84-tab pack	£2.09	£2.09	BNF[32]
5-flouro uracil[1]	120-tab pack	£34.49		Amazon (cost); MIMs (dosing)
	90-tab pack	£15.95		Amazon (cost); Medscape (dosing)

Notes: * assumed to be a cost to the Cancer Drugs Fund, budgeted separately to direct NHS resources. 1: One treatment cycle of 716mg requires one 500mg vial and one 250mg vial. 2: 750mg bd per m^2 at average 1.79m^2 is 2,685mg per day for 14 days, equivalent to six 500mg tablets per day, 84 per treatment cycle. 3: 40mg/m^2 per treatment cycle, average body surface area 1.79m^2, approximates to 100mg. Equates to two 50mg vials. 4: 5million IU every other day, effectively 6million IU 14 times per 28-days. 5: 200mg per m^2 od at 1.79m^2 over four days. Equates to two 180mg capsules per day. 6: One 50mg plaster per day. 7: 12mg per day for 28 days. Equates to six 2mg tablets per day, or 168 per 28-day cycle. 8: 5mg three times a day, or 84 tablets per 28-days.

Use of SSAs in pNETs

The proportion of patients using SSAs for tumour suppression in stable disease was based on the proportions reported in clinical trials, adjusted in an indirect treatment comparison

conducted by Novartis (Novartis evidence submission, section 4.7.2) Adjusted rates are presented in Table 128. We assumed that the SSA usage was equally split between octreotide and lanreotide, and that SSA usage following sunitinib would be the same as for everolimus.

Table 128 Proportion of patients using SSAs prior to progression in clinical trials

Comparator	Trial	Arm	Proportion using SSAs[1]
Everolimus	RADIANT-3	Active	37.7%
		Placebo	39.9%
Sunitinib	A6181111	Active	36.8%[2]

Notes: 1: This proportion was split equally between octreotide and lanreotide; 2: OR = 1.04 [95% CI: 0.478 – 2.262]

The proportion of patients using SSAs for tumour suppression post-progression are based on targeted treatment utilisation (proportion) following progression in the RADIANT-3 trial, data provided on request by Novartis. The proportion using targeted treatments following progression after everolimus was 23%; in the absence of a better source this was assumed to be a fair estimate for patients progressing after sunitinib. In the best supportive care arm of RADIANT-3, 19.2% of patients were treated with targeted treatments following progression. In both active and best support strategies, target treatments were assumed to be 50% octreotide 20mg, and 50% lanreotide 90mg.

SSAs were not used in stable disease for symptom control, however we did include this resource in progressive disease. The proportion of patients was the same across active treatment and best supportive care strategies, and sourced from the unpublished UK utilisation survey presented in the Novartis submission. The average number of SSA administrations at 500mcg was 1.9 per patient per cycle.

Use of SSAs in GI and Lung NETs evaluation and GI (midgut) NETs evaluation

The proportion of patients using SSAs for tumour suppression are based on octreotide utilisation in the RADIANT-4 trial. The estimates used are unpublished but reported in the clinical study report.[142]. Estimates used in the model are presented in Table 129. We made the assumption that SSA utilisation concurrent and following sunitinib treatment would be the same as observed for everolimus.

Table 129 Proportion of patients using SSAs in GI and lung NET evaluation, and GI (midgut) NETs evaluation

Comparator	Disease	Proportion using SSAs
Active treatment	Stable	1.95%
BSC	Stable	1.03%
Active treatment	Progressed, initial cycle	29.80%
	Progressed, subsequent cycles	1.95%
BSC	Progressed, initial cycle	22.74%
	Progressed, subsequent cycles	1.03%

Use of drugs adjunct to 177Lu-DOTATATE

Advice from expert clinicians is that use of anti-emetics and parenteral amino-acids should be standard practice in support of treatment with 177Lu-DOTATATE. Similar to the approach

adopted by AAA we assumed that every treatment cycle of 177Lu-DOTATATE (adjusted for relative dose intensity) was accompanied by a 5-day course of anti-emetic (2mg granisetron, unit cost £50.38) and amino-acid supplement (an intravenous infusion of Vamin 18, unit cost £26.70).

Chemotherapy post-progression

For the pNETs evaluation we adopted unpublished chemotherapy rates from RADIANT-3, provided by Novartis and presented in Table 130. (Additional although slightly different data were provided in Table 3.7 of appendix 3 of the Novartis evidence submission to NICE on the rate of subsequent treatments in RADIANT-3, for patients who progress following active treatment (29.4%) and best supportive care (29.1%)). In the absence of post-progression treatment information for patients in trial A618111 we assumed the same rates for people who progressed following sunitinib as was observed for everolimus.

Table 130 Use of chemotherapy post-progression in RADIANT-3

Treatment	Proportion of patients	Number of cycles
5-flourouracil	21.9%	2.5
Doxorubicin	28.1%	1.66
Streptozocyn	31.3%	2.14

For the GI and lung NETs evaluation, and GI (midgut) evaluation, we adopted chemotherapy utilisation rates from RADIANT-4 (unpublished, supplied in the Novartis evidence submission), presented Table 131.

Table 131 Use of chemotherapy post-progression in RADIANT-4

Treatment	Arm	Proportion	Number of cycles
5-flourouracil	EVE + BSC	2.8%	1.45
	BSC	1.1%	
Streptozocyn	EVE + BSC	2.8%	1.45
	BSC	1.1%	
Temozolomide	EVE + BSC	14.2%	3.08
	BSC	11.4%	
Capecitabine	EVE + BSC	14.2%	3.08
	BSC	11.4%	

Other supportive drug therapies

Other therapies are used to support patients with NETs in addition to the use of SSAs, including analgesics, anti-emetics, and anti-diarrhoeals. We included the cost of these therapies in the GI and lung NETs evaluation, and the GI (midgut) NETs evaluation, using utilisation rates supplied in the Novartis evidence submission which are based on RADIANT-4 (unpublished). These are presented in Table 132. No equivalent utilisation estimates were identified for other supportive therapies for patients with P NETs, so no costs of this type were included.

Table 132 Use of other supportive drug therapies in RADIANT-4

Treatment	Arm	Disease	Proportion
Analgesic (lidocaine)	EVE + BSC	Stable	12.7%
	BSC	Progressed	6.2%
Corticosteroid (dexamethasone)	EVE + BSC	Stable	31.7%
	BSC	Progressed	10.3%
Glucocorticoid (prednisone)	EVE + BSC	Stable	41.5%
	BSC	Progressed	11.3%
Anti-emetics (prochlorperazine)	EVE + BSC	Stable	2.9%
	BSC	Progressed	3.1%
Anti-diarrhoeals (Biofermin/ saccchromyces boulardii)	EVE + BSC	Stable	5.8%
	BSC	Progressed	5.2%

7.1.5.6.3 Cost of drug administration

There is significant variation across the comparator treatments in the resource requirements for their administration. Everolimus and sunitinib are ingested orally as a tablet and capsule respectively and are usually self-administered, whereas 177Lu-DOTATATE is administered in the secondary care setting by intravenous infusion over 20-30 minutes.[143, 144] The cost of hospital pharmacy dispensing, applied at each outpatient clinic visit, was included in our costing for the oral preparations. This was 12 minutes of hospital pharmacist time equating to £14.40.

In contrast the administration of 177Lu-DOTATATE is resource intensive. As a radiolabeled and intravenously delivered drug it requires specialist oversight and a hospital setting. AAA concur in their data submission (Section 2, p.25) whereby their expectation of routine treatment is delivery 'in a nuclear medicine department within a secondary care hospital as an outpatient appointment'. However, we are guided by expert clinical opinion (Consultants in Nuclear medicine) that current standard practice is to admit patients overnight. We understand that selected patients at a single specialist centre in England are managed as day-cases, and this approach may be expanded in the future.

Table 133 presents the costing for the drug administration resource requirement of 177Lu-DOTATATE. The estimated quantity of resource is the average of elicited from two NHS Consultants in Nuclear medicine. Unit costs were obtained from standard sources.[118 145]

Table 133 Resource requirement for the administration of 177Lu-DOTATATE

Resource	Quantity*	Unit Cost	Cost of resource type
Hospital admission	90%	£586.93 [a]	£528.24
Day case	10%	£720.78 [a]	£72.08
Nuclear medicine Consultant	2.5 hours	£137.00 [b]	£342.50
General medicine Consultant	0.25 hours	£137.00 [b]	£34.50
Radiographer	1.5 hours	£40.00 [b]	£60
Physicist (Band 7)	0.5 hours	£52.00 [b]	£26
Total			£1,063.07

Notes: * This is the average quantity of two estimates. a. National Schedule of Reference Costs 2014-15 for hospital services, Non-elective inpatient stays (short stays), National average. b. Unit costs of Health and Social Care 2015. (L. Curtis, PSSRU), NHS in England.

The costs associated with the administering supportive treatments are presented in Table 134. Unit costs were obtained from standard sources.[118] [145] Supportive treatments in Table 127 and Table 132 but not listed here did not attract an administration cost, and the cost of dispensing was not included for any supportive treatment.

Table 134 Unit cost of administering supportive treatments

Administration	Visit	Treatments	Unit cost
Intravenous/intramuscular injection	First [a]	5-flouro uracil, doxorubicin, streptozocin, lanreotide	£239.12
	Subsequent [b]		£326.46
Subcutaneous injection	Any	Octreotide	£22.00 [c]

Notes: a. HRG currency code SB12Z: deliver simple parenteral chemotherapy at first attendance. b. HRG currency code SB15Z: deliver subsequent elements of chemotherapy cycle; c. 15 minutes of hospital nurse time (band 5) at £88 per hour (PSSRU Unit costs 2015).

7.1.5.6.4 Cost of medical management and disease monitoring

Medical management and disease monitoring resource estimates include the following categories of resource:

- Hospitalisation: general and emergency
- Outpatient clinic consultation
- Procedures and tests
- Other supportive procedures

In the absence of published disease-specific detailed estimates of NHS resourcing we relied on a source of unpublished evidence supplied by Novartis to tell us which resources are used and what the expected rates of utilisation were. In an industry sponsored survey nine physicians from seven UK centres were asked in 2016 to confirm the nature of NETs resourcing (type and rate) from a previous resource use survey of 32 clinicians in England in 2011. The validation process was framed in the context of personal practice in the previous year, across various disease stages and primary tumour locations.

The physicians were asked to list the various types of resources that a patient with NETs requires during the course of the disease and estimate the number of times a patient would see physicians each month. The resource use for the given NET patient population was then calculated as a weighted average of the annual number treated by each clinician relative to the total number treated annually across all clinicians. These estimates were then weighted according to the respective proportions of patients with pNETs in RADIANT-3, and GI NETs and lung NETs in the RADIANT-4, to determine resource use for the overall trial populations.

For the BSC strategy in the P NETs evaluation, which was not modelled by Novartis, the resource utilisation of patients with stable disease was assumed to be the same as presented for active treatment. For patients with P NETs who progressed on BSC the resource utilisation was assumed to be equal to those who progressed on active treatments.

In some instances we modified the raw survey findings for our modelling:

- The frequency of resource use of people who progressed following active treatment was adjusted downward according to the proportion of people who resided ‘in observation’ in

clinical trials (32.7% following progression on active treatment, 33.3% following BSC), which was effectively BSC.

- The frequency of consultations, and procedures and tests, for people with stable pNETs receiving BSC was reduced to below estimates for active treatment. The reduction was proportionate to the difference observed between active treatment and BSC in GI and Lung and GI (midgut) NETs, approximately 4:1 for consultations and 2:1 for tests/procedures.
- The frequencies of consultation between people with GI and Lung NETs / GI (midgut) NETs and the medical oncologist were adjusted downward to the average of estimates from our expert clinicians. Utilisation survey estimates gathered by Novartis appeared high in absolute terms but also compared to frequencies in people with pNETs.

We used standard sources for unit costing of disease management and monitoring.[118] These are presented in Table 135.

Table 135 Unit costs of admissions, consultations, procedures and tests

Resource	Unit	Unit cost
Hospitalisation	Per admission	
Hospitalisation, general admission		£586.93
Hospitalisation, emergency admission		£147.30
Outpatient clinic consultation	Per consultation	
Medical oncologist		£158.54
Surgeon		£132.95
Palliative Care		£185.92
Respirologist		£156.29
Nurse specialist		£37.26
Dietician		£69.64
Primary physician		£37.26
Other physician		£69.64
Procedures and tests	Per procedure / test	
Abdominal ultrasound		£55.17
Echocardiography		£81.48
CT scan, chest abdominal pelvic, conventional		£124.53
CT scan, conventional		£111.61
Pulmonary angiogram, conventional		£238.25
CT scan, chest abdominal pelvic, helical/spiral		£124.53
CT scan, head, helical/spiral		£111.61
Pulmonary angiogram, helical/spiral		£238.25
MRI		£181.76
Chest X-ray		£42.12
Octreoscan / SRS		£806.32
I131 mIBG scan		£348.54
FDG PET		£492.51
Pro-BNP		£20.37
Standard blood test – biomarkers		£1.19
Special blood test - other		£3.01

Rates of hospital resources are presented in Table 136 for the pNET evaluation and Table 137 for the GI and Lung NET, and GI (midgut) NET evaluations.

Table 136 Base case frequency of resource use in pNETs per 28-days

Resource	Stable disease	Progressive disease	Stable disease	Progressive disease
	Active	BSC	Active	BSC
Hospitalisation				
Hospitalisation, general admission	0	0	0.0577	0.0577
Hospitalisation, emergency admission	0	0	0	0
Outpatient clinic consultations				
Primary physician, initial cycle	0.2737	0.0690	0.7437	74.37
Primary physician, subsequent cycles	0.2737	0.0690	0.3380	33.80
Another physician, initial cycle	0.0805	0.0203	1.3846	1.3846
Another physician, subsequent cycles	0.0805	0.0203	0.3776	0.3776
Procedure or Test				
Abdominal ultrasound	0.0241	0.0252	0.0321	0.0321
CT scan, chest abdominal pelvic, conventional	0.1449	0.0713	0.1731	0.1731
Octreoscan / SRS	0.0080	0.0081	0	0
MRI	0.0241	0.0159	0.0192	0.0192
Chest X-ray	0	0	0.0128	0.0128
Standard blood test - biomarker	0.2254	0.0660	0.3333	0.3333
Special blood test - other	0.5715	0.4280	0.7051	0.7051

Table 137 Base case frequency of resource use in GI and lung NETs, and GI (midgut) NETs, per 28-days

Resource	Stable disease	Progressive disease	Stable disease	Progressive disease
	Active	BSC	Active	BSC
Hospitalisation				
Hospitalisation, general admission	0.0357	0.0357	0.0005	0.0052
Hospitalisation, emergency admission	0.0357	0.0357	0.0350	0.0348
Outpatient clinic consultations				
Medical oncologist	0.4137	0.1041	0.3977	0.3958
Surgeon	0.0463	0.0477	0.0182	0.0182
Palliative Care	0	0.2295	0.1022	0.1041
Respirologist	0	0.0172	0.0189	0.0189
Nurse specialist	0.0750	0.0226	0	0
Dietician	0.0444	0.0462	0.0127	0.0129
Procedure or Test				
Abdominal ultrasound	0.0073	0.0076	0.0091	0.0091
Echocardiography	0.0176	0	0.0162	0.0160
CT scan, chest abdominal pelvic, conventional	0.1166	0.0573	0.0453	0.0452
CT scan, head, conventional	0	0	0.0006	0.0006
Pulmonary angiogram, conventional	0	0	0.0006	0.0006
CT scan, chest abdominal pelvic, helical/spiral	0.2009	0.0573	0.1754	0.1741
CT scan, head, helical/spiral	0	0	0.0001	0.0001
Pulmonary angiogram, helical/spiral	0	0	0.0028	0.0028
MRI	0.0989	0.0653	0.0902	0.0894
Chest X-ray	0.0065	0.0067	0.0052	0.0053
Octreoscan / SRS	0.0771	0.0780	0.0375	0.0372
I131 mIBG scan	0.0022	0.0022	0	0
FDG PET	0.0009	0	0	0
Pro-BNP	0.0278	0.0278	0	0
Standard blood test - biomarker	3.4318	1.0060	2.6808	2.6592
Special blood test - other	0.8824	0.6610	1.3154	1.3107

Other supportive procedures following progression

Additional supportive procedures were included in the pNETs evaluation based on patient level data from RADIANT-3 supplied by Novartis in their evidence submission. These are presented in Table 138.

Table 138 Supportive procedures in post-progression from RADIANT-3

Procedure	Unit cost	Initial progression cycle		
		Active	BSC	
Radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Chemoembolisation	[redacted]	[redacted]	[redacted]	[redacted]

Notes: a, National schedule of reference costs 2014-15, HRG Data: Code SC28Z [Deliver a Fraction of Interstitial Radiotherapy]; b, National schedule of reference costs 2014-15, HRG Data: Code YR57Z [Percutaneous, Chemoembolisation or Radioembolisation, of Lesion of Liver]; c, in accordance with data in Novartis evidence submission, Appendix 7 Subsequent treatments in RADIANT-3, PBO arm.

Similarly, supportive treatments were included in the costing for the GI and lung NET, and GI (midgut) NET evaluations. These rates of utilisation are based on patient level data from RADIANT-4 supplied by Novartis in their evidence submission, and are presented in Table 139.

Table 139 Supportive procedures post-progression from RADIANT-4 (Central Review)

Procedure	Unit cost	Initial progression cycle	
		Following Active	Following BSC
Hepatic artery embolization	[redacted]	[redacted]	[redacted]
Chemoembolization	[redacted]	[redacted]	[redacted]
Radiofrequency ablation	[redacted]	[redacted]	[redacted]
Selective internal radiation therapy (SIRT)	[redacted]	[redacted]	[redacted]

Notes: a: National schedule of reference costs 2014-15, HRG Data: Code SC28Z [Deliver a Fraction of Interstitial Radiotherapy]; b: National schedule of reference costs 2014-15, HRG Data: Code YR57Z [Percutaneous, Chemoembolisation or Radioembolisation, of Lesion of Liver]; c: in accordance with data in Novartis evidence submission, Appendix 7 Subsequent treatments in RADIANT-3, PBO arm.

7.1.5.6.5 Cost of adverse event management

Adverse events experienced by patients on treatment attract additional healthcare resources. To approximate the cost of managing those treatment-related events which could influence the cost-effectiveness of included treatments we included only grade 3 and 4 adverse events (SAEs) occurring in at least 2 per cent of either arm of trial patients (National Cancer Institute Common Terminology Criteria for Adverse Events).

In the evaluation of pNETs this included SAEs reported in RADIANT-3 and A6181111 clinical trials. In the evaluation of GI and lung NETs, as well as GI (midgut) NETs, this included SAEs reported in RADIANT-4 and NETTER-1 clinical trials.

In pNETs, an indirect treatment comparison was conducted to match the trial populations of A6181111 and NETTER-1 to the trial populations of the respective RADIANT trial. For each active treatment in the three evaluations an odds ratio was applied to the weighted average rate to give a relative rate by strategy for each event type. In GI and Lung NETs, and GI (midgut) NETs, the unadjusted proportion of patients experiencing an SAE as reported in RADIANT-4 and NETTER-1 was used.

Based on the assumption that no patient reported more than one SAE of any specific type during their time on treatment, we applied the costs of SAE management to only the initial Markov cycle in the progression-free health state.

Table 140 Included serious adverse events in the pNETs evaluation by proportion (%) and treatment strategy

Event	Everolimus	Sunitinib	Best supportive care
Neutropenia	0.2%	5.5%	0.2%
Hypertension	0.2%	4.4%	0.2%
Palmer-planter erythro-dysesthesia	0.2%	2.8%	0.2%
Leukopenia	0.2%	2.8%	0.2%
Diarrhoea	3.4%	2.0%	0.5%
Stomatitis	7.1%	1.7%	0.2%
Thrombocytopenia	4.2%	1.7%	0.2%
Anaemia	6.1%	0.2%	0.2%
Hyperglycaemia	5.4%	1.9%	2.0%
Fatigue/Lethargy	2.5%	0.7%	0.5%
Infections	2.5%	0.5%	0.5%
Pneumonitis	2.7%	0.2%	0.2%
Nausea	2.7%	0.7%	0.2%
Asthenia	1.0%	1.3%	1.0%
Decreased appetite/Anorexia	0.2%	1.2%	1.2%

Table 141 Included serious adverse events in the GI and Lung NETs evaluation by proportion (%) and treatment strategy

Event	Everolimus	Best supportive care
Diarrhoea	7.4%	2.0%
Stomatitis	8.9%	0.0%
Anaemia	4.0%	1.0%
Hyperglycaemia	3.5%	0.0%
Fatigue/Lethargy	3.5%	1.0%
Infections	6.9%	0.0%
Peripheral oedema	2.0%	1.0%
Pyrexia	2.0%	0.0%

Table 142 Included serious adverse events in the GI (midgut) NETs evaluation by proportion (%) and treatment strategy

Event	Everolimus	177Lu-DOTATATE	Best supportive care
Hypertension	6.8%		1.7%
Diarrhoea	11.1%	5.0%	3.4%
Stomatitis	7.7%		0.0%
Anaemia	6.8%	1.7%	1.7%
Fatigue/Lethargy	5.1%	1.7%	1.7%
Infections	12.8%		3.4%
Peripheral oedema	2.6%	1.7%	1.7%
Pyrexia	1.7%		0.0%
Abdominal pain	5.1%	3.4%	6.9%

7.1.5.6.6 Cost of end-of-life

On the basis that the average cost of health resource in the final weeks of the life of a cancer patient is a reasonable surrogate for patients with a neuroendocrine tumour, we have used an estimate from the literature for cancer patients in England and Wales (£4,346.19). This includes elective and non-elective inpatient admissions, outpatient appointments, accident and emergency (A&E) visits, district nurses, and general practitioner (GP) visits from the point at which a strong opioid is first used. [120]

7.1.6 Checking the model for wiring errors

The economic model was checked in three ways. First, all calculations in the model were performed by one person and checked by another person. Second, the results of the model were checked by construction of an independent simplified model. Third, the reasonableness of outputs given extreme input values was checked. For example, total mean life years are expected to equal to total mean QALYs when all utility are set to 1.

7.2 Cost effectiveness results

7.2.1 Base case results

In this section, we report the outputs of our base-case analysis on a per tumour location basis assuming list price for everolimus and sunitinib (Table 143, Table 144, Table 145, Table 146, Table 147 and Table 148).

7.2.1.1 Pancreatic NETs

According to the model predictions (Table 143), the highest mean survival time is expected in patients with pNETs treated with sunitinib (6.39 years); intermediate mean survival time (4.69 years) is predicted in patients treated with everolimus; and the lowest mean survival time is expected in patients treated with BSC (3.46 years). Similarly, the highest mean QALYs are in patients treated with sunitinib followed by QALYs for patients treated with everolimus and BSC only. Also, the highest costs are predicted in patients from sunitinib arm, followed by costs for patients in the everolimus and BSC arms, with the costs of drug acquisition being the major driver of the total costs.

The resulting mean ICER for everolimus vs. BSC is at £45,493. Since this figure is higher than the ICERs for sunitinib vs. everolimus, sunitinib and BSC extendedly dominate everolimus, so that, ultimately, the relevant comparison is sunitinib vs. BSC, for which the ICER is £20,717.

Table 143: PenTAG base-case results for pancreatic NETs

	Sunitinib	Everolimus	BSC	Sunitinib vs. Everolimus	Everolimus vs BSC	Sunitinib vs.BSC
Life years (mean, undiscounted)	6.39	4.69	3.46	-1.70	1.23	2.93
QALYs (mean, discounted)	[redacted]	[redacted]	[redacted]	-0.73	0.59	1.32
Total costs (mean, discounted)	£43,192	£42,646	£15,761	£546	£26,885	£27,431
ICER (Cost / QALY)				£745	£45,493	£20,717

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; QALYs, quality-adjusted life years

The breakdown of life years, QALYs and costs outcomes is presented in Table 144. It may be noted that while sunitinib incurs higher incremental per patient drug acquisition costs over BSC than everolimus does (£27,431 vs. £26,885), sunitinib more than compensates for that excess in costs through the larger corresponding incremental gain in QALYs over BSC (1.32 vs. 0.59). The majority of the difference in QALY outcomes originates from survival time in the post-progression health state (1.89 vs. 0.52), which has the same associated health related quality of life under both treatment options.

Table 144: PenTAG base-case detailed results for pancreatic NETs

	Sunitinib	Everolimus	BSC	Sunitinib vs Everolimus	Everolimus vs. BSC	Sunitinib vs. BSC
Life years (mean, undiscounted)						
Pre-progression	1.60	1.28	0.57	0.32	0.71	1.03
Post-progression	4.79	3.41	2.89	1.37	0.52	1.89
Total	6.39	4.69	3.46	1.70	1.23	2.93
QALYs (mean, discounted)						
Pre-progression	[redacted]	[redacted]	[redacted]	0.18	0.43	0.62
Post-progression	[redacted]	[redacted]	[redacted]	0.55	0.16	0.71
Total	[redacted]	[redacted]	[redacted]	0.73	0.59	1.32
Costs (mean, discounted)						
Pre-progression						
Drug acquisition	£22,216	£25,547	£2,003	-£3,331	£23,544	£20,213
Drug administration	£1,308	£1,104	£510	£204	£594	£798
Medical management	£952	£776	£184	£176	£592	£768
AEs	£89	£132	£15	-£43	£117	£74
Total (pre-progression)	£24,566	£27,559	£2,712	-£2,994	£24,847	£21,853
Post-progression						
Drug acquisition	£8,120	£6,113	£4,660	£2,006	£1,453	£3,460
Drug administration	£1,949	£1,468	£1,106	£482	£361	£843
Medical management	£4,993	£3,759	£3,394	£1,234	£365	£1,599
End-of-life care	£3,565	£3,747	£3,889	-£182	-£142	-£324
Total (post-progression)	£18,627	£15,087	£13,049	£3,540	£2,038	£5,578
Total	£43,192	£42,646	£15,761	£546	£26,885	£27,431
ICER (Cost / QALY)				£745	£45,493	£20,717

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; QALY, quality-adjusted life year

7.2.1.2 GI and lung NETs

The comparison between treatment with everolimus and BSC for GI and lung NETs patient subpopulation yielded an ICER of £44,557 (Table 145), exceeding the upper bound of the NICE's threshold range. Treatment of these patients with everolimus results in better survival (6.21 years vs. 4.82 for BSC). Likewise, the treatment costs in everolimus arm are higher; they are driven by the drug acquisition costs in pre- and post-progression health states (Table 146).

Table 145: PenTAG base-case results for GI and lung NETs

	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	6.21	4.82	1.39
QALYs (mean, discounted)	3.74	3.05	0.69
Total costs (mean, discounted)	£47,334	£16,526	£30,809
ICER (Cost / QALY)			£44,557

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 146: PenTAG base-case detailed results for GI and lung NETs

	Everolimus	BSC	Everolimus vs.BSC
Life years (mean, undiscounted)			
Pre-progression	1.42	0.83	0.59
Post-progression	4.79	3.99	0.80
Total	6.21	4.82	1.39
QALYs (mean, discounted)			
Pre-progression	1.04	0.65	0.38
Post-progression	2.70	2.39	0.31
Total	3.74	3.05	0.69
Costs (mean, discounted)			
Pre-progression			
Drug acquisition	£26,054	£376	£25,679
Drug administration	£147	£2	£144
Medical management	£4,141	£2,038	£2,102
AEs	£171	£34	£137
Total (pre-progression)	£30,513	£2,450	£28,063
Post-progression			
Drug acquisition	£4,331	£2,511	£1,820
Drug administration	£21	£10	£11
Medical management	£8,886	£7,822	£1,064
End-of-life care	£3,583	£3,732	-£149
Total (post-progression)	£16,822	£14,076	£2,746
Total	£47,334	£16,526	£30,809
ICER (Cost / QALY)		£44,557	

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

7.2.1.3 Gastrointestinal (midgut) NETs

In our analysis, treatment of patients from the gastrointestinal NETs subpopulation with everolimus and BSC results in survival time of 7.5 years and 7.05 years, respectively (Table 147). In patients treated with everolimus, predicted QALYs are slightly higher than in BSC arm (4.37 vs. 4.12).

The mean costs of £55,842 per patient were incurred in everolimus arm. The costs in BSC arm were £21,119 per patient. Drug acquisition was the major cost component in this analysis (Table 148).

The resulting ICER for everolimus vs. BSC is £199,233.

Table 147: PenTAG base-case results for everolimus in GI NETs

	Everolimus	BSC	Everolimus vs. BSC

Life years (mean, undiscounted)	7.50	7.05	0.44
QALYs (mean, discounted)	4.37	4.19	0.17
Total costs (mean, discounted)	£55,842	£21,119	£34,723
ICER (Cost / QALY)			£199,233

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; QALY, quality-adjusted life year

Table 148: PenTAG base-case detailed results for everolimus in GI NETs

	Everolimus	BSC	Everolimus vs.BSC
Life years (mean, undiscounted)			
Pre-progression	2.08	1.44	0.65
Post-progression	5.42	5.62	-0.20
Total	7.50	7.05	0.44
QALYs (mean, discounted)			
Pre-progression	1.49	1.10	0.38
Post-progression	2.88	3.09	-0.21
Total	4.37	4.19	0.17
Costs (mean, discounted)			
Pre-progression			
Drug acquisition	£31,805	£635	£31,170
Drug administration	£178	£4	£174
Medical management	£5,945	£3,449	£2,495
AEs	£287	£105	£182
Total (pre-progression)	£38,215	£4,194	£34,021
Post-progression			
Drug acquisition	£4,637	£3,260	£1,377
Drug administration	£23	£13	£10
Medical management	£9,515	£10,155	-£640
End-of-life care	£3,452	£3,497	-£45
Total (post-progression)	£17,627	£16,925	£702
Total	£55,842	£21,119	£34,723
ICER (Cost / QALY)			£199,233

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; QALY, quality-adjusted life year

In Table 149 and Table 150 we present results for 177Lu-DOTATATE for treating GI (midgut) NETs. This analysis incorporates background mortality as explained in section 7.1.5.2.

Table 149: PenTAG results for 177Lu-DOTATATE in gastrointestinal (midgut) NETs

	Everolimus	177Lu-DOTATATE	BSC	Everolimus vs. BSC	177Lu-DOTATATE vs. everolimus	177Lu-DOTATATE vs. BSC
Life years (mean, undiscounted)	5.75	6.66	4.90	0.85	0.91	1.76
QALYs (mean, discounted)	3.57	4.19	3.11	0.45	0.63	1.08
Total costs (mean, discounted)	£52,018	£83,667	£16,628	£35,390	£31,649	£67,039

ICER (Cost / QALY)	£78,330	£50,499	£62,158

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; QALY, quality-adjusted life year

Table 150: PenTAG detailed results for 177lu-DOTATATE in gastrointestinal (midgut) NETs

	Everolimus	177Lu-DOTATATE	BSC	Everolimus vs. BSC	177Lu-DOTATATE vs. everolimus	177Lu-DOTATATE vs. BSC
Life years (mean, undiscounted)						
Pre-progression	2.07	5.41	1.43	0.63	3.35	3.98
Post-progression	3.68	1.25	3.46	0.22	-2.43	-2.22
Total	5.75	6.66	4.90	0.85	0.91	1.76
QALYs (mean, discounted)						
Pre-progression	1.48	3.51	1.10	0.38	2.03	2.41
Post-progression	2.09	0.68	2.01	0.08	-1.41	-1.33
Total	3.57	4.19	3.11	0.45	0.63	1.08
Costs (mean, discounted)						
Pre-progression						
Drug acquisition	£31,786	[redacted]	£633	£31,152	[redacted]	[redacted]
Drug administration	£178	[redacted]	£4	£174	[redacted]	[redacted]
Medical management	£5,904	[redacted]	£3,437	£2,466	[redacted]	[redacted]
AEs	£287	[redacted]	£105	£182	[redacted]	[redacted]
Total (pre-progression)	£38,155	[redacted]	£4,180	£33,975	[redacted]	[redacted]
Post-progression						
Drug acquisition	£3,349	£1,093	£2,117	£1,232	-£2,256	-£1,024
Drug administration	£16	£5	£8	£8	-£11	-£3
Medical management	£6,871	£2,242	£6,595	£276	-£4,629	-£4,353
End-of-life care	£3,627	£3,522	£3,728	-£101	-£105	-£206
Total (post-progression)	£13,863	£6,862	£12,448	£1,415	-£7,001	-£5,586
Total	£52,018	£83,667	£16,628	£35,390	£31,649	£67,039
ICER (Cost / QALY)				£78,330	£50,499	£62,158

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NETs, neuroendocrine tumours; QALY, quality-adjusted life year

7.2.2 Subgroup analyses

The AG did not consider any other subgroups from the NICE Scope apart from patients with pancreatic, GI and Lung, and GI (midgut) NETs.

7.2.3 Scenario analyses

A range of scenario analyses were conducted, including:

1. For pNETs, using PFS data based on local investigator assessment for everolimus instead of the PFS data from central independent review used in the base case; for GI and lung, using PFS data based on local investigator assessment instead of the PFS data from central independent review used in the base case analysis.

2. For pNETs, OS data from ITT analysis instead of the RPSFT-adjusted OS data used in the base case analysis.
3. Alternative set of utility values presented in Table 120 and Table 121, section Model parameters7.1.5.
4. Alternative set of OS and PFS curves, allowing for the parametric form of the best fitting survival functions to differ across arms in a given comparison; for pNETs, the parametric PFS curve under everolimus and BSC alone was changed to the log-normal and log-logistic functions, respectively, while OS under everolimus was altered to the log-normal function; for GI and lung NETs, PFS under everolimus and BSC alone was changed to the log normal, while OS under the two strategies was changed to the log logistic; all other model specifications remained as in the base case.
5. Limit the analysis to PFS, in recognition of the uncertainty associated with OS outcomes in this clinical area that arise from the immaturity of the OS data and cross-over and active subsequent treatment use.
6. A scenario analysis including 1st cycle drug acquisition costs, which were omitted in the base case.
7. A scenario analysis for GI midgut and GI and lung with different costs of disease monitoring corresponding to the quantities of physician visits adopted by the Novartis model; these were larger than our base case values, which reflected the opinion of our clinical experts; we altered values to be between 2 to 2.6 times the base case value in stable disease and 1.5 in progressive disease.
8. Apply 0% discount to costs and benefits.

7.2.3.1 Local assessment

When we changed the PFS data for everolimus from central review to the local investigator assessment data reported in the main study publications, we found that in pNETs the ICER for everolimus increased by £18 from the base case value of £45,493 and that the ICER for sunitinib, which was affected indirectly through the Bucher type adjustment to its PFS, decreased from the base case value of £20,717 to £19,586. In GI and lung NETs the ICER changed from £44,557 to £44,252 (Table 151).

Table 151: PenTAG scenario analysis results with PFS local investigator data

Tumour location	Treatment	Treatment or comparator	ICER
Pancreas	Everolimus	BSC	£45,511
	Sunitinib	BSC	£19,586
GI and lung	Everolimus	BSC	£44,252

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.3.2 ITT analysis for pNETs

Using the ITT data from the A6181111 and RADIANT-3 trials in pNETs, produced ICERs that are three times as large for everolimus (reaching an ICER of £136,000; Table 152) and twice as large for sunitinib (£37,217) as their respective base case values. These changes reflect the influence of adjusting for the effects on OS of cross-over to the targeted treatment in the placebo arms of both trials, which occurred in 69% of placebo arm patients in the sunitinib trial and 85% of such patients in the everolimus trial.

Table 152: PenTAG scenario analysis results based on OS ITT data in pNETs

Treatment	Treatment or comparator	ICER
Everolimus	BSC	£136,455
Sunitinib	BSC	£37,217

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; OS, overall survival

7.2.3.3 Alternative set of utility values

Increasing the utility values of pNETs in stable disease by 0.09 and keeping the values in progressive disease practically unchanged, to correspond to the values in Swinburn et al 2011,[146] reduces the ICER of everolimus by 10% to £41,246, as expected given the larger quantity of life lived in stable disease under the everolimus strategy than the BSC only strategy. Likewise the ICER to sunitinib is reduced by 6% to £19,411.

Utility values for everolimus in GI and Lung and GI midgut were increased by 0.01 in stable disease and reduced by 0.01 in progressive disease, while simultaneously reducing the utilities in stable disease with BSC alone by 0.03 and increasing utility in progressive disease under the BSC alone strategy by 0.02; for GI midgut these changes were applied at the same time as utilities under lutetium were increased by 0.02 in both disease states. These changes increased the ICERs of everolimus by 12% in GI and lung, and 7% in GI (midgut), and decreased the ICER of lutetium by 7% (see Table 143 for ICER values).

Table 153: PenTAG scenario analysis results with different utility values

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£41,246
	Sunitinib	BSC	£19,411
GI (midgut)	Everolimus	BSC	£352,801
	177Lu-DOTATATE	BSC	£57,745
GI and lung	Everolimus	BSC	£49,949

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.3.4 Alternative set of OS and PFS curves

When the parametric survival models for everolimus and BSC alone were changed from proportional hazards to accelerated failure time forms, the ICER of sunitinib in pNETs practically remained the same whereas that of everolimus in pNETs declined by 33% to £28,098 (Table 154). In contrast, everolimus in GI/NETs became less effective than BSC alone in terms of discounted QALYs, despite its larger life expectancy, i.e. 7.11 vs. 6.84 years; this result is explained by the different timing in which quality of life benefits take place, so that when the discount rate is switched to zero everolimus becomes the strategy with the larger QALYs (data not shown). Thus the relative advantage in health outcomes with everolimus tends to occur in the latter period. At the 3.5% annual discount rates such advantage occurs too late in time and everolimus becomes inferior to BSC in GI and lung NETs.

Table 154: PenTAG scenario analysis results for alternative OS and PFS curves

Tumour location	Treatment	PFS	OS	Comparator	PFS	OS	ICER
Pancreas	Everolimus	Loglogistic	Lognormal	BSC	Lognormal	Exponential	£28,098
	Sunitinib	Exponential	Exponential	BSC	Lognormal	Exponential	£20,726
GI and lung	Everolimus	Lognormal	Loglogistic	BSC	Lognormal	Loglogistic	BSC dominant

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival

7.2.3.5 Analysis limited to PFS

Due to the inherent uncertainty in the OS data caused by treatment cross-over from placebo to targeted treatments and its immaturity in GI and lung and GI midgut locations, alternative analyses that limit the measurement of costs and benefits until disease progression provide a good robustness test of our results. In this scenario, sunitinib sees its ICER increase by 75% to £35,448, while everolimus in pNETs increases by 26% to £57,493 (Table 155). In GI and lung the ICER of everolimus increases from its base case value of £44,557 to £73,086. Everolimus has a an ICER that is 21% larger than that in GI and lung, suggesting less value for money in this patient subgroup and higher cost-effectiveness in the non-midgut GI and lung population. Furthermore, 177Lu-DOTATATE's ICER is less than half that of everolimus, which at £30,115 suggests the PRRT treatment may have better longer term outcomes than everolimus.

Table 155: PenTAG scenario analysis results limiting analytical horizon to PFS

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£57,493
	Sunitinib	BSC	£35,448
GI (midgut)	Everolimus	BSC	£88,801
	177Lu-DOTATATE	BSC	£30,115
GI and lung	Everolimus	BSC	£73,086

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.3.6 Background mortality adjustments to OS and PFS curves

Adjusting for background mortality has limited effect on results in pNETs and GI and lung. In GI midgut the ICER for everolimus declines from about £200,000 in the base case to £78,330 with background mortality adjustment (Table 156). This reflects the high degree of uncertainty in the extrapolation of survival outcomes in the GI midgut, where we did have access to OS but had to impute it from the available PFS data for this subgroup. Also in GI midgut the base case analysis that includes 177-Lu-DOTATATE adopts a background mortality adjustment due to the immaturity of OS data in NETTER-1 from which 177Lu-DOTATATE derives its effectiveness data. Thus in Table 156 we present the ICER for this treatment without adjusting for background mortality, which reduces its ICER form £62,158 to £43,348.

Table 156: PenTAG scenario analysis results on background mortality

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£44,032
	Sunitinib	BSC	£21,594
GI (midgut)	Everolimus	BSC	£78,330
	177Lu-DOTATATE (no mortality adjustment)	BSC	£43,348
GI and lung	Everolimus	BSC	£46,687

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.3.6.1 First-cycle costs and disease monitoring

Accounting for first cycle costs of subsequent treatments and disease monitoring intensity in GI and lung and GI midgut has a minor effect on results as evidenced by results in Table 157 and Table 158.

Table 157: PenTAG scenario analysis results on first-cycle costs

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£45,288
	Sunitinib	BSC	£20,624
GI (midgut)	Everolimus	BSC	£208,095
	177Lu-DOTATATE	BSC	£61,619
GI and lung	Everolimus	BSC	£47,205

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

Table 158: PenTAG scenario analysis results for disease monitoring

Tumour location	Treatment	Comparator	ICER
GI (midgut)	Everolimus	BSC	£205,437
	177Lu-DOTATATE	BSC	£64,513
GI and lung	Everolimus	BSC	£46,249

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.3.6.2 Scenario analysis with 0% discount rate

As evidenced previously by results in the scenario analysis that altered the parametric survival curves to more optimistic forms, the discount rate has an influential role in the results as treatments tend to yield significant benefits in the long-term. This may be seen in both pNETs and GI and lung locations in Table 159.

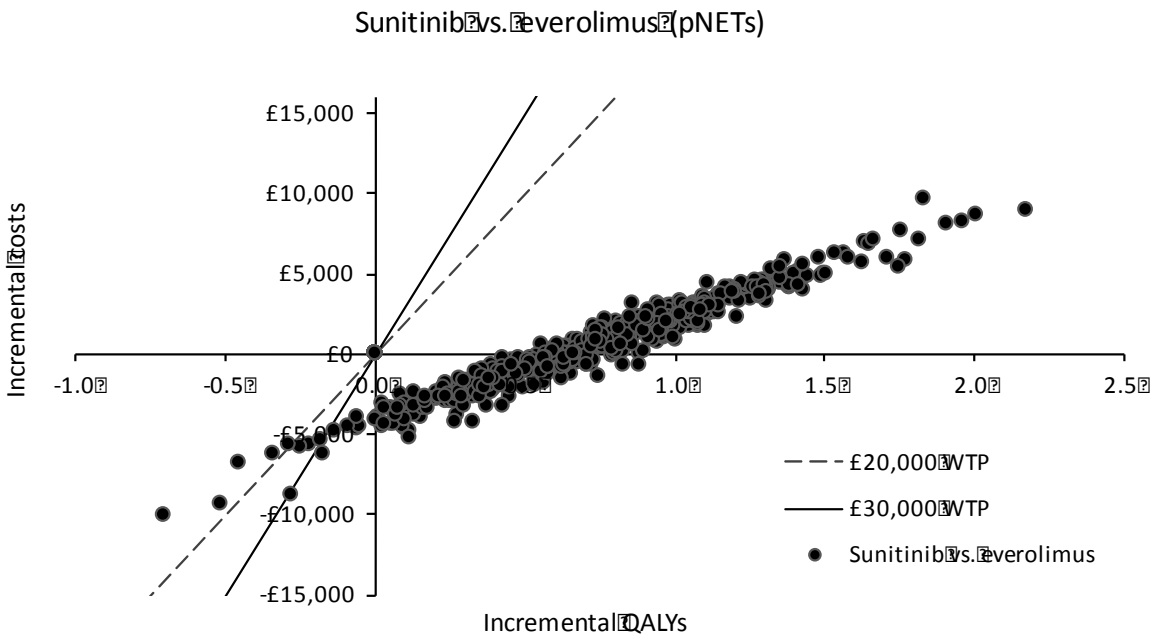
Table 159: PenTAG scenario analysis results without discounting

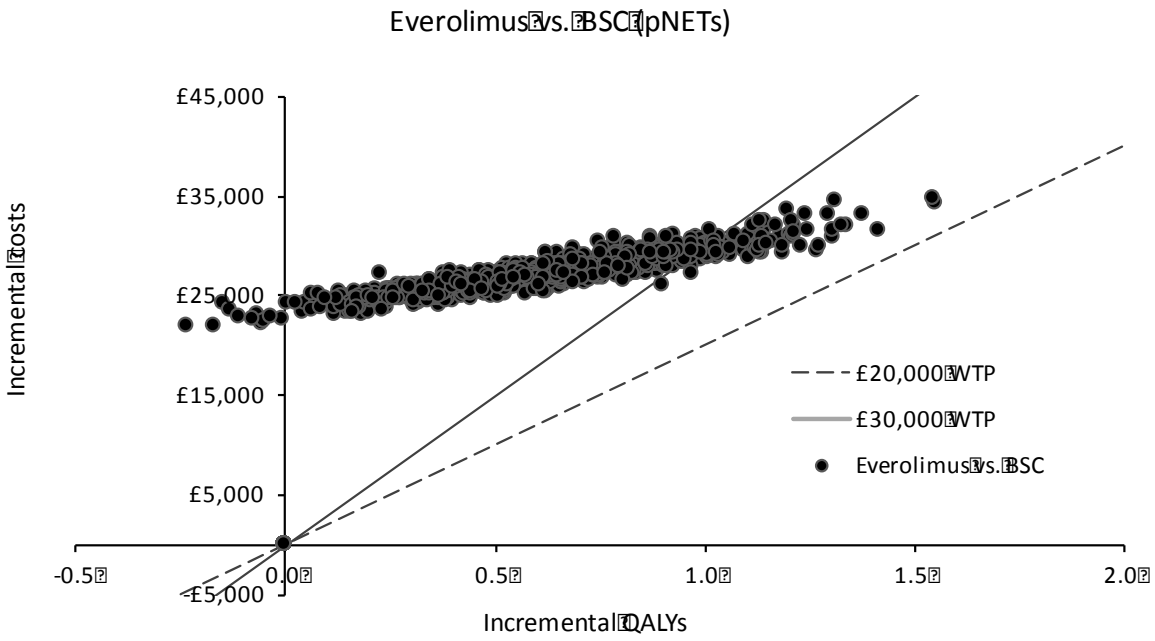
Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£38,021
	Sunitinib	BSC	£17,605
GI (midgut)	Everolimus	BSC	£131,512
	177Lu-DOTATATE	BSC	£49,907
GI and lung	Everolimus	BSC	£34,367

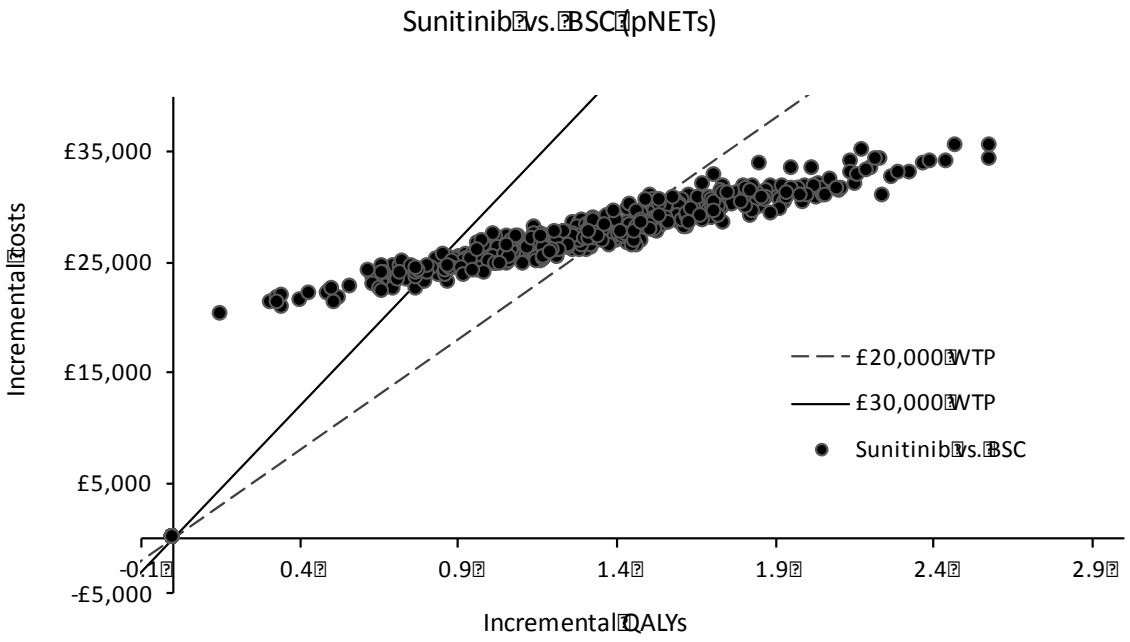
Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

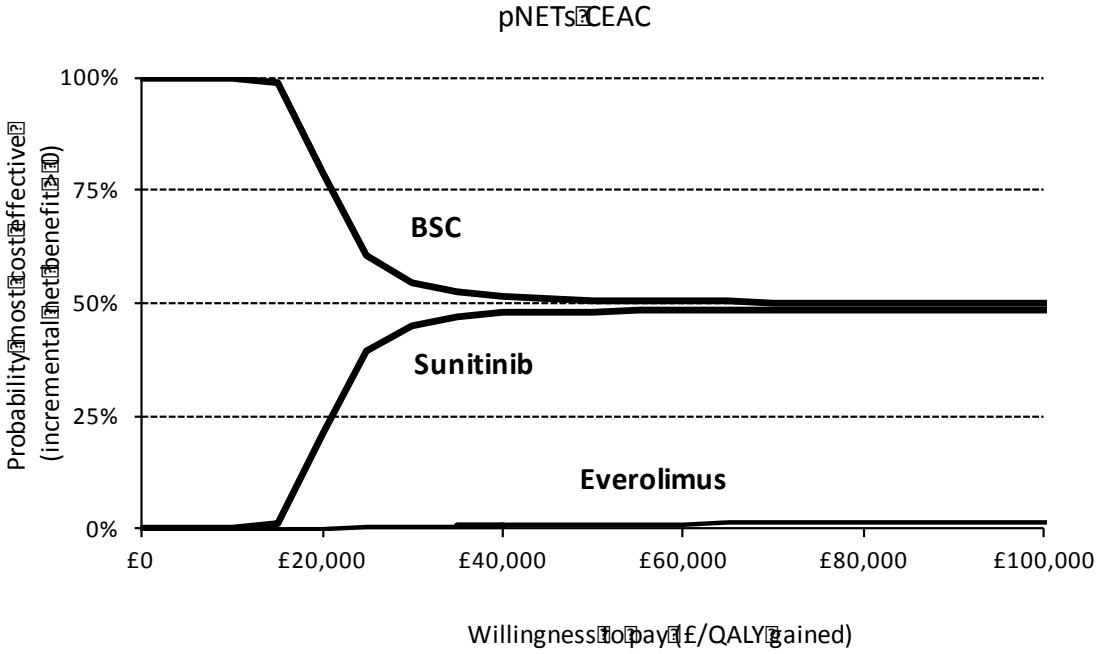
7.2.4 Probabilistic sensitivity analyses

7.2.4.1 Pancreatic NETs





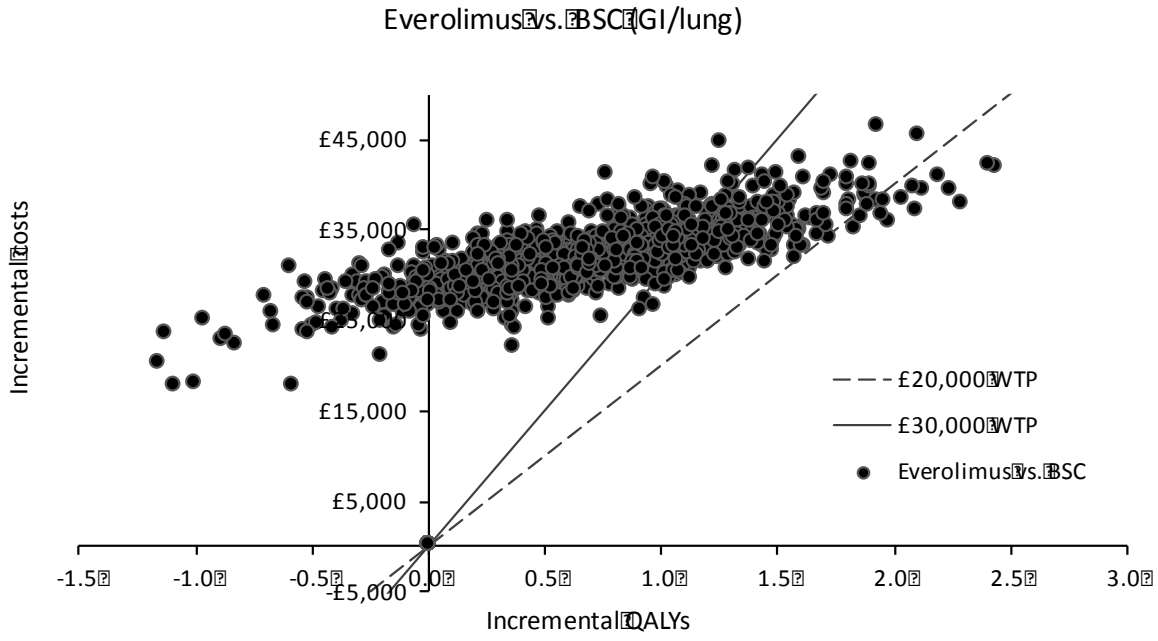


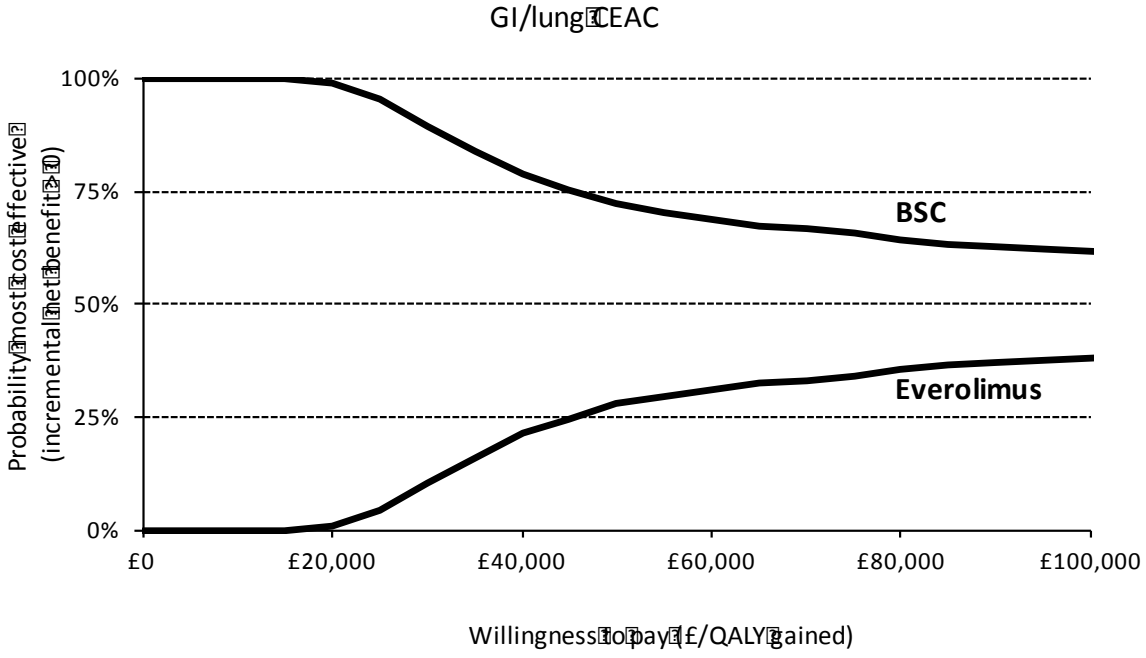


The probability that everolimus for pNETs is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 0% and 0.6%, respectively.

The probability of being the most cost-effective treatment of sunitinib for pNETs at a willingness-to-pay threshold of £20,000 per QALY is 21.2%; at £30,000/QALY, sunitinib is the most cost-effective treatment with probability of 44.8%.

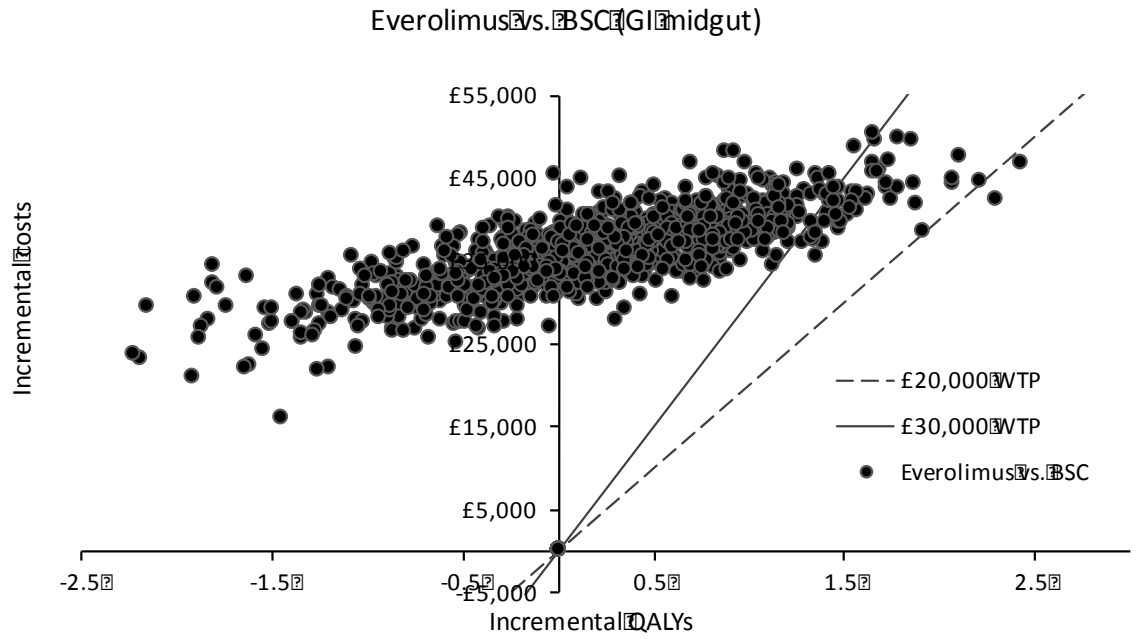
7.2.4.2 GI and lung NETs

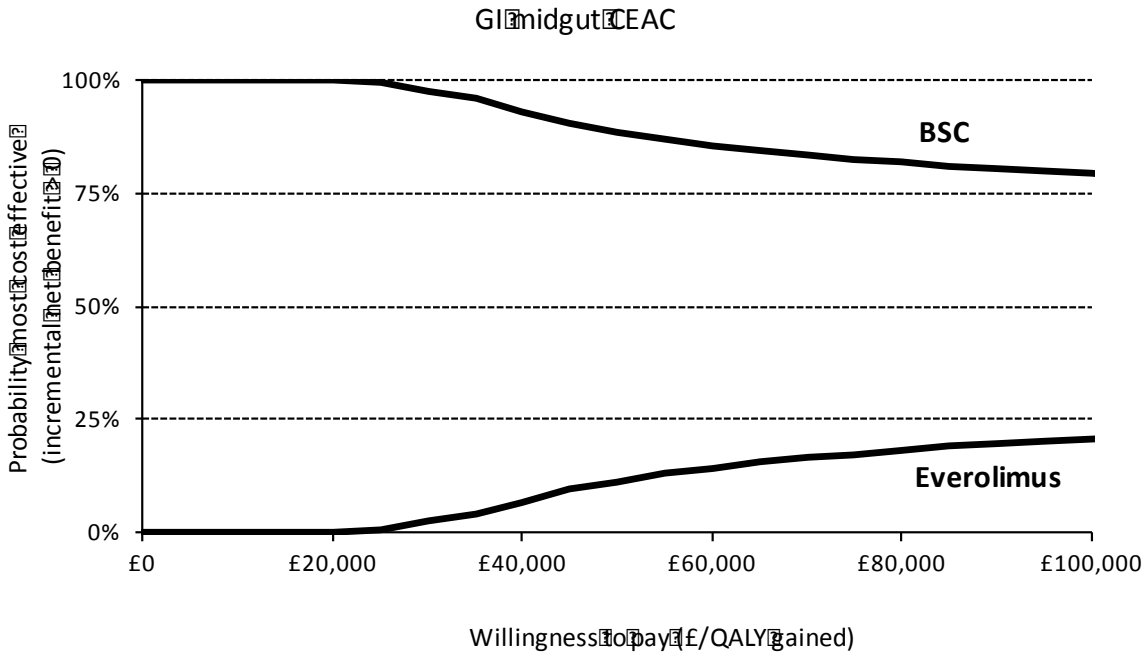




The probability that everolimus for GI and lung is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 0.9% and 10.5%, respectively.

7.2.4.3 GI midgut NETs





The probability that everolimus for GI (midgut) is the most cost-effective treatment at the willingness to pay thresholds of £20,000 per QALY and £30,000 per QALY is 0.1% and 2.5%, respectively.

7.2.5 Deterministic sensitivity analyses

We varied parameters to either side of their point estimates by 20%, except for utility differences between SD and PD, which were varied by 40%.

7.2.5.1 Pancreatic NETs

In pNETs the OS hazard ratio is the most influential parameter in the model, particularly in relation to the ICER for everolimus, which varies from £25,000 to £105,000 with the treatment effect parameter variation of 20% around the mean point estimate (Figure 57). Other influential parameters include relative dose intensity and treatment duration. The utility of PD and SD are the four most influential parameter in the model, with a larger influence on sunitinib's ICER (Figure 58).

Figure 57: Tornado analysis for everolimus in pNETs

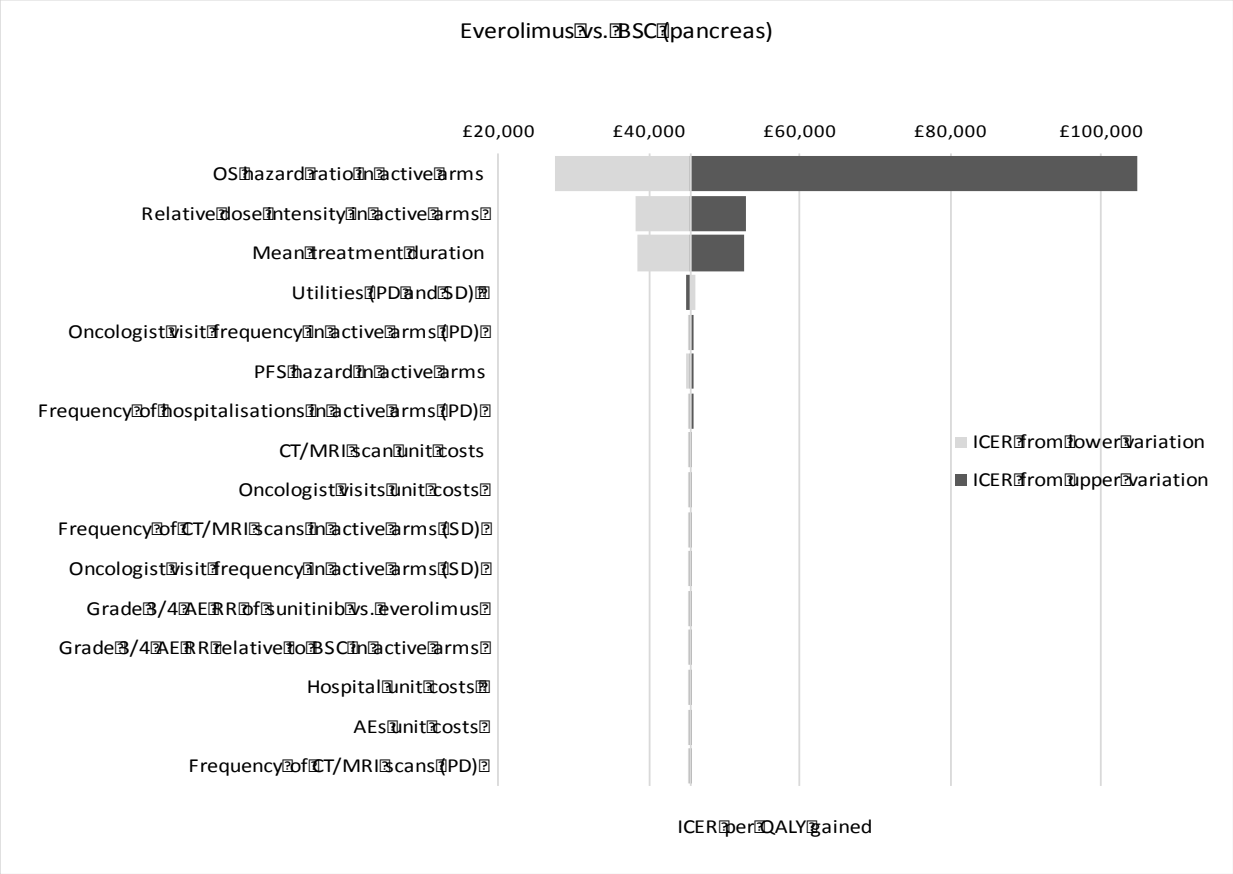
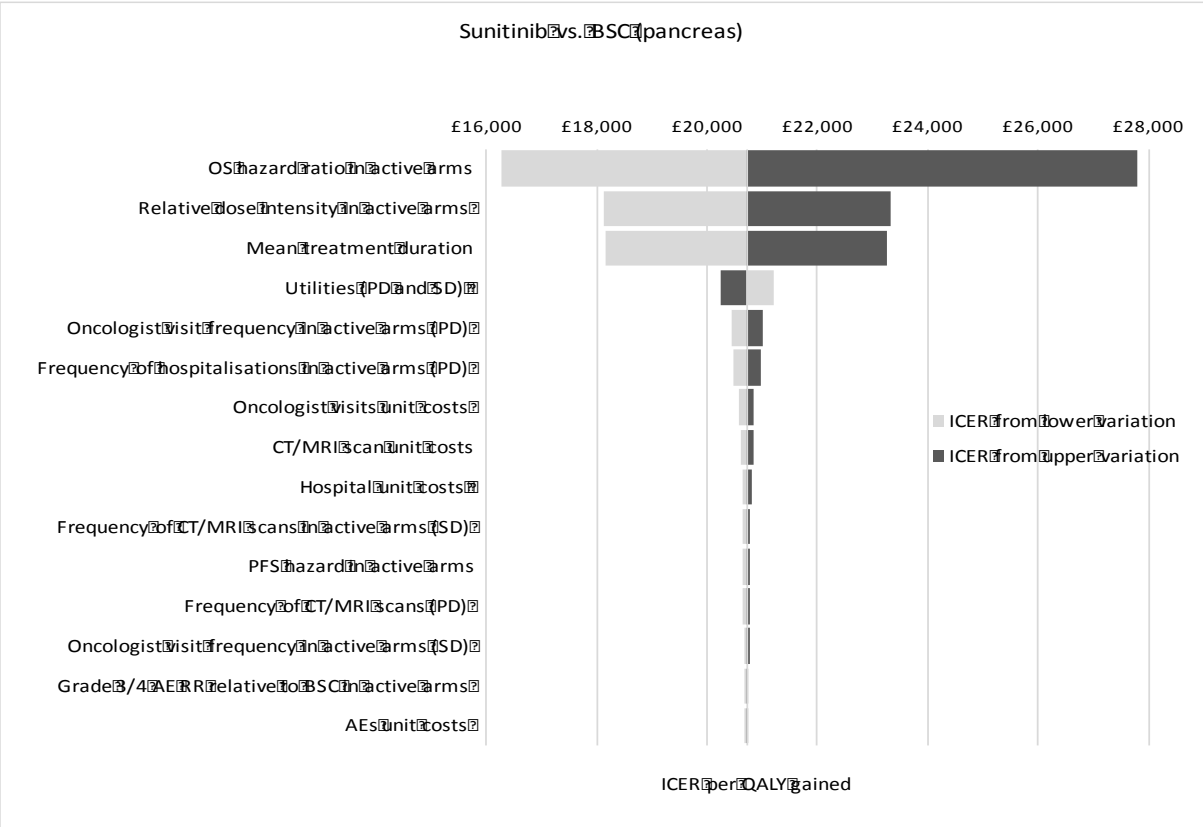


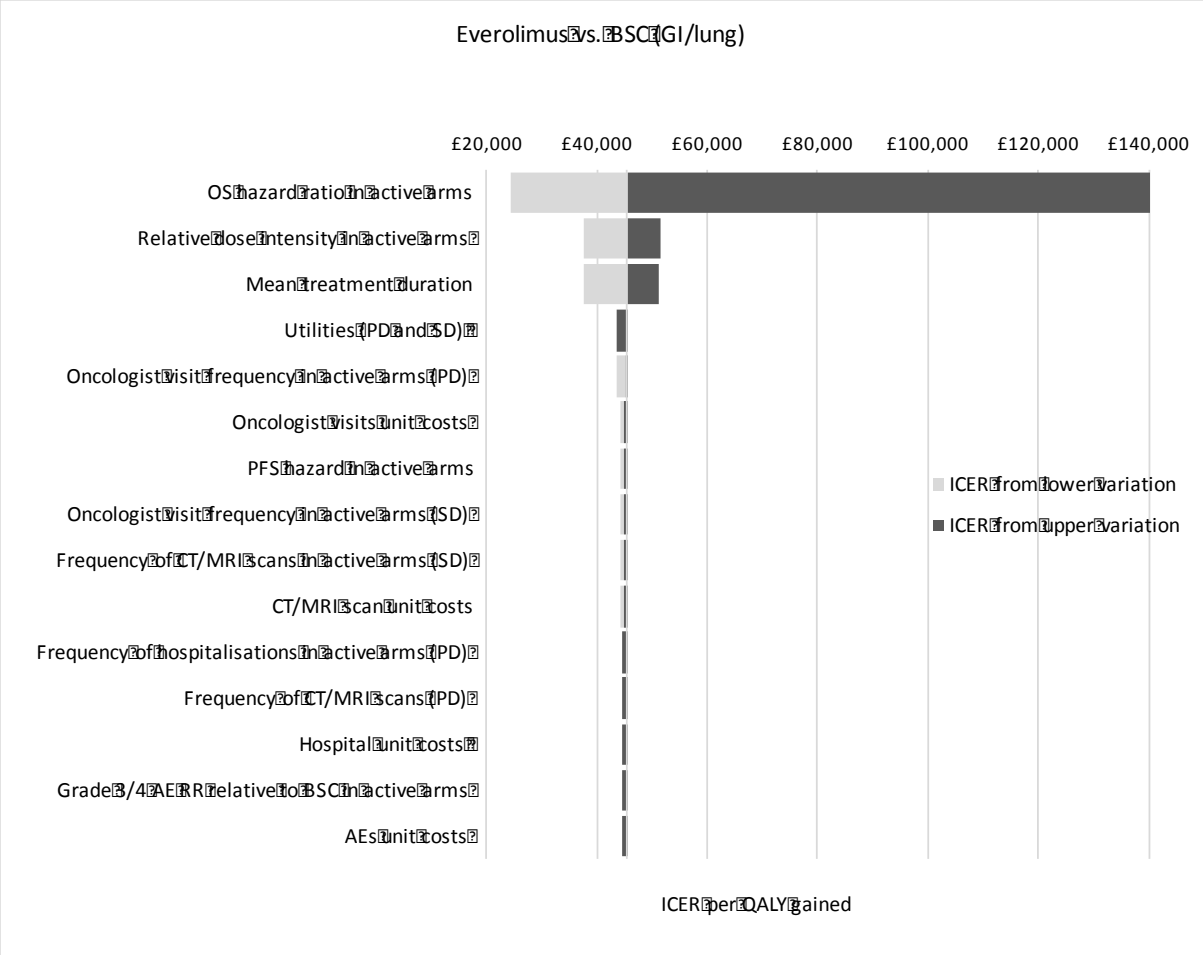
Figure 58: Tornado analysis for sunitinib in pNETs



7.2.5.2 GI and lung NETs

Similar results to those found for pNETs apply in GI and lung NETs, with variations around the point estimate of the OS hazard ratio by 20% yielding an increase of 300% or a decrease of about 50% in the ICER of everolimys, relative dose intensity and mean treatment duration have smaller but significant effects (Figure 59).

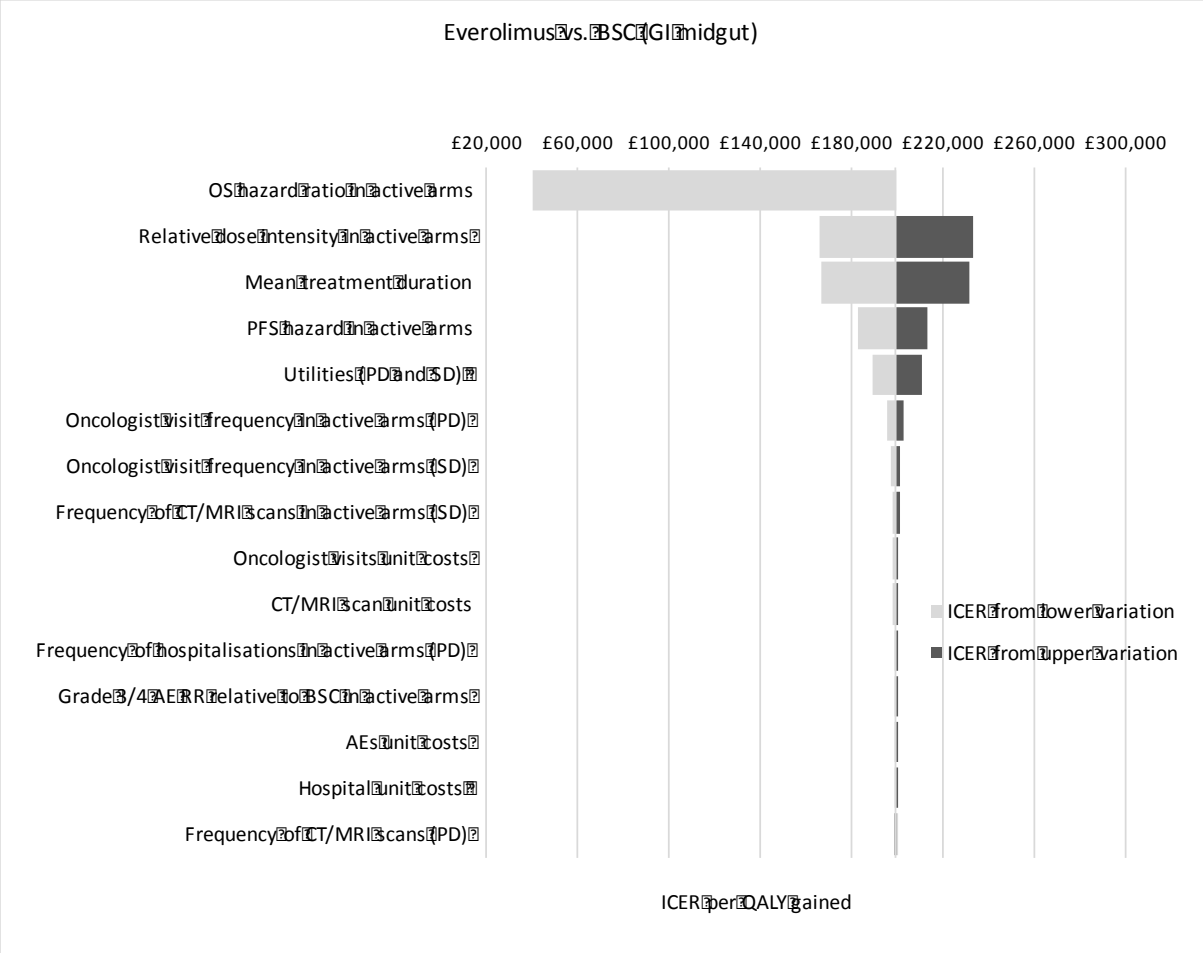
Figure 59: Tornado analysis of everolimus in GI and lung



7.2.5.3 GI midgut NETs

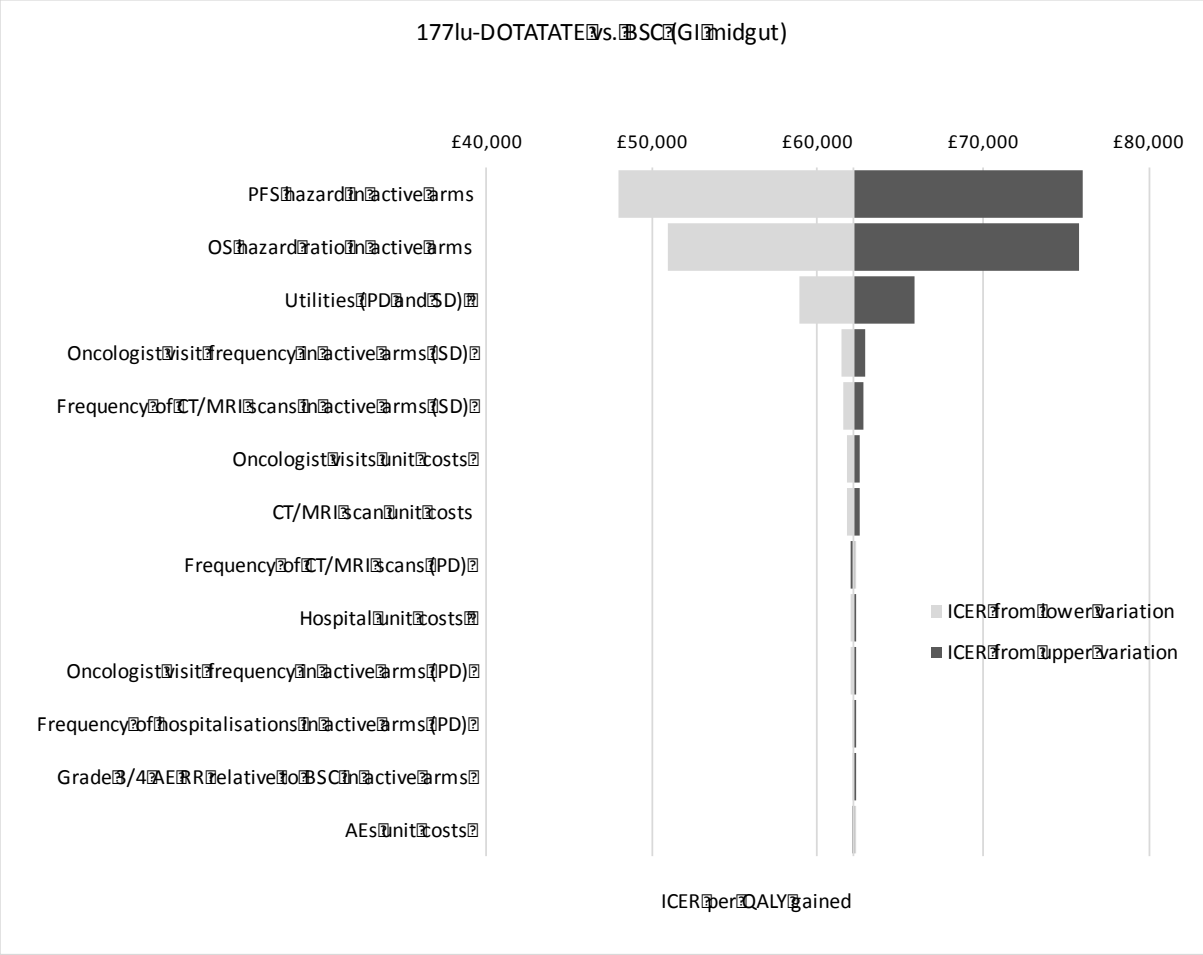
The OS hazard ratio is still the most influential parameter; varying it by 20% above and below the base case produces an ICER that varies from £43,000 to dominated value (shown in Figure 60 as a missing bar to the left side of the point estimate). Unlike for treatments in other locations, the ICER for everolimus in GI midgut was sensitivity to the variation in the PFS hazard ratio. This however is partly an artefact of how OS was populated in the model; while for other locations we had OS data available, for GI midgut we did not and thus had to rely on imputation based on PFS differences with the placebo plus BSC arm in RADIANT-4. As a consequence, part of the effect of PFS depicted in Figure 60 is an indirect effect through OS.

Figure 60: Tornado analysis of everolimus in GI midgut



The cost-effectiveness of 177Lu-DOTATATE is almost equally sensitive to the OS and PFS hazard ratios, with utilities the third most influential parameter.

Figure 61: Tornado analysis of 177Lu-DOTATATE in GI midgut



7.3 Comparison of the AG results to company results

Our model results can be compared to those of the companies in three areas:

- Everolimus, sunitinib and BSC in pNETs
- Everolimus and BSC in GI and Lung NETs
- Everolimus, 177Lu-DOTATATE and BSC in GI NETs

In all analyses, drug list prices, not PAS prices are assumed. Life-years are not discounted.

7.3.1 Everolimus, sunitinib and BSC in pNETs

- **Life-years.** The estimation of expected life-years between our model and Novartis's and AAA's models differed substantially for sunitinib but were consistent for everolimus. Novartis assumed no difference in PFS or OS between everolimus and sunitinib (mean of 4.62 life-years for both treatments), whereas we estimated a superior PFS and OS for people treated with sunitinib (OS of 6.39 years versus 4.62 years). AAA's OS estimate was significantly larger for sunitinib (8.19 years for sunitinib and 4.62 years for everolimus). Differences are due to the adoption of three different methodological approaches, including differences in parametric distribution selected for PFS/OS extrapolation. AAA did not adjust for treatment cross-over in their MTC; Novartis used an assumption of no difference in OS from the outset; we

used publicly available survival curves with statistical adjustment for treatment cross-over for each trial in our MTC.

- **Quality-adjusted life-years.** After adjusting for quality-of-life, our own and Novartis's QALY estimates for everolimus remained similar ([redacted] and 2.73), but AAA's estimate of time with stable disease is higher, resulting in a higher estimate of total QALYs (3.25). Our estimate of sunitinib QALYs was greater than that of everolimus, due to longer PFS and OS. Novartis estimated fewer QALYs with sunitinib than everolimus in spite of equal PFS and OS, due to differences in dis-utility from serious adverse events. From a MTC of the most up to date evidence submitted to NICE, we found the difference in the incidence of AEs between the two treatments to be unlikely to result in meaningful utility differences.
- **Costs.** Treatment strategy estimates of total cost were consistent across models, including the within-model similarity between everolimus and sunitinib. Novartis found the cost of treatments to be less, but this is accounted for by their inclusion of other drug treatments under Disease monitoring and management. The same methodological difference is behind the differences in component costing in post-progression. AAA's estimate of everolimus and sunitinib strategy costs were significantly higher (227% and 289% respectively). In each case, this is accounted for by the over-costing of the acquisition of the active drug, due to the company's assumption that treatment would continue until disease progression.
- **Incremental analysis vs. BSC.** Given that neither Novartis nor AAA included a BSC care strategy, it is not possible to compare our ICERs of everolimus vs. BSC and sunitinib vs. BSC with company estimates.

Table 160: PenTAG vs company base case results in pNETs

	Everolimus			Sunitinib			BSC
	PenTAG	**Novartis**	**AAA**	**PenTAG**	**Novartis**	**AAA**	**PenTAG**
Pre-progression							
Drug acquisition**	£25,547	£21,782	[redacted]	£22,216	£21,994	£59,557	£2,003
Drug administration	£1,104	*	[redacted]	£1,308	*	£0	£510
Disease monitoring and management	£776	£5,343	[redacted]	£952	£5,242	£2,290	£184
SAE management	£132	£678	[redacted]	£89	£2,101	£91	£15
Post-progression			[redacted]				
Drug acquisition	£6,363	£2,216	[redacted]	£8,368	£2,216	£56,667	£4,939
Drug administration	£1,706	*	[redacted]	£2,187	*	£965	£1,422
Disease monitoring and management	£3,798	£7,206	[redacted]	£5,032	£7,206	£5,138	£3,447
SAE management	£0	£0	[redacted]	£0	£0	£205	£0
Death							
End-of-life	£3,747	£3,836	[redacted]	£3,565	£3,836	£0	£3,889
Total costs pre-progression	£27,559	£27,802	[redacted]	£24,566	£29,337	£61,939	£2,712
Total costs post-progression	£11,867	£9,422	[redacted]	£15,587	£9,422	£62,976	£9,808
Total costs	**£43,173**	**£41,061**	[redacted]	**£43,718**	**£42,596**	**£124,914**	**£16,409**
Life-years pre-progression***	1.28	1.18	[redacted]	1.60	1.18	2.22	0.57
Life-years post-progression***	3.41	3.44	[redacted]	4.79	3.44	5.98	2.89
Total Life-years*	4.69	4.62	[redacted]	6.39	4.62	8.19	3.46
QALYs pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	0.87	1.60	0.38
QALYs post-progression	[redacted]	[redacted]	[redacted]	[redacted]	1.84	3.74	1.53
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	**2.71**	**5.34**	**1.91**

Notes: *Drug administration costs were not presented separately, but included within the cost of drug acquisition. **We included the acquisition of supportive drugs as well as targeted drugs in this cost category, whereas Novartis included supportive drug costs in the disease management category. *** Undiscounted life-years

Key: BSC = Best supportive care.

7.3.2 Everolimus and BSC in GI and Lung NETs

Overall there was consistency between the cos-effectiveness results produced by us and Novartis.

- **Life-years.** For people receiving BSC our own model and Novartis's model found expected life-years to be similar, at 4.82 and 4.77, respectively, with 0.83 and 0.87 years of stable disease before progression. For people receiving everolimus we estimated life expectancy as 6.21 years versus Novartis's 5.79, and a lower respective proportion with stable disease (23% versus 27%). This is caused by our higher estimate of OS and lower estimate of PFS from our parametric extrapolation.
- **Quality-adjusted life-years.** For people receiving BSC we estimated a lower quality of life for people pre- and post- progression compared to Novartis, so despite a similar PFS and OS, total QALYs for BSC estimated by Novartis was slightly higher than our own (3.51 QALYs versus 3.05 QALYs). Similarly, for people receiving everolimus we found our higher estimates of PFS and OS were more heavily adjusted for loss of quality-of-life compared to Novartis, so that our estimate of total QALYs for everolimus was lower than Novartis's (3.74 versus 4.28). This is because of the fact that while Novartis used the same utility values for stable disease and disease progression across arms, we adopted treatment arm-specific utility estimates for stable disease, which is likely lower for everolimus than BSC.
- **Costs.** Our estimate of the cost of BSC was significantly less than that of Novartis (£16,526 versus £25,817 per person) because Novartis estimated the cost of disease monitoring and management, as twice as high as did we in the Novartis model and partly because we modelled fewer physician consultations. Our estimate of everolimus cost was also lower (£47,334 versus £59,720). This was again due to our lower rate of resource utilisation for disease monitoring and management.
- **Incremental analysis.** We estimated the ICER for everolimus versus BSC was £44,557 per QALY gained. Novartis found the ICER was £43,642 per QALY gained. We estimated BSC was £30,809 less costly with 0.69 fewer QALYs. Novartis found BSC was £33,903 less costly with 0.78 fewer QALYs.

Table 161: PenTAG vs Novartis base case findings in GI and Lung NETs

	Everolimus		BSC	
	PenTAG	**Novartis**	**PenTAG**	**Novartis**
Pre-progression				
Drug acquisition**	£26,054	£26,881	£376	£0
Drug administration	£147	*	£2	*
Disease monitoring and management	£4,141	£8,583	£2,038	£2,799
SAE management	£171	£601	£34	£87
Post-progression				
Drug acquisition	£4,331	£2,927	£2,511	£3,312
Drug administration	£21	*	£10	*
Disease monitoring and management	£8,886	£17,205	£7,822	£15,918
SAE management	£0	£0	£0	£0
Death				
End-of-life	£3,583	£3,524	£3,732	£3,702
Total costs pre-progression	£30,513	£36,064	£2,450	£2,886
Total costs post-progression	£13,238	£20,132	£10,343	£19,230
Total costs	**£47,334**	**£59,720**	**£16,526**	**£25,817**
Life-years pre-progression***	1.42	1.68	0.83	0.89
Life-years post-progression***	4.79	5.51	3.99	4.90
Total Life-years*	6.21	7.19	4.82	5.79
QALYs pre-progression	1.04	1.23	0.65	0.68
QALYs post-progression	2.70	3.05	2.39	2.83
Total QALYs	**3.74**	**4.28**	**3.05**	**3.51**

Notes: *Drug administration costs were not presented separately, but included with the cost of drug acquisition. . **We included the acquisition of supportive drugs as well as targeted drugs in this cost category, whereas Novartis included supportive drug costs in the disease management category. ***Undiscounted life-years

Key: BSC = Best supportive care

Table 162: Incremental analysis of everolimus versus BSC in GI and Lung NETs

	PenTAG	Novartis
Pre-progression		
Drug acquisition**	£25,679	£26,881
Drug administration	£144	*
Disease monitoring and management	£2,102	£5,784
SAE management	£137	£513
Post-progression		
Drug acquisition	£1,820	-£385
Drug administration	£11	*
Disease monitoring and management	£1,064	£1,287
SAE management	£0	£0
Death		
End-of-life	-£149	-£178
Total costs pre-progression	£28,063	£33,178
Total costs post-progression	£2,895	£902
Total costs	**£30,809**	**£33,903**
Life-years pre-progression***	0.59	0.78
Life-years post-progression***	0.80	0.61
Total Life-years*	1.39	1.40
QALYs pre-progression	0.38	0.56
QALYs post-progression	0.31	0.22
Total QALYs	**0.69**	**0.78**
Cost / LY gained	£22,213	£33,298
Cost / QALY gained	**£44,557**	**£43,642**

Notes: *Drug administration costs were not presented separately, but included with the cost of drug acquisition. . **We included the acquisition of supportive drugs as well as targeted drugs in this cost category, whereas Novartis included supportive drug costs in the disease management category. ***Undiscounted life-years. Abbreviations: BSC = Best supportive care

7.3.3 Everolimus, 177Lu-DOTATATE and BSC in GI (midgut) NETs

For GI NETs, we modelled everolimus, 177Lu-DOTATATE and BSC, whereas AAA modelled only everolimus and 177Lu-DOTATATE.

Our estimates of survival and costs for people who were treated with everolimus were significantly different, although there was some consistency in the costing of the 177Lu-DOTATATE strategy.

- **Life-years.** AAA's estimates of OS for everolimus and 177-Lu-DOTATATE were substantially less than our own. For 177Lu-DOTATATE the difference in life expectancy (4.79 in AAA versus 6.66 in AG) is due to the different methods of OS extrapolation, as AAA used a proportional hazards treatment effect on a baseline Weibull distribution function, which showed an increasing trend in death risk, whereas we used an exponential distribution, which is characterised by a constant risk of death, supplemented by background mortality risk. AAA did not provide any statistical evidence in support of their proportional hazards model for 177Lu-DOTATATE in NETTER-1; We fitted separate parametric curves to 177Lu-DOTATATE in NETTER-1 and found that the exponential was the model with the best goodness-of-fit statistics. The differences in survival time were most pronounced

in the case of PPS following everolimus, where AAA included lung and other non-midgut NET patients from RADIANT-4 in their calculation, and baseline risk of progression and death for both everolimus and 177Lu-DOATATE was that of people treated with octreotide 60 mg; we instead used the midgut subgroup of RADIANT-4 as the reference patient population, to which patients treated with 177Lu-DOTATATE were matched by a Bucher-type indirect comparison adjustment method.

- **Quality-adjusted life-years.** Our estimates of QALYs for everolimus and 177Lu-DOTATATE were also higher than AAA's (3.57 versus 1.87 for everolimus; 4.19 versus 3.29 for 177Lu-DOTATATE), although reduced by our lower estimate of utility for both pre- and post- progression. So the difference total QALYs between models was driven by the difference in life-year estimates. We found that BSC produced fewer QALYs than our estimates for active treatments (3.11 QALYs).
- **Costs.** We found totals costs for 177Lu-DOTATATE to be higher than for everolimus, consistent with AAA. However, our estimates were lower than those of AAA, and there were significant differences in component costs. Comparing everolimus across models, the singular significant difference in cost is drug acquisition, and this is because AAA costed everolimus treatment until progression, and did not adjust for relative dose intensity. In RADIANT-4 the median time to progression was 11 months, compared to 9.3 months median time on treatment, and RDI was 79.4%. Comparing 177Lu-DOTATATE across models there was agreement in total cost but notable differences in disease monitoring and management in stable disease, drug acquisition in progressive disease, and end-of-life costs. This is because AAA did not include the cost of hospital consultations, assumed every patient was treated with octreotide from progression until death, and opted not to include end-of-life / palliative care costs. In summation, these under- and over-estimations were counter-balancing.
- **Incremental analysis.** AAA did not include a BSC care strategy so a comparison of incremental pairing 177Lu-DOTATATE versus BSC with our own could not be made.

Table 163: PenTAG vs AAA base case findings in GI NETs

	Everolimus		177Lu-DOTATATE	BSC	
	PenTAG	AAA	PenTAG	AAA	PenTAG
Pre-progression					
Drug acquisition	£31,786	[redacted]	£59,187	£59,633	£633
Drug administration	£178	[redacted]	£3,482	£1,820	£4
Disease monitoring and management	£5,904	[redacted]	£14,051	£2,702	£3,437
SAE management	£287	[redacted]	£85	£304	£105
Post-progression		[redacted]			
Drug acquisition	£3,349	[redacted]	£1,093	£21,235	£2,117
Drug administration	£16	[redacted]	£5	£723	£8
Disease monitoring and management	£6,871	[redacted]	£2,242	£1,925	£6,595
SAE management	£0	[redacted]	£0	£108	£0
Death					
End-of-life	£3,627	[redacted]	£3,522	-	£3,728
Total costs pre-progression	£38,155	[redacted]	£76,805	£64,459	£4,180
Total costs post-progression	£13,863	[redacted]	£6,862	£23,991	£12,448
Total costs	**£52,018**	[redacted]	**£83,667**	**£88,450**	**£16,628**
Life-years pre-progression**	2.07	[redacted]	5.41	2.66	1.43
Life-years post-progression**	3.68	[redacted]	1.25	2.13	3.46
Total Life-years*	5.75	[redacted]	6.66	4.79	4.90
QALYs pre-progression	1.48	[redacted]	3.51	1.97	1.10
QALYs post-progression	2.09	[redacted]	0.68	1.31	2.01
Total QALYs	**3.57**	[redacted]	**4.19**	**3.29**	**3.11**

Notes: ** Undiscounted.
Key: BSC = Best supportive care.

7.4 Discussion

In patients with neuroendocrine tumours of pancreatic origin, sunitinib plus BSC was estimated to incur a cost per QALY gained over BSC alone of £17,890. Everolimus was found to be an inefficient treatment option, since it achieves QALY gains over BSC at a higher average cost than sunitinib (i.e. it is 'extendedly dominated') in this patient population. Therefore sunitinib is cost-effective in the NHS at the upper NICE threshold range of £30,000.

(As discussed below, sunitinib also meets the End of Life Criteria by NICE in the patient population of the A6181111 RCT, since it extends mean overall survival in patients with pNET by more than 3 months, relative to placebo plus BSC, where life expectancy is not significantly different from 24 months at conventional levels of statistical significance.)

These results are based on an indirect comparison of two RCTs in different patient populations. Assessment of the extent of heterogeneity across the trials and relative effectiveness between treatments is complicated by the fact that there is substantial treatment cross-over from placebo to the active arms in those trials. The companies sponsoring the two treatments have conducted statistical analyses that seek to adjust for such cross-over. The AG asked companies to provide the code and data to be able to replicate their cross-over adjusted analyses of OS and understand whether the methods are likely to be comparable. The sponsor of everolimus provided such information to close to the

end of the reviewing period to allow the AG to review and incorporate that evidence in this report. The sponsor of sunitinib provided the trial data but no the code to replicate the results of their cross-over adjusted analysis of OS. This leaves a crucial source of uncertainty unaddressed, since the available cross-over adjusted OS curves from published reports, which we used to inform our base case analysis, suggest that life expectancy in the placebo arm of the everolimus trial (RADIANT-3) is 30% larger than life expectancy in the placebo arm of the sunitinib trial (A6181111; 18 versus 14 months).

Our analyses extend the evaluation in pNETs submitted by the companies to include the BSC only arm in the evaluation, in line with the NICE scope for this assessment. There is no clear justification for excluding this treatment option from the analysis, especially since the RCTs in this patient population have themselves included such treatment option as the control arm. More importantly, advice from our clinical experts suggests that in advanced, unresectable or metastatic patients with progressive disease who are asymptomatic giving no active initial treatment is a treatment option in practice.

In the GI or Lung NET patient population, the available head to-head trial evidence from the phase III RADIANT-4 RCT suggests that everolimus is not cost-effective at the upper NICE threshold of £30,000 even after adjusting for the negotiated PAS discount. Contrary to the analysis submitted to NICE by the company sponsoring everolimus, we have adopted different utility values in stable disease to acknowledge the effect of treatment on patient health related quality of life. While the company found that everolimus is [redacted] after applying the PAS discount, we found that the ICER is £39,323. Our analysis reveals that the company's results were not robust to limited variations in the interpretation of the same available data (deriving from the RADIANT-4 RCT and the company's resource use survey) used to populate model parameter values and specify the survival time structure in the model.

We have also extended the economic evaluation of everolimus to the GI midgut population based on subgroup analyses of PFS published by the company and found everolimus to have an ICER of £135,000 per QALY gained over BSC. This analysis is subject to high levels of uncertainty due to lack of OS data specific to this patient subgroup, which was addressed by assuming that the OS treatment effect of everolimus was proportional to its PFS treatment effect in this population. Moreover, in RADIANT-4, the source of the effectiveness data for this analysis, randomisation was not stratified according to the midgut location, and thus the resulting PFS evidence in the midgut subgroup is subject to a lower level of internal validity.

We conducted scenario analyses for the GI (midgut) location where evidence from the NETTER-1 trial from the 177Lu-DOTATATE arm was matched to the midgut population of RADIANT-4 by assuming that the control arm in NETTER-1 represents the same treatment as that given in the placebo plus BSC arm in RADIANT-4. Since this assumption has been questioned by our clinical experts and there is no published evidence on NETTER-1 available at the time of writing, we consider this analysis with reservation. Subject to these caveats, 177Lu-DOTATATE is associated with higher QALY benefits over BSC than everolimus does, and achieves those benefits at a lower cost per QALY than everolimus (i.e. it extendedly dominates it), but its ICER of £74,000 relative to BSC is well above the NICE threshold.

8 End of life

For each of NET locations considered in our analyses, we estimated life expectancy as the area under the OS Kaplan–Meier curve of the placebo plus BSC arm that was used as the source of data in the AG model. In pNETs the curve used in these analyses was the placebo K-M curve adjusted by the RPSFT method (Yao et al. 2016, Raymond et al. 2016), whereas for GI-only, where only unadjusted K-M data were available (cross-over in placebo arm was 6%, Yao et al. 2016), the ITT placebo K-M curve was used. The results are presented in Table 164.

Mean survival estimates from head to head trials show that the null hypothesis that the pNETs population in A6181111 meets the life expectancy end of life criterion is not rejected by the data since the 95% confidence interval of the extrapolated (to a maximum age of 100 years) mean survival in the placebo arm (95% CI: 16-27) crosses the 24 month threshold. In other words, the data support the view that life expectancy with BSC only in A6181111 may be 2 years or less. In contrast, the pNETs population of RADIANT-3 has an extrapolated mean in the placebo arm that is statistically significantly higher than 24 months (95% CI: 34-54). The same results is obtained fro GI/Lung, where the data rejects the null hypothesis that the life expectancy of the population is less than 24 months (95% CI: 43-86) at the 5% significance level.

Sunitinib is estimated to have a mean treatment effect of 5.9 months, using observed data in A6181111, or 38.5 months, using a parametric (exponential) survival curves fitted to the OS data of the two trials arms and extrapolated to 100 years of age. The treatment effect of everolimus in RADIANT-3 is 1.6 months, using observed data, and 14.7 with extrapolated survival. The respective estimates for everolimus in GI or lung NETs are 2.6 and 16.6.

Table 164: Life expectancy and extension to life observed in each trial (in months)

	pNETs		**GI/Lung**
	Restricted mean at end of follow-up (area under the K-M)		
	RADIANT-3[1]	A6181111	RADIANT-4
Placebo+BSC	18.3 (17.2, 19.4)	14.5 (12.6, 16.3)	29.1 (26.1, 32.1)
Everolimus+BSC	19.9 (19.0, 20.9)		
Sunitinib+BSC		20.4 (18.9, 22.0)	31.7 (29.9, 33.5)
Treatment effect (Active treatment arm - placebo arm)	1.6	5.9	2.6
	Extrapolated mean using exponential survival function*		
Placebo+BSC	3.32 3.36	1.71	4.09 4.84
	41.6 (33.9, 53.6)	20.5 (16.4, 27.4)	57.9 (43.5, 86.2)
Everolimus+BSC	56.3 (48.2, 67.7)		74.5 (60.0, 97.8)
Sunitinib+BSC		59.0 (55.8, 80.0)	
Treatment effect (Active treatment arm - placebo arm)	14.7	38.5	16.6

Notes:[1] Restricted to maximum observed time (24 months) in arm (placebo plus BSC) with the shortest length of follow-up *Restricted at 40 years after the start of treatment ~100 years of age.

In conclusion, the end of life criteria may only be met by sunitinib in the pNETs population of A6181111. In GI or Lung NETs life expectancy does not meet the end of life criteria set by NICE.

9 Discussion

9.1 Aim

The key objectives of this technology assessment report, in keeping with the Final NICE Scope, are two-fold. Firstly to estimate the clinical effectiveness of three interventions (everolimus, 177Lu-DOTATATE and sunitinib) for treating unresectable or metastatic neuroendocrine tumours with disease progression. The second objective is to establish the cost effectiveness of these interventions. The comparator treatments are chemotherapy, interferon alpha and best supportive care.

During the course of this review, NICE consulted on amendments to the original Final NICE Scope. Originally, lanreotide was included as an intervention and octreotide as a comparator. In the revised Final Scope, agreed on 18th August 2016, lanreotide and octreotide were dropped.

9.2 Clinical effectiveness evidence

The interventions of interest were everolimus (NETs of pancreatic, gastrointestinal or lung origin), 177Lu-DOTATATE (NETs of pancreatic or GI origin) and sunitinib (pNETs).

Three trials, RADIANT-3, A6181111 and RADIANT-4, met the inclusion criteria for the clinical effectiveness systematic review.

The risk of bias within the trials was low and remained consistent between the three studies regarding selection, performance, detection, attrition and reporting bias.

9.2.1 Clinical effectiveness results: pancreatic NETs

Key results only are given here. A fuller summary of the results is given in the Scientific Summary in Section 4.5.

Two trials provided evidence for the effectiveness of everolimus (RADIANT-3) and sunitinib (A6181111) in the treatment of pNETs. Both interventions were compared to placebo. BSC was also given in both the intervention and placebo arms, for both trials.

Evidence consistently suggested a treatment effect in favour of both everolimus plus BSC and sunitinib plus BSC when compared to placebo plus BSC for the outcomes of interest.

Treatment with everolimus was associated with a 66% reduction in the risk of progression or death (HR 0.34 [95% CI 0.26, 0.44], by central review). Similarly, the treatment with sunitinib was associated with a 68% reduction in the risk of progression or death (HR 0.32 [95% CI 0.18, 0.55]).

Crossover from the placebo arm to the treatment arm was 73% in RADIANT-3 and 69% in A6181111. The crossover significantly compromised the OS results. The hazard ratio for unadjusted overall survival from RADIANT-3 was reported to be 0.94 (95% CI 0.73, 1.20; p=0.30) and for A6181111 0.73 (95% 0.50, 1.06; p=0.094). Using the RPSFT model the hazard ratio for overall survival from RADIANT-3 was reported to be 0.60 (95% CI 0.09, 3.95) and for A6181111 0.34 (95% 0.14, 1.28; p=0.094).

Overall, adverse events were more commonly reported following treatment with everolimus and sunitinib than with placebo.

We compared everolimus to sunitinib in a simple indirect treatment comparison (ITC) using the Bucher method.

9.2.2 Clinical effectiveness results: GI / lung NETs

One trial (RADIANT-4) provided evidence for the effectiveness of treatments in GI and lung NETs of everolimus plus BSC.

Evidence consistently suggested a treatment effect in favour of the use of everolimus plus BSC compared to placebo plus BSC for the outcomes of interest. Treatment with everolimus was associated with a 52% reduction in the risk of disease progression or death (HR 0.48 [95% CI 0.28, 0.54]). For OS, treatment with everolimus plus BSC was associated initially with 36% improvement for individuals with lung and GI NETs compared to placebo (HR 0.64 [0.40, 1.05]). However, follow-up data from the company submission reports a 27% improvement in OS following treatment with everolimus (HR 0.73 [95% CI 0.48, 1.11]) which is however unadjusted for cross-over.

Overall, adverse events were more commonly reported following treatment with everolimus compared to placebo.

9.2.3 Clinical effectiveness results: GI NETs

Following a data request from us to Novartis, results from RADIANT-4 were provided for people recruited with just GI NETs.

Median PFS for GI NETs from RADIANT-4 was 13.1 months for treatment with everolimus and 5.4 months for placebo (HR 0.56, [95% CI 0.37, 0.84]). OS estimated from a Kaplan-Meier at the 25th percentile was [redacted] in the everolimus arm compared to [redacted] in the placebo arm.

Overall, adverse events were more commonly reported following treatment than receiving placebo for people with GI NETs.

9.2.4 Clinical effectiveness results: Lung NETs

Following a data request from us to Novartis, results from RADIANT-4 were provided for people recruited with just lung NETs.

Everolimus was associated with a 50% reduction in the risk of disease progression compared to placebo. Survival was improved by 44% following everolimus treatment compared with placebo. Adverse events were more commonly reported following treatment with everolimus than placebo.

9.2.5 Strengths and limitations of clinical effectiveness review

9.2.5.1 Strengths of clinical effectiveness review

A strength of this report is that a systematic review of RCTs for everolimus, 177Lu-DOTATATE and everolimus in people with unresectable or metastatic neuroendocrine tumours with disease progression has been conducted to evaluate relative efficacy. In the absence of head-to-head RCTs, an ITC was conducted to assess relative efficacy of everolimus to sunitinib for pNETs and everolimus to 177Lu-DOTATATE for GI NETs for the outcomes PFS, OS, RRs, and AEs.

9.2.5.2 Limitations of clinical effectiveness review

- We were unable to compare 177Lu-DOTATATE with everolimus and sunitinib in individuals with pNETs, as the NETTER-1 RCT did not include patients with pNETs.
- We were unable to compare any intervention with chemotherapy or interferon-alpha, as there was no randomised evidence.
- In several instances, we were forced to rely on clinical results from the companies, rather than extracting the data from peer-reviewed publications.
- We had to make many strong assumption in the ITC comparing everolimus and 177Lu-DOTATATE in GI NETs. Primarily that octreotide 30mg is equivalent to placebo + BSC, therefore these analyses should be treated with caution.

9.3 Cost-effectiveness

9.3.1 Systematic review of cost-effectiveness studies

We reviewed the cost-effectiveness literature, according to the criteria set by the effectiveness review complemented with criteria for inclusion of costing studies relevant to the UK, economic evaluation of interventions, and modelling studies in this clinical area.

We identified three full economic evaluation studies, all relating to targeted treatments for advanced pNETs in patients with progressive disease in countries other than the UK (US, Mexico and Poland). Two of these studies compared sunitinib plus BSC with BSC alone, and one study compared everolimus with sunitinib. All of these studies were supported by the companies sponsoring the treatments in question.

One study conducted in the US and sponsored by Novartis found that everolimus was cost-effective compared to sunitinib, based on an ICER equivalent to £30,524 per QALY gained relative to sunitinib at 2015 UK prices. This study was based on an indirect comparison of relative outcomes against placebo for RADIANT-3 and A6181111. A strength of the study was its use of matching methods that acknowledge the heterogeneity in patient populations across trials (Signorovitch et al. 2009). A weakness was its omission of BSC alone as a comparator in its own right, especially since both RADIANT-3 and A61811111 included such treatment option as a control arm.

A second study in Mexico and sponsored by Pfizer found that sunitinib was cost-effective based on an ICER equivalent to £32,842 per QALY gained relative to BSC alone at 2015 UK prices. The study was based on the A6181111 trial data. A strength of the study was its assessment of quality of life using patient reported outcomes in the trial. A weakness of the study is its omission of active treatment comparator in the economic evaluation. Another limitation is the fact that the study did not adjust for the effect on OS of treatment cross-over from placebo to sunitinib in the open label phase of A6181111, which results in an underestimation of health benefits and likely overestimation of the ICER of initial treatment with sunitinib.

A third study was conducted in Poland and also sponsored by Pfizer found that the sunitinib was cost-effective based on an ICER equivalent to £33,866 per QALY gained relative to BSC alone at 2015 prices. The study was based on the A6181111 trial data. A strength of the study was its adjustment for the effect of cross-over from placebo to sunitinib in the open label phase of A6181111. A limitation is the lack of active treatment comparator in the

evaluation. Another limitation in the study is its use of outdated data from the trial and limited reporting of methods used to measure utility values. This was the only identified full report on a study conducted in this clinical area in Europe.

A fourth study, the only one identified for the UK, and also sponsored by Pfizer was reported as a conference poster. This summarised the evidence submitted to the SMC on sunitinib compared with placebo in Scotland, according to which sunitinib was cost-effective based on an ICER of £24,244 relative to BSC alone at 2015 prices. The strength of the study is its adjustment for the effect of treatment cross-over from placebo to sunitinib on OS. The main limitation was the lack of adequate methodological detail available from this report.

9.3.2 Critique of company model submissions

Of the three companies that submitted evidence to NICE, two included economic evaluations in their submission. Novartis evaluated treatments in pNETs and GI and lung NETs. AAA evaluated treatments in pNETs and GI NETs. Pfizer did not submit any economic evaluation.

The economic evaluation by Novartis used a partitioned survival model of sunitinib vs. everolimus in pNETs, based on an indirect comparison of placebo controlled outcomes in A6181111 and RADIANT-3. The company found that sunitinib dominated everolimus, since it had lower costs and more QALYs. This result was derived from assuming equal PFS and OS outcomes between treatments, which in turn was based on the confidence intervals found in their indirect treatment effectiveness comparison; i.e. PFS HR of 1.08 (95%CI 0.59-1.99) and RPFST-adjusted OS HR of 1.39 (95% CI 0.17-11.72). As a result, the only health benefit criterion on which treatments were compared was health related quality of life (state utility values) before disease progression (utility values after progression were assumed to be the same between treatments). However in the absence of utility data for everolimus from RADIANT-3, the company imputed treatment differences according the incidence of adverse events and values of their associated disutilities from a preference elicitation survey of the general public based on vignettes designed by clinical experts. The assumption of equal outcomes of PFS and OS and the poor quality of the utility data, which does not meet the NICE requirement that health related quality of life data be derived from actual patient outcomes, hampers the value of this evidence for NICE decisions. Furthermore, the data used from A6181111 by this Novartis evaluation appears to be outdated.

A second evaluation by Novartis assessed everolimus plus BSC relative to BSC alone in the nonfunctional GI and lung NETs population using data from RADIANT-4. Novartis found that everolimus had an ICER of £43,642 per QALY gained relative to BSC alone or and ICER of [redacted] when a PAS discount of [redacted] is applied to the list price. The main strength of this assessment was its use of data from RADIANT-4 to populate the model parameters. The main limitation is the immaturity of the OS data in the trial, the lack of treatment cross-over to targeted treatments, and the lack of adjustment for treatment switching before disease progression (13% and 14% in everolimus and placebo arms, respectively), which was dealt by censoring data for switching cases at the time of switch. Finally the study adopted a high frequency of oncologist visits.

AAA submitted an evaluation in pNETs of 177Lu-DOTATATE versus everolimus and sunitinib but the value of the resulting evidence is questionable since it was based on NETTER-1 data, which included only midgut patients. Further, it lacked BSC as a relevant comparator. The company also submitted an assessement of 177-Lu-DOTATATE vs everolimus in GI NET sub-population of somatostatin subtype receptor positive (SSTR+)

patients that produced a base case ICER of [redacted] This evidence is also of limited quality as it involved indirect comparison of NETTER-1 outcome data with data from RADIANT-4, which included non-midgut GI and lung NETs. This also omitted BSC alone, relevant comparator. There was also some limitation in that costs did not include resource use for disease monitoring, e.g. oncologist visits and the costs of 177Lu-DOTATATE administration were underestimated.

9.3.2.1 *Strengths and limitations of evidence form company model submissions*

The company submissions benefit from having individual patients from the few trials available to inform the current assessment. The main limitation with their submitted evidence is the lack of adequate comparators for the case of pNETs and the lack of adequate comparisons with 177Lu-DOTATATE in the NETTER-1 population of GI midgut NETs. In GI and lung NETs the main issue is the selective use of utility data that is available from RADIANT-4, in particular the use of the same utility values in stable disease and disease progression for the two treatment strategies, everolimus plus BSC and BSC alone, when treatment specific values are available.

The available evidence from the submitted models provides cost information that is not found in the publicly available sources. In particular details on the frequency of patients using medications or non-medical treatments in stable disease and disease progression in GI and lung NETs from RADIANT-4 are uniquely available from this source. On the other hand, the evidence on treatment regimens used and the frequency of contacts with health professionals is based on a validation of a previous expert survey, which provided limited data on resource use for these patients in progressive disease. Cost data on pNETs is limited, particularly for A6181111, which for example, did not collect information on treatments used after disease progression.

Given the limitations of the evidence from industry submission and the literature, the AG requested from Novartis individual patient data to replicate some of the indirect comparisons in pNETs presented as additional analysis using matching methods and individual patient data for RADIANT-4. The company declined to provide such data, noting that, for pNETs the additional analyses in question did not inform their economic evaluation. However, the company did agree to provide data on their adjustment of OS outcomes for cross-over in A6181111, which the AG could use to replicate the company's findings submitted to NICE. Pfizer also agreed to provide their individual patient data and code for their own cross-over adjusted OS results but only individual data from an outdated data cut-off were provided, and in the absence of the code and updated OS data the AG could not replicate the company's findings. We did manage however, to conduct exploratory analyses for the matched indirect comparison matching the A6181111 sample of individual patient data to the RADIANT-4 baseline characteristics. This highlighted the limitations associated with simple standard Bucher type comparisons underpinning the Novartis submission, originating from the small sample size of A6181111 and the consequent imbalance in key baseline characteristics between trial arms, i.e. performance status, time since diagnosis, and number of disease sites.

In the light of the above limitations of the evidence base, development of an independent de novo economic model was undertaken by the AG.

9.3.3 Independent economic assessment

The AG built a three health state partitioned survival model in two NETs patient populations. One was of patients with advanced pNETs, and evaluated sunitinib plus BSC, everolimus plus BSC and BSC alone over a lifetime horizon. These analyses were based on Bucher-type indirect comparisons of outcomes from the RADIANT-3 and A6181111 trials. The second evaluation compared everolimus plus BSC with BSC alone in patients with nonfunctional GI and lung NETs, based on the RADIANT-4 trial data. In addition, we conducted subgroup analysis of everolimus plus BSC, BSC alone, and 177Lu-DOTATATE plus octreotide 30 mg in the GI midgut population using PFS data for this subgroup from RADIANT-4 and indirectly comparative data on 177-Lu-DOTATATE from NETTER-1.

The models were populated with parameter estimates from time to event analyses of recreated individual patient OS and PFS survival data digitized from the latest OS and PFS K-M curves from published sources and industry submissions. Resource use model parameters were populated with data from the Novartis submission, with modifications to reflect our clinical experts' opinions of resource use intensity associated with disease monitoring. Prices other details adhered to the NICE reference case specifications.

In the pNETs population, we found that sunitinib had an ICER of £20,717 relative to BSC alone, at the current list price. The corresponding figure for everolimus was £45,493. This figures imply that sunitinib is superior to everolimus since it may achieve the same amount of benefit at lower cost to the NHS. In the GI and lung population everolimus had an ICER of £44,557 per QALY relative to BSC alone. In the GI midgut subgroup, the ICER for everolimus relative to BSC alone was £199,233 per QALY. It must be noted that results in the GI midgut subgroup are affected by a high level of uncertainty due to PFS-based imputation of OS outcomes in the model, since we did not have available actual OS data on this subgroup of RADIANT-4 patients.

In our additional indirect comparison in the GI midgut population (adjusting for background mortality), for everolimus we found an ICER of £78,330 per QALY relative to BSC alone at list price; the respective figure for 177Lu-DOTATATE plus octreotide 30 mg was £62,158 per QALY. Both these and results from a scenario analysis based on outcomes up to disease progression produced lower ICERs relative to BSC alone for 177Lu-DOTATATE than for everolimus.

Our scenario analyses in the pNETs patient population show that the cost-effectiveness of targeted treatments relies critically on adjusting for the effects of cross-over from placebo to sunitinib on OS. At list prices, the ICERs for initial treatment with sunitinib and everolimus relative to BSC were £37,217 and £136,455 per QALY, respectively, without adjustment for cross-over; that is, 1.5 and 3 times the base case values. Our sensitivity analyses suggest that there is a high degree of uncertainty arising from the immaturity of OS data in GI and lung and from NETTER-1 data. In particular, there is evidence that the cost-effectiveness of everolimus in GI and lung depends on benefits that arise in the latter years of life, and it is thus sensitive to the discount rate.

The above numbers appear to suggest that sunitinib's values are more robust than those of everolimus in both pNETs and GI and lung, which are more sensitive to adjustment for treatment cross-over and the effect of the time horizon and discounting. Also 177Lu-DOTATATE was found to produce the largest health benefits of all treatment strategies investigated for GI midgut NETs, 1.76 years and 0.91 more years of life than the BSC alone

and everolimus strategies. This figures are remarkable, especially since the fact that octreotide 60 was given in the control arm would suggest that the health benefits of 177Lu-DOTATATE relative to other treatments are underestimated in our analysis.

9.3.3.1 Strengths and limitations of the independent economic assessment

Our analysis on pNETs are based on the most up to date effectiveness data from the RCT informing the indirect comparison of the targeted treatments sunitinib and everolimus. However the indirect comparison underlying our economic analysis was of a simple Bucher type, unadjusted for any differences in the baseline characteristics across the two trials. Our cost-effectiveness results may thus be biased if indeed the patients in the two trials come from populations with different prognoses. Our comparison of the PFS curves of the BSC arms across trials suggest that the disease of the two patient groups have different propensities to progress and, given the theoretical and empirical evidence linking PFS and OS outcomes, associated death risks. In such case the results would remain valid if the proportional effect of targeted treatments over BSC alone is constant across levels of baseline disease and death risks.

[redacted].

Nevertheless, caveats are due with respect to the small size of the A6181111 trials which resulted in an imbalance in key baseline characteristics. A Bucher type analysis does not adequately deal with bias arising from such imbalance in baseline characteristics across arms within the same trial.

[redacted]

Our findings on 177LU-DOTATATE are based on limited quantity and quality of data available for the indirect comparison with everolimus. The immaturity of the available effectiveness data from NETTER-1, and the fact that the control arm is octreotide 60mg and therefore of a different nature to best supportive care in the RADIANT-4 midgut subgroup, suggests that these results need to be considered with caution. It is not clear in particular whether the midgut subgroup of RADIANT-4 represents a patient population with similar prognoses as that in NETTER-1. Nevertheless, our scenario and sensitivity analyses, adjusting for the extent of optimism in our long term survival projections suggest that based on the early evidence from NETTER-1, 177Lu-DOTATATE may produce at least as much value for money as everolimus does in the GI midgut NETs patient population.

Further research is required to investigate the robustness of the findings presented here. In particular, availability of individual patient data from RADIANT-3 would allow to test for such robustness and would be better suited for that task than the individual patient data on A6181111 made available to us by Pfizer. This is because RADIANT-3 is of a larger size and therefore less subject to instability due to small effective sample sizes remaining after matching, than A6181111.

The current study seeks to provide evidence to inform the optimal choice of initial treatment in advanced, progressive pNETs and GI and lung NETs. The nature of the available evidence limited our analysis and the type of questions that we could address. Our assessment therefore provides very limited information on questions such as choice of treatment sequences. Another important question on which the present analysis may shed some light is the question of whether targeted treatments may be given initially or after disease progression in patients who have progressive disease. Further availability of data on

subsequent treatments after disease progression may allow more precise answers than those allowed by this assessment.

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Appendix 1. Literature search strategies

Literature searching was undertaken in May 2016 and our bibliographic literature searching was updated in November 2016.

Searching of bibliographic and on-going trials databases

The search strategies below were run on May 19th 2016 and re-run on September 29th 2016.

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: OVID

Data parameters: 1946 to Present

Date searched: Thursday May 19th 2016

Searcher: CC

Hits: 1334

#	Searches	Results
1	exp Neuroendocrine Tumors/	146579
2	Carcinoma, Neuroendocrine/	2939
3	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	46552
4	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	52214
5	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	70454
6	1 or 2 or 3 or 4 or 5	292693
7	(everolimus or afinitor or affinitor or VOTUBIA or Zortress or CERTICAN or xience or RAD001 or "RAD 001" or SDZ RAD or SDZ-RAD or SDZRAD or 159351-69-6).ti,ab,kw. or Everolimus/	4765
8	(Lanreotide or Somatuline or ITM-014 or 108736-35-2).ti,ab,kw.	701
9	(Lutetium-177 DOTATATE or Lutetium or DOTATATE or lutecium or Lutetium 177 or Lutetium-177 or Lutetium177 or 177LU or 177 LU or Lu177 or LU 177 or Lutathera or 14265-75-9).ti,ab,kw.	969
10	(Sunitinib or sutent or SU011248 or "SU 011248" or SU11248 or SU 11248 or suo11248 or su010398 or "su 010398" or su010398 or pha 2909040ad or pha2909040ad or 557795-19-4).ti,ab,kw.	4011

11	7 or 8 or 9 or 10	9910
12	6 and 11	1334

Database: EMBASE

Host: OVID

Data parameters: 1946 to Present

Date searched: Thursday May 19th 2016

Searcher: CC

Hits: 4863

#	Searches	Results
1	exp neuroendocrine tumor/	60694
2	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	62025
3	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	68495
4	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	109421
5	1 or 2 or 3 or 4	273156
6	(everolimus or afinitor or affinitor or VOTUBIA or Zortress or CERTICAN or xience or RAD001 or "RAD 001" or SDZ RAD or SDZ-RAD or SDZRAD or 159351-69-6).ti,ab,kw.	10357
7	everolimus/	18280
8	(Lanreotide or Somatuline or ITM-014 or 108736-35-2).ti,ab,kw.	1072
9	angiopeptin/	2770
10	(Lutetium-177 DOTATATE or Lutetium or DOTATATE or lutecium or Lutetium 177 or Lutetium-177 or Lutetium177 or 177LU or 177 LU or Lu177 or LU 177 or Lutathera or 14265-75-9).ti,ab,kw.	2025
11	lutetium 177/	1859

12	(Sunitinib or sutent or SU011248 or "SU 011248" or SU11248 or SU 11248 or suo11248 or su010398 or "su 010398" or su010398 or pha 2909040ad or pha2909040ad or 557795-19-4).ti,ab,kw.	7888
13	sunitinib/	16334
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	37159
15	5 and 14	4863

Database: The Cochrane Library

Host: Wiley Host

- Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015
- Cochrane Central Register of Controlled Trials : Issue 4 of 12, April 2016
- Health Technology Assessment Database : Issue 2 of 4, April 2016
- NHS Economic Evaluation Database : Issue 2 of 4, April 2015

Date searched: Thursday May 19th 2016

Searcher: CC

Hits: 247

ID	Search	Hits
#1	MeSH descriptor: [Neuroendocrine Tumors] explode all trees	1523
#2	MeSH descriptor: [Carcinoma, Neuroendocrine] this term only	10
#3	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs)	2515
#4	((neuro or endocrine or carcinoid* or carcinoma*) near/5 (tumour* or tumor*))	1608
#5	(((low* or intermediate) near/3 grade) or ("grade 1" or "grade 2"))	6921
#6	#1 or #2 or #3 or #4 or #5	12098
#7	(everolimus or afinitor or affinitor or VOTUBIA or Zortress or CERTICAN or xience or RAD001 or "RAD 001" or SDZ RAD or SDZ-RAD or SDZRAD or 159351-69-6)	1484
#8	MeSH descriptor: [Everolimus] this term only	390
#9	(Lanreotide or Somatuline or ITM-014 or 108736-35-2)	137
#10	(Lutetium-177 DOTATATE or Lutetium or DOTATATE or lutecium or Lutetium 177 or Lutetium-177 or Lutetium177 or 177LU or 177 LU or Lu177 or LU 177 or Lutathera or 14265-75-9)	105

#11 (Sunitinib or sutent or SU011248 or "SU 011248" or SU11248 or SU 11248 or suo11248 or su010398 or "su 010398" or su010398 or pha 2909040ad or pha2909040ad or 557795-19-4) 436

#12 #7 or #8 or #9 or #10 or #11 2097

#13 #6 and #12 251

Database: Web of Science

Host: Thomson Reuters

- Science Citation Index Expanded (SCI-EXPANDED) --1900-present
- Social Sciences Citation Index (SSCI) --1956-present
- Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
- Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present

Date searched: Thursday May 19th 2016

Searcher: CC

Hits: 1875

# 10	1,875	#9 AND #4 Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets. ☐	Select to delete this set. ☐
# 9	16,520	#8 OR #7 OR #6 OR #5 Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets. ☐	Select to delete this set. ☐
# 8	6,271	**TOPIC:** (((Sunitinib or sutent or SU011248 or "SU 011248" or SU11248 or SU 11248 or suo11248 or su010398 or "su 010398" or su010398 or pha 2909040ad or pha2909040ad or 557795-19-4))) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets. ☐	Select to delete this set. ☐

# 7	2,331	**TOPIC:** (((Lutetium-177 DOTATATE or Lutetium or DOTATATE or lutecium or Lutetium 177 or Lutetium-177 or Lutetium177 or 177LU or 177 LU or Lu177 or LU 177 or Lutathera or 14265-75-9))) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets.	Select to delete this set.
# 6	1,080	**TOPIC:** (((Lanreotide or Somatuline or ITM-014 or 108736-35-2))) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets.	Select to delete this set.
# 5	7,488	**TOPIC:** (((everolimus or afinitor or affinitor or VOTUBIA or Zortress or CERTICAN or xience or RAD001 or "RAD 001" or SDZ RAD or SDZ-RAD or SDZRAD or 159351-69-6))) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets.	Select to delete this set.
# 4	405,576	#3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets.	Select to delete this set.
# 3	76,335	**TOPIC:** (((((low* or intermediate) near/2 grade) or ("grade 1" or "grade 2")))) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets.	Select to delete this set.
# 2	41,490	**TOPIC:** ((((neuro or endocrine or carcinoid* or carcinoma*) near/2 (tumour* or tumor*)))) Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years	Edit	Select to combine sets.	Select to delete this set.

#		
1	296,189	**TOPIC:** (((Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs)))
		Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years

Trials Register: Current Controlled Trials

Date Searched: Wednesday May 25th 2016

Searched via: http://www.isrctn.com/

Total studies identified: 24

Duplicates removed: 0

Unique studies to screen: 24

Field searched	Search terms	N identified	N for screening
Text Search	everolimus	12	12
Text Search	afinitor	0	0
Text Search	affinitor	1	0
Text Search	VOTUBIA	9	1
Text Search	Zortress	0	0
Text Search	CERTICAN	0	0
Text Search	xience	3	0
Text Search	RAD001	3	0
Text Search	"RAD 001"	0	0
Text Search	SDZ RAD	0	0
Text Search	SDZRAD	0	0
Text Search	159351-69-6	0	0

Field searched	Search terms	N identified	N for screening
Text Search	Lanreotide	1	1
Text Search	Somatuline	0	0
Text Search	ITM-014	0	0
Text Search	108736-35-2	0	0

Field searched	Search terms	N identified	N for screening
Text Search	Lutetium-177	0	0
Text Search	Lutetium	0	0
Text Search	Lutathera	0	0

Field searched	Search terms	N identified	N for screening
Text Search	Sunitinib	9	9
Text Search	Sutent	4	1
Text Search	SU 011248	0	0
Text Search	557795-19-4	0	0

Trials Register: Clinical Trials.Gov

Date Searched: Thursday May 26th 2016

Searched via: https://clinicaltrials.gov/ct2/search/advanced

Total studies identified: 173

Duplicates removed: 18

Unique studies to screen: 155

Field searched	Search terms	N identified	N for screening
Text Search	Conditions: Neuroendocrine Interventions: Everolimus	85	85
Text Search	Conditions: NETs Intervention: Everolimus	12	1
Text Search	Conditions: Neuroendocrine Intervention: afinitor	85	7
Text Search	Conditions: NETs Intervention: afinitor	12	0
Text Search	Population: Neuroendocrine Intervention: afinitor	0	0
Text Search	Conditions: NETs Intervention: afinitor	0	0
	VOTUBIA		
	Conditions: Neuroendocrine Intervention: Zortress	85	3
Text Search	Conditions: NETs	12	0

	Intervention: Zortress		
Text Search	Conditions: Neuroendocrine Intervention: CERTICAN	85	0
Text Search	Conditions: NETs Intervention: CERTICAN	12	0
Text Search	Conditions: Neuroendocrine Intervention: xience	0	0
Text Search	Conditions: NETs Intervention: xience	0	0
Text Search	Conditions: Neuroendocrine Intervention: RAD001	85	0
Text Search	Conditions: NETs Intervention: RAD001	12	0
Text Search	"RAD 001"	3	0
Text Search	SDZ RAD	0	0
Text Search	SDZRAD	0	0
Text Search	159351-69-6	1	0

Field searched	Search terms	N identified	N for screening
Text Search	Conditions: Neuroendocrine Intervention: Lanreotide	17	17
	Conditions: NETs Intervention: Lanreotide	6	0
Text Search	Conditions: Neuroendocrine Intervention: Somatuline	17	0
	Conditions: Neuroendocrine Intervention: Somatuline	6	0
Text Search	ITM-014	0	0
Text Search	108736-35-2	0	0

Field searched	Search terms	N identified	N for screening
Text Search	Lutetium	21	21
Text Search	Lutathera	1	1

Field searched	Search terms	N identified	N for screening
Text Search	Conditions: Neuroendocrine Intervention: Sunitinib	33	33
Text Search	Conditions: NETs Intervention: Sunitinib	33	0
Text Search	Conditions: Neuroendocrine Intervention: Sutent	33	1
Text Search	Conditions: NETs Intervention: Sutent	0	0
Text Search	Conditions: Neuroendocrine Intervention: SU 011248	33	1
Text Search	Conditions: Neuroendocrine Intervention: SU 011248	0	0
Text Search	557795-19-4	0	0

Web searching

Web-site: FDA Web-site

Searched via URL: http://www.fda.gov/Drugs/

Date Searched: Monday 6th July 2016

search term	hits	included
Everolimus	87	7
Afinitor	40	4
lanreotide	31	1
Lutetium-177	0	0
Lutetium	3	0
Dotatate	4	0
Sunitinib	61	3

Web-site: Drugs@FDA

Searched via URL: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Date Searched: Monday 6th July 2016

search term	hits	included
Everolimus/ Zortess	2	2

search term	hits	included
lanreotide	0	0

search term	hits	included
Lutetium-177	0	0
Lutetium	6	1

search term	hits	included
Sunitinib	2	2

European Medicines Agency

Searched via:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp

Date Searched: Monday 6th July 2016

search term	hits	included
Everolimus	2	2

search term	hits	included
lanreotide	0	0

search term	hits	included
Lutetium-177	0	0
Lutetium	6	1

search term	hits	included
Sunitinib	2	2

Appendix 2. Additional literature search strategies

Search one: RCTs of Octreotide

The first search attempted to identify studies reporting randomised controlled trials (RCTs) of Octreotide.

Database(s): **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results	Annotations
1	Octreotide/	6852	
2	(Octreotide or Octreotida or Octreotidum or Octrotide or Sandostatin or sandostatina or sandostatine or longastatin or longastatina or OncoLar or samilstin or sandstatin or "SMS 201-995" or "sms201 995" or sms201995 or "sms 201995" or "sms 995" or "sdz 201995" or sdz201995 or "sms 995aaa" or "1607842-55-6" or "UNII-H92K6Q47Q9" or "H92K6Q47Q9").ti,ab,kw.	7788	
3	1 or 2	9404	
4	exp Neuroendocrine Tumors/	149135	
5	Carcinoma, Neuroendocrine/	3058	
6	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	47802	
7	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	53142	
8	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	72758	
9	4 or 5 or 6 or 7 or 8	299124	
10	3 and 9	2558	
11	randomized controlled trial.pt.	428443	
12	10 and 11	36	

EMBASE

#	Searches	Results	Annotations
1	exp neuroendocrine tumor/	62334	
2	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	63805	
3	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	69708	
4	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	112582	
5	1 or 2 or 3 or 4	279923	
6	octreotide/	18643	
7	(Octreotide or Octreotida or Octreotidum or Octrotide or Sandostatin or sandostatina or sandostatine or longastatin or longastatina or OncoLar or samilstin or sandstatin or "SMS 201-995" or "sms201 995" or sms201995 or "sms 201995" or "sms 995" or "sdz 201995" or sdz201995 or "sms 995aaa" or "1607842-55-6" or "UNII-H92K6Q47Q9" or "H92K6Q47Q9").ti,ab,kw.	10946	
8	6 or 7	20348	
9	5 and 8	6168	
10	randomized controlled trial/	416370	
11	9 and 10	72	

COCHRANE CENTRAL

Search Name:

Date Run: 16/08/16 16:04:21.525

Description:

ID Search Hits

#1 MeSH descriptor: [Octreotide] this term only 573

#2 (Octreotide or Octreotida or Octreotidum or Octrotide or Sandostatin or sandostatina or sandostatine or longastatin or longastatina or OncoLar or samilstin or sandstatin or "SMS 201-995" or "sms201 995" or sms201995 or "sms 201995" or "sms 995" or "sdz 201995" or

sdz201995 or "sms 995aaa" or "1607842-55-6" or "UNII-H92K6Q47Q9" or "H92K6Q47Q9"):ti,ab,kw 1067

#3 #1 or #2 1067

#4 MeSH descriptor: [Neuroendocrine Tumors] explode all trees 1532

#5 MeSH descriptor: [Carcinoma, Neuroendocrine] this term only 10

#6 (Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs):ti,ab,kw 1740

#7 ((neuro or endocrine or carcinoid$1 or carcinoma$1) near/5 (tumour$ or tumor$)):ti,ab,kw 45

#8 (((low$ or intermediate) near/3 grade) or ("grade 1" or "grade 2")):ti,ab,kw 5575

#9 #4 or #5 or #6 or #7 or #8 8701

#10 #3 and #9 111

#11 randomized controlled trial:pt 398696

#12 #10 and #11 28

Search two: searches for dosing studies

The second search attempted to identify dosing or dose-ranging studies.

Database(s): **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results	Annotations
1	Octreotide/	6855	
2	(Octreotide or Octreotida or Octreotidum or Octrotide or Sandostatin or sandostatina or sandostatine or longastatin or longastatina or Oncolar or samilstin or sandstatin or "SMS 201-995" or "sms201 995" or sms201995 or "sms 201995" or "sms 995" or "sdz 201995" or sdz201995 or "sms 995aaa" or "1607842-55-6" or "UNII-H92K6Q47Q9" or "H92K6Q47Q9").ti,ab,kw.	7789	
3	1 or 2	9407	
4	(dos* adj5 stud*).ti,ab,kw.	72876	

5	3 and 4	112

Database(s): **Embase** 1974 to 2016 August 17

Search Strategy:

#	Searches	Results	Annotations
1	Octreotide/	18635	
2	(Octreotide or Octreotida or Octreotidum or Octrotide or Sandostatin or sandostatina or sandostatine or longastatin or longastatina or Oncolar or samilstin or sandstatin or "SMS 201-995" or "sms201 995" or sms201995 or "sms 201995" or "sms 995" or "sdz 201995" or sdz201995 or "sms 995aaa" or "1607842-55-6" or "UNII-H92K6Q47Q9" or "H92K6Q47Q9").ti,ab,kw.	10948	
3	1 or 2	20343	
4	(dos* adj5 stud*).ti,ab,kw.	103372	
5	3 and 4	171	

Search three: Chemotherapy

The third search attempted to identify RCTs of chemotherapy use in NETs.

(All searched 05/09/2016)

Search Name: Cochrane Library

Date Run: 05/09/16 11:10:19.257

Description:

ID Search Hits

#1 MeSH descriptor: [Neuroendocrine Tumors] explode all trees 1553

#2 MeSH descriptor: [Carcinoma, Neuroendocrine] this term only 10

#3 (Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETS or NF-NETS or NFNETs) 2590

#4 ((neuro or endocrine or carcinoid* or carcinoma*) near/5 (tumour* or tumor*)) 1654

#5 #1 or #2 or #3 or #4 5557

#6 (chemotherapy or chemo therap*) 45476

#7 #5 and #6 1132 (Trials 802)

Database(s): **Embase** 1974 to 2016 September 02

Search Strategy:

#	Searches	Results	Annotations
1	exp neuroendocrine tumor/	62582	
2	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	64123	
3	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	69943	
4	1 or 2 or 3	172631	
5	chemotherapy/	119461	
6	(chemotherapy or chemo therap$).ti,ab,kw.	443631	
7	5 or 6	457535	
8	randomized controlled trial/	418791	
9	4 and 7 and 8	106	

Database(s): **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results	Annotations
1	exp Neuroendocrine Tumors/	149452	
2	Carcinoma, Neuroendocrine/	3074	
3	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	47967	
4	exp Neuroendocrine Tumors/	149452	
5	Carcinoma, Neuroendocrine/	3074	
6	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	47967	
7	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	53239	
8	4 or 5 or 6 or 7	229980	

9	(chemotherapy or chemo therap$).ti,ab,kw.	291430
10	randomized controlled trial.pt.	429552
11	8 and 9 and 10	251

Appendix 3. Included Citations

Trial	Reference	Type
RADIANT-3	Bohas CL, Yao JC, Hobday TJ, Van Cutsem E, Wolin EM, Panneerselvam A, et al. Efficacy and safety of everolimus in patients with advanced low-or intermediate-grade pancreatic neuroendocrine tumors previously treated with chemotherapy: RADIANT-3 subgroup analysis. Journal of Clinical Oncology Conference. 2013;31.	Abstract
	Chambers J, Reed N, Mansoorc W, Ross P, Grossman A. Phase-3 randomized trial of everolimus (RAD001) vs. placebo in advanced pancreatic NET (RADIANT-3). Regulatory Peptides. 2010;164 (1):6-7.	Abstract
	Hobday T, Pommier R, Cutsem EV, Panneerselvam A, Saletan S, Winkler RE, et al. Analysis of progression-free survival (PFS) by prior chemotherapy use and updated safety in radiant-3: A randomized, double-blind, placebo-controlled, multicenter, phase III trial of everolimus in patients with advanced low-or intermediate-grade pancreatic neuroendocrine tumors (PNET). Pancreas. 2012;41 (2):345.	Abstract
	Hobday TJ, Capdevila J, Saletan S, Panneerselvam A, Pommier RF. Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Multivariate analysis of progression-free survival from the RADIANT-3 trial. Journal of clinical oncology [Internet]. 2011; 29(15 suppl. 1).	Abstract
	Horsch D, Lombard-Bohas C, Lincy J, Saletan S, Kocha W. A randomized, double-blind, placebo-controlled, multicenter phase iii trial of everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET) (RADIANT-3): Updated safety results. Endocrine reviews [Internet]. 2011; 32(3 Meeting Abstracts).	Abstract
	Ito T. Current status of mTOR inhibitor as a new therapeutic strategy for advanced pancreatic endocrine tumors. Annals of oncology [Internet]. 2011; 22:[ix30 p.].	Abstract
	Ito T, Okusaka T, Ikeda M, Igarashi H, Morizane C, Nakachi K, et al. Everolimus for Advanced Pancreatic Neuroendocrine Tumours: A Subgroup Analysis Evaluating Japanese Patients in the RADIANT-3 Trial. Japanese Journal of Clinical Oncology. 2012;42:903-11.	Full Text
	Ito T, Okusaka T, Ikeda M, Tajima T, Kasuga A, Fujita Y, et al. Everolimus versus placebo in Japanese patients with advanced pancreatic neuroendocrine tumors (pNET): Japanese subgroup analysis of RADIANT-3. Journal of clinical oncology [Internet]. 2011; 29(4 suppl. 1).	Abstract
	Lombard-Bohas C, Cutsem E, Capdevila J, Vries EGE, Tomassetti P, Lincy J, et al. Updated survival and safety data from radiant-3 - A randomized, double-blind, placebo-controlled, multicenter, phase III trial of everolimus in patients with advanced pancreatic neuroendocrine tumours (pNET). European journal of cancer [Internet]. 2011; 47:[S459 p.].	Abstract
	Lombard-Bohas C, Yao JC, Hobday T, Van Cutsem E, Wolin EM, Panneerselvam A, et al. Impact of prior chemotherapy use on the efficacy of everolimus in patients with advanced pancreatic neuroendocrine tumors: a subgroup analysis of the phase III RADIANT-3 trial. Pancreas. 2015;44:181-9.	Full Text
	Okusaka T, Ito T, Ikeda M, Igarashi H, Morizane C, Nakachi K, et al. Phase III trial of everolimus in advanced pancreatic neuroendocrine tumors (RADIANT-3): Overall population and Japanese subgroup analysis. Annals of oncology [Internet]. 2012; 23:[xi15 p.]	Abstract
	Okusaka T, Ito T, Ikeda M, Tajima T, Kasuga A, Fujita Y, et al. Efficacy and safety of everolimus in Japanese patients with advanced pancreatic neuroendocrine tumors (pNET): Japanese subgroup analysis of radiant-3. Neuroendocrinology. 2011;94:37-8.	Abstract
	Pavel M, Unger N, Borbath I, Ricci S, Hwang TL, Brechenmacher T, et al. Quality-of-life (QoL) assessments in patients (pts) with pancreatic neuroendocrine tumors (pNET) enrolled in the open-label, phase 3b, multicenter, expanded access study of everolimus in pts with advanced NET. European Journal of Cancer. 2013;49:S619.	Abstract
	Pavel ME, Lombard-Bohas C, Cutsem E, Lam DH, Kunz T, Brandt U, et al. Everolimus in patients with advanced, progressive pancreatic neuroendocrine tumors: Overall survival results from the phase III RADIANT-3 study after adjusting for crossover bias. Journal of clinical oncology [Internet]. 2015; 33(15 suppl. 1).	Abstract
	Pommier R, Yao J, Hobday T, Van Cutsemv E, Wolin E, Panneerselvam A, et al. Efficacy and Safety of Everolimus in Patients with Advanced Low- or Intermediate-grade Pancreatic Neuroendocrine Tumors Previously Treated with Chemotherapy: A Subgroup Analysis of the RADIANT-3 Trial. Pancreas. 2014;43:501-.	Abstract
	Pommier RF, Wolin EM, Panneerselvam A, Saletan S, Winkler RE, Van Cutsem E. Impact of prior chemotherapy on progression-free survival in patients (pts) with advanced pancreatic neuroendocrine tumors (pNET): Results from the RADIANT-3 trial. Journal of Clinical Oncology Conference: ASCO Annual Meeting. 2011;29.	Abstract
	Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Cutsem E, Sachs C, et al. Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Updated results of a randomized, double-blind, placebo-controlled, multicenter phase III trial (RADIANT-3). Journal of clinical oncology [Internet]. 2011; 29(4 suppl. 1).	Abstract
	Shah MH, Oberg K, Ito T, Lombard-Bohas C, Wolin EM, Van Cutsem E, et al. Treatment of pancreatic neuroendocrine tumors (pNET) with everolimus: Improved progression-free survival compared with placebo (RADIANT-3). Pancreas. 2011;40 (2):331-2.	Abstract
	Strosberg JR, Lincy J, Winkler RE, Wolin EM. Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Updated results of a randomized, double-blind, placebo-controlled, multicenter, phase III trial (RADIANT-3). Journal of clinical oncology [Internet]. 2011; 29(15 suppl. 1).	Abstract
	Wolin E, Pommier R, Lincy J, Winkler R, Yao J. Updated results from the randomized, double-blind, placebo-controlled, multicenter, phase III trial (RADIANT-3) of everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET). American Journal of Gastroenterology. 2011;106:S59.	Abstract

Trial	Reference	Type
	Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Lam D, Kunz T, et al. Everolimus (EVE) for advanced, progressive pancreatic neuroendocrine tumors (PNET): Final overall survival (OS) from a randomized, double-blind, placebo (PBO)-controlled, multicenter phase 3 radiant-3 study. Neuroendocrinology. 2015;102 (1-2):134.	Abstract
	Yao JC, Pavel M, Lombard-Bohas C, van Cutsem E, Lam D, Kunz T, et al. Everolimus (EVE) for the treatment of advanced pancreatic neuroendocrine tumors (pNET): final overall survival (OS) results of a randomized, double-blind, placebo (PBO)-controlled, multicenter phase iii trial (RADIANT-3). Annals of Oncology. 2014;25.	Abstract
	Yao JC, Pavel M, Lombard-Bohas C, van Cutsem E, Lam D, Kunz T, et al. Everolimus (EVE) for the Treatment of Advanced Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results of a Randomized, Double-Blind, Placebo (PBO)-Controlled, Multicenter Phase 3 Trial (RADIANT-3). Pancreas. 2015;44:362-.	Abstract
	Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. The New England Journal of Medicine [Internet]. 2011; 364(6):[514-23 pp.].	Full Text
	Yao JC, Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Van Cutsem E, et al. A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus in patients with advanced pancreatic neuroendocrine tumors (PNET) (radiant-3). Annals of Oncology. 2010;21:viii4-viii5.	Abstract
	Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. Journal of Clinical Oncology. 2016. 12 epub.	
RADIANT-4	Singh S, Carnaghi C, Buzzoni R, Pommier RF, Raderer M, Tomasek J, et al. Efficacy and safety of everolimus in advanced, progressive, nonfunctional neuroendocrine tumors (NET) of the gastrointestinal (GI) tract and unknown primary: A subgroup analysis of the phase III RADIANT-4 trial. Journal of Clinical Oncology Conference. 2016;34.	Abstract
	Yao J, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus in advanced nonfunctional neuroendocrine tumors (NET) of lung or gastrointestinal (GI) origin: Efficacy and safety results from the placebo-controlled, double-blind, multicenter, Phase 3 RADIANT-4 study. European Journal of Cancer (varpagings) [Internet]. 2015; 51:[S709-s10 pp.].	Abstract
	Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Safety and Efficacy of Everolimus in Advanced Nonfunctional Neuroendocrine Tumors (NET) of Lung or Gastrointestinal (GI) Origin: Findings of the Randomized, Placebo-Controlled, Double-blind, Multicenter, Phase 3 RADIANT-4 Study. Pancreas. 2016;45:487-.	Abstract
	Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968-77.	Full Text
	Yao JC, Singh S, Wolin E, Voi M, Pacaud LB, Lincy J, et al. RADIANT-4: Efficacy and safety of everolimus in advanced, nonfunctional neuroendocrine tumors (NET) of the lung or gastrointestinal (GI) tract. Annals of Oncology. 2015;26:ix40.	Abstract
	Pavel ME, Strosberg JR, Bubuteishvili-Pacaud L, Degtyarev E, Neary M, Hunger M, et al. Health-related quality of life (HRQoL) in patients with advanced, nonfunctional, well-differentiated gastrointestinal (GI) or lung neuroendocrine tumors (NET) in the phase 3 RADIANT-4 trial. Journal of Clinical Oncology. 2016;34(15):e15657.	Abstract
	Singh S, Pavel ME, Strosberg JR, Bubuteishvili-Pacaud L, Degtyarev E, Neary M, et al. Association of disease progression, health-related quality of life (HRQoL), and utility in patients (pts) with advanced, nonfunctional, well-differentiated gastrointestinal (GI) or lung neuroendocrine tumors (NET) in the phase 3 RADIANT-4 trial. Journal of Clinical Oncology. Conference. 2016: 34	Abstract
	Anonymous, FROM ECC 2015-neuroendocrine cancer: RADIANT-4 trial-NET improvement with everolimus? Nature Reviews Clinical Oncology. 2015. 12:684	Abstract
	Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin EM, et al. Everolimus (EVE) in advanced, nonfunctional, welldifferentiated neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin: Second interim overall survival (OS) results from the RADIANT-4 study. Journal of Clinical Oncology. Conference. 2016. 34:	Abstract
A6181111	Faivre S, Niccoli P, Raoul JL, Bang Y, Borbath I, Valle JW, et al. Updated overall survival (OS) analysis from a phase III study of sunitinib vs placebo in patients (PTS) with advanced, unresectable pancreatic neuroendocrine tumor (NET). Annals of Oncology. 2012;23:ix376.	Abstract
	Hammel P, Castellano D, Van Cutsem E, Niccoli P, Faivre S, Patyna S, et al. Evaluation of progression-free survival by blinded independent central review in patients with progressive, well-differentiated pancreatic neuroendocrine tumors treated with sunitinib or placebo. Pancreas. 2011;40 (2):327.	Abstract
	Ishak J, Valle J, Van Cutsem E, Lombard-Bohas C, Ruszniewski P, Sandin R, et al. Overall survival (OS) analysis of sunitinib (SU) after adjustment for crossover (CO) in patients with pancreatic neuroendocrine tumors (NET). Neuroendocrinology. 2011;94:27-8.	Abstract
	Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, Valle JW, et al. Updated safety and efficacy results of the phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of pancreatic neuroendocrine tumors (NET). Journal of Clinical Oncology Conference. 2010;28.	Abstract
	Raoul JL, Niccoli P, Bang YJ, Borbath I, Lombard-Bohas C, Metrakos P, et al. Sunitinib (SU) vs placebo for treatment of progressive, well-differentiated pancreatic islet cell tumours: Results of a phase III, randomised, double-blind trial. European Journal of Cancer, Supplement. 2009;7 (2-3):361.	Abstract
	Raymond E. Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors (vol 364, pg 501, 2011). New England Journal of Medicine. 2011;364:1082-.	Full Text
	Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.[Erratum appears in N Engl J Med. 2011 Mar 17;364(11):1082]. New England Journal of Medicine. 2011;364:501-13.	Erratum to Full Text

Trial	Reference	Type
	Raymond E, Harmon C, Niccoli P, Metrakos P, Borbath I, Bang Y, et al. Impact of baseline Ki-67 index and other baseline characteristics on outcome in a study of sunitinib (SU) for the treatment of advanced, progressive pancreatic neuroendocrine tumor (NET). Neuroendocrinology. 2011;94:41.	Abstract
	Raymond E, Niccoli P, Castellano D, Valle JW, Hammel P, Raoul JL, et al. Sunitinib (SU) in patients with advanced, progressive pancreatic neuroendocrine tumors (pNET): Final overall survival (OS) results from a phase III randomized study including adjustment for crossover. Journal of Clinical Oncology Conference. 2016;34.	Abstract
	Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, et al. Evidence of activity and clinical benefit with sunitinib in patients with pancreatic Neuroendocrine Tumors (NET). Annals of Oncology. 2010;21:vi13.	Abstract
	Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, et al. Updated overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) of sunitinib (SU) versus placebo (PBO) for patients (Pts) with advance unresectable pancreatic neuroendocrine tumors (NET). Journal of Clinical Oncology Conference: ASCO Annual Meeting. 2011;29.	Abstract
	Raymond E, Niccoli P, Raoul J, Bang Y, Borbath I, Lombard-Bohas C, et al. Cox proportional hazard analysis of sunitinib (SU) efficacy across subgroups of patients (pts) with progressive pancreatic neuroendocrine tumors (NET). Journal of Clinical Oncology Conference. 2010;28.	Abstract
	Raymond E, Seitz JF, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, et al. Sunitinib for the treatment of advanced, progressive pancreatic neuroendocrine tumors. Neuroendocrinology. 2010;92 (1):54-5.	Abstract
	Valle J, Faivre S, Raoul J, Bang Y, Patyna S, Lu DR, et al. Phase III trial of sunitinib (SU) versus placebo (PBO) for treatment of pancreatic neuroendocrine tumors (net): Impact of somatostatin analogue (SSA) treatment on progression-free survival (PFS). Annals of Oncology. 2010;21:viii264.	Abstract
	Valle J, Niccoli P, Raoul JL, Bang YJ, Borbath I, Cutsem E, et al. Updated overall survival data from a phase III study of sunitinib vs. placebo in patients with advanced, unresectable pancreatic neuroendocrine tumour (NET). European journal of cancer [Internet]. 2011; 47:[S462 p.].	Abstract
	Van Cutsem E, Dahan L, Patyna S, Klademenos D, Lu DR, Chao R, et al. Evaluation of progression-free survival (PFS) by blinded independent central review (BICR) in patients (PTS) with progressive, welldifferentiated pancreatic neuroendocrine tumours (NET) treated with sunitinib (SU) or placebo. Annals of Oncology. 2010;21:viii235.	Abstract
	Van Cutsem E, Seitz JF, Raoul J, Valle JW, Faivre SJ, Patyna S, et al. Evaluation of progression-free survival by blinded independent central review in patients with progressive, well-differentiated pancreatic neuroendocrine tumors treated with sunitinib or placebo. Journal of Clinical Oncology Conference. 2011;29.	Abstract
	Vinik A, Bang Y, Raoul J, Valle JW, Metrakos P, Horsch D, et al. Patient-reported outcomes (PROs) in patients (pts) with pancreatic neuroendocrine tumors (NET) receiving sunitinib (SU) in a phase III trial. Journal of Clinical Oncology Conference. 2010;28.	Abstract
	Vinik A, Bang YJ, Raoul JL, Valle J, Metrakos P, Horsch D, et al. Sunitinib for treatment of pancreatic neuroendocrine tumors: Patient-reported outcomes and efficacy across patient subgroups in a phase III trial. Pancreas. 2011;40 (2):334-5.	Abstract
	Vinik A, Cutsem EV, Niccoli P, Raoul JL, Bang YJ, Borbath I, et al. Progression-free survival (PFS) by blinded independent central review (BICR) and updated overall survival (OS) of sunitinib versus placebo for patients with progressive, unresectable, well differentiated pancreatic neuroendocrine tumor (NET). Pancreas [Internet]. 2012; 41(2):[350 p.].	Abstract
	Vinik A, Van Cutsem E, Niccoli P, Raoul JL, Bang YJ, Borbath I, et al. Updated results from a phase III trial of sunitinib versus placebo in patients with progressive, unresectable, well-differentiated pancreatic neuroendocrine tumor (NET). Journal of Clinical Oncology Conference. 2012;30.	Abstract
NETTER-1	Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. 177-Lu-Dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: Results of the phase III NETTER-1 trial. European Journal of Cancer. 2015;51:S710.	Abstract
	Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. 177-Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumors: Results of the Phase III NETTER-1 Trial. Pancreas. 2016;45:483-.	Abstract
	Strosberg JR, Wolin EM, Chasen B, Kulke MH, Bushnell DL, Caplin ME, et al. NETTER-1 phase III: Progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-Dotatate. Journal of Clinical Oncology Conference. 2016;34.	Abstract
	Anonymous, FROM ECC 2015-neuroendocrine cancer: SSA therapies-¹⁷⁷Lu-DOTATATE is a better one in NETTER-1. Nature Reviews Clinical Oncology. 2015: 12:684	Abstract

Appendix 4. Table of excluded studies with rationale

Table 165: Table of excluded studies

No.	Author	Year	Title	Journal	Exclusion Reason
1	Adlbrecht, C. W., C.	2007	Targeted radionuclide therapy with 90Y- and 177-Lu-DOTATOC in patients with neuroendocrine tumors (Structured abstract)	Health Technology Assessment Database	Design
2	Anonymous	2012	Everolimus 10 mg and pancreatic neuroendocrine tumours: many adverse effects and uncertain benefit	Prescrire International	Design
3	Anonymous	2012	Sunitinib and pancreatic neuroendocrine tumours. More assessment needed	Prescrire International	Design
4	Anonymous	2014	Lanreotide slows growth of neuroendocrine cancer	Cancer Discovery	Design
5	Anonymous	2016	Everolimus for Advanced, Progressive, Nonfunctional Neuroendocrine Tumors (NET) of the Gastrointestinal (GI) Tract: Efficacy and Safety From a RADIANT-4 Subgroup Analysis	Clinical Advances in Hematology & Oncology	Design
6	Anonymous	2016	NETTER-1 Phase III in Patients With Midgut Neuroendocrine Tumors Treated With 177Lu-DOTATATE: Efficacy and Safety Results	Clinical Advances in Hematology & Oncology	Design
7	Anonymous	2015	Erratum to Real-World Study of Everolimus in Advanced Progressive Neuroendocrine Tumors (The Oncologist, (2014) 19, 966-974)	Oncologist	No Data
8	Anonymous	2015	Retraction Note to: A randomized phase II study of everolimus for advanced pancreatic neuroendocrine tumors in Chinese patients.[Retraction of Yao J, Wang JY, Liu Y, Wang B, Li YX, Zhang R, Wang LS, Liu L. Med Oncol. 2014 Dec;31(12):251; PMID: 25395378]	Medical Oncology	Retracted
9	Anthony L, Bajetta E, Kocha W, Panneerselvam A, Saletan S, O'Dorisio T.		Efficacy and safety of everolimus plus octreotide LAR in patients with colorectal neuroendocrine tumors (NET): Subgroup analysis of the phase III RADIANT-2 trial.	American Journal of Gastroenterology	Design – RADIANT2
10	Anthony L, Singh N, Passos VQ, Pavel M, Oberg K, Yao JC.	2011	Impact of prior somatostatin analog use on PFS in the phase III radiant-2 trial of everolimus + octreotide lar vs placebo + octreotide lar in patients with advanced neuroendocrine tumors.	Pancreas	Design – RADIANT2
11	Anthony LB, Pavel ME, Hainsworth JD, Kvols LK, Segal S, Horsch D, et al.	2012	Impact of previous somatostatin analogue use on the activity of everolimus in patients with advanced neuroendocrine tumors: Analysis from the Phase III RADIANT-2 trial.	Neuroendocrinology	Design – RADIANT2
12	Anthony LB, Peeters M, Hainsworth JD, Baudin E, Hoersch D, Klimovsky J, et al.	2015	Everolimus plus octreotide LAR versus placebo plus octreotide LAR in patients with advanced neuroendocrine tumors (NET): Effect of prior somatostatin analog therapy on progression-free survival in the RADIANT-2 trial.	Journal of Clinical Oncology Conference: ASCO Annual Meeting	Design – RADIANT2

13	Antonuzzo, A. R., S.; Galli, L.; Conte, P. F.	1998	Long-acting lanreotide in the treatment of neuroendocrine tumors (NETs)	Annals of Oncology	Design
14	Bajetta, E. G., V.; Procopio, G.	2009	Activity of sunitinib in patients with advanced neuroendocrine tumors	Journal of Clinical Oncology	Design
15	Barni, S. B., K. F.; Ghilardi, M.; Cabiddu, M.; Maspero, F.; Cremonesi, M.; Petrelli, F.	2012	The impact of anemia in advanced solid tumors treated with sorafenib (SO) and sunitinib (SU): A pooled analysis of 6 trials	Annals of Oncology	Design
16	Baudin, E. C., D.; Kaltsas, G.; Gross, D.; Lebrec, J.; Tsuchihashi, Z.; Klimovsky, J.; Saletan, S.; Yao, J.; Wolin, E.	2011	Correlation of PFS and chromogranin a and 5-hydroxyindoleacetic acid levels in patients with advanced neuroendocrine tumors: Phase III radiant-2 study results	Annals of Oncology	No Data
17	Baudin, E. W., E. M.; Castellano, D. E.; Kaltsas, G.; Lebrec, J.; Tsuchihashi, Z.; Klimovsky, J.; Saletan, S.; Yao, J. C.; Gross, D.	2011	Effect of everolimus plus octreotide LAR treatment on chromogranin A and 5-hydroxyindoleacetic acid levels in patients with advanced neuroendocrine tumors: Phase III RADIANT-2 study results	Journal of Clinical Oncology. Conference: ASCO Annual Meeting	No Data
18	Baudin, E. W., E.; Castellano, D.; Kaltsas, G.; Lebrec, J.; Tsuchihashi, Z.; Saletan, S.; Gross, D.	2011	Effect of everolimus + octreotide lar treatment on 5-hydroxyindoleacetic acid levels in patients with advanced neuroendocrine tumors: Phase III radiant-2 study results	Neuroendocrinology	No Data
19	Baudin, E. W., E.; Castellano, D.; Kaltsas, G.; Panneerselvam, A.; Tsuchihashi, Z.; Saletan, S.; Yao, J. C.; Gross, D.	2011	Correlation of PFS with early response of chromogranin a and 5-hydroxyindoleacetic acid levels in pts with advanced neuroendocrine tumours: Phase III radiant-2 study results	European Journal of Cancer	No Data
20	Bechter, O. E. U., N.; Borbath, I.; Ricci, S.; Hwang, T. L.; Park, Y. S.; Tomasek, J.; Raef, H.; Laohavinij, S.; Louis, L. J.; Panneerselvam, A.; Saletan, S.; Stergiopoulos, S. G.; Pavel, M. E.	2013	Open-label, phase IIIb, multicenter, expanded access study of everolimus in patients with advanced neuroendocrine tumors (NET)	Journal of Clinical Oncology. Conference	Design
21	Berruti, A. P., A.; Terzolo, M.	2011	Advances in pancreatic neuroendocrine tumor treatment: [2]	New England Journal of Medicine	Design
22	Blumenthal, G. M. C., P.; Zhang, J. J.; Tang, S.; Sridhara, R.; Murgo, A.; Justice, R.; Pazdur, R.	2012	FDA approval summary: sunitinib for the treatment of progressive well-differentiated locally advanced or metastatic pancreatic neuroendocrine tumors	The Oncologist	Design
23	Bodei, L. B., M.; Cremonesi, M.; Rocca, P.; Ferrari, M.; Grana, C.; Chinol, M.; Paganelli, G.	2005	Receptor radionuclide therapy with Lu-177-DOTA(0) -Tyr(3)-octreotate (Lu-177-DOTATATE) in endocrine tumors: preliminary results	European Journal of Nuclear Medicine and Molecular Imaging	Design
24	Bodei, L. C., M.; Grana, C.; Bartolomei, M.; Baio, S.; Bufi, G.; Fiorenza, M.; Obenaus, E.; Paganelli, G.	2006	Receptor radionuclide therapy with Lu-177-DOTATATE in neuroendocrine tumours	European Journal of Nuclear Medicine and Molecular Imaging	Design
25	Boussion, H. H., P.	2015	Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors	Oncologie	Language
26	Buil-Bruna, N. D., M.; Manon, A.; Nguyen, T. X. Q.; Troconiz, I. F.	2016	Relationship Between Lanreotide Autogel, Chromogranin A and Progression-Free Survival in Patients With Gastroenteropancreatic Neuroendocrine Tumors	Pancreas	No Data
27	Buil-Bruna, N. D., M.; Manon, A.; Nguyen, T. X.; Troconiz, I. F.	2016	Establishing the Quantitative Relationship Between Lanreotide Autogel, Chromogranin A, and Progression-Free Survival in Patients with Nonfunctioning Gastroenteropancreatic Neuroendocrine Tumors	AAPS Journal	No Data

28	Buil-Bruna, N. D., M.; Manon, A.; Thi Xuan, Q. N.; Troconiz, I.	2015	Relationship between lanreotide autogel, chromogranin A and progression-free survival in patients with gastroenteropancreatic neuroendocrine tumours	European Journal of Cancer	No Data
29	Caplin, M. E. B., E.; Ferolla, P.; Filosso, P.; Garcia-Yuste, M.; Lim, E.; Oberg, K.; Pelosi, G.; Perren, A.; Rossi, R. E.; Travis, W. D. et al.	2015	Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids	Annals of Oncology	Design
30	Caplin, M. E. P., A. T.; Ruszniewski, P.; Pavel, M. E.; Cwikla, J. B.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Grp, Clarinet Study	2015	Antitumor Effects With Lanreotide Autogel/Depot (LAN) in Patients With Metastatic Enteropancreatic (EP) Neuroendocrine Tumors (NETs): Interim Results of the CLARINET Extension Study	Pancreas	Treatment - Clarinet
31	Caplin, M. E. P., M.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Martinez, S.; Blumberg, J.; Ruszniewski, P.; Investigators, Clarinet	2014	Lanreotide in metastatic enteropancreatic neuroendocrine tumors	New England Journal of Medicine	Treatment - Clarinet
32	Caplin, M. E. P., M.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Martinez, S.; Gomez-Panzani, E.; Ruszniewski, P.	2016	Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: The CLARINET open-label extension study	Endocrine-Related Cancer	Treatment - Clarinet
33	Caplin, M. E. R., P. B.; Pavel, M. E.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wall, L. R.; Rindi, G.; Langley, A.; Blumberg, J.	2014	Progression-free survival (PFS) with lanreotide autogel/depot (LAN) in enteropancreatic NETs patients: The CLARINET extension study	Journal of Clinical Oncology	Design
34	Caplin, M. P., A.; Liyanage, N.; Gomez-Panzani, E.; Blumberg, J.; Uk,; Ireland Neuroendocrine, Tumour; Grp, Clarinet Study	2014	Lanreotide Autogel Significantly Improves Tumor Progression-Free Survival in Patients with Non-Functioning Gastroenteropancreatic Neuroendocrine Tumors: Results of the CLARINET Study	Pancreas	Treatment - Clarinet
35	Caplin, M. P., M.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Chromogranin A (CgA) and PFS Outcomes in Lanreotide Autogel (LAN) in Patients with Metastatic Enteropancreatic (EP-) NETs: Data from the CLARINET Study	Neuroendocrinology	Design
36	Caplin, M. P., M.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Antitumor treatment with Lanreotide Autogel 120 mg (LAN) for Enteropancreatic (EP-)NET: Update from the CLARINET Open-Label Extension (OLE) Study	Neuroendocrinology	Design
37	Caplin, M. P., M.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Health-Related Quality of Life (HRQoL) with Lanreotide Autogel (LAN) 120 mg in Patients with Enteropancreatic (EP-)NETs: Post Hoc Analyses from the CLARINET Study	Neuroendocrinology	Treatment - Clarinet
38	Caplin, M. R., P.; Pavel, M.; Cwikla, J.; Phan, A.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wall, L.; Rindi, G.; Langley, A.; Blumberg, J.	2014	Progression-free survival (PFS) and tumor growth with lanreotide autogel (LAN) in patients (Pts) with enteropancreatic NETs: Results from clarinet, a randomized, double-blind, placebo (Pbo)-controlled study	Neuroendocrinology	Treatment - Clarinet
39	Caplin, M. R., P.; Pavel, M.; Cwikla, J.; Phan, A.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wall, L.; Rindi, G.; Liyanage, N.; Blumberg, J.	2013	A randomized, double-blind, placebo-Controlled study of Lanreotide Antiproliferative Response in patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET)	European Journal of Cancer	Treatment - Clarinet

40	Castellano D, Bajetta E, Panneerselvam A, Saletan S, Kocha W, O'Dorisio T, et al.	2013	Everolimus Plus Octreotide Long-Acting Repeatable in Patients With Colorectal Neuroendocrine Tumors: A Subgroup Analysis of the Phase III RADIANT-2 Study.	Oncologist	Design – RADIANT2
41	Castellano D, Bajetta E, Panneerselvam A, Saletan S, Kocha W.	2011	Subgroup analysis of patients with colorectal neuroendocrine tumors (NET) in the phase III radiant-2 study comparing everolimus plus octreotide LAR with placebo plus octreotide LAR.	Annals of Oncology	Design – RADIANT2
42	Clark, O. H. A., J. A.; Benson, Iii A. B.; Berlin, J. D.; Blaszkowsky, L. S.; Byrd, D.; Choti, M. A.; Doherty, G. M.; Engstrom, P. F.; Gibbs, J. F.; Heslin, M. J.; Kandeel, F.; Kessinger, A.; Kulke, M. H.; Kunz, P.; Kvols, L.; Olson Jr, J. A.; Ratliff, T. W.; Salem, R.; Saltz, L.; Schteingart, D. E.; Shah, M. H.; Shibata, S.	2009	Neuroendocrine tumors	JNCCN Journal of the National Comprehensive Cancer Network	Design
43	Dasari, A. P., A. T.; Caplin, M. E.; Pavel, M. E.; Cwikla, J. B.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Lanreotide depot/autogel (LAN) in midgut neuroendocrine tumors (NETs): A subgroup analysis from the CLARINET study	Journal of Clinical Oncology	Treatment - Clarinet
44	Dasari, A. P., A. T.; Caplin, M. E.; Pavel, M. E.; Cwikla, J. B.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Lanreotide depot/autogel (LAN) in patients with neuroendocrine tumors (NETs) aged > 65 vs. >65 years: Subgroup analyses from the CLARINET study	Journal of Clinical Oncology	Treatment - Clarinet
45	De Herder, W. W.	2012	Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)	Best Practice and Research: Clinical Gastroenterology	Design
46	De Herder, W. W. N., B.; Scoazec, J. Y.; Pauwels, S.; Kloppel, G.; Falconi, M.; Kwekkeboom, D. J.; Oberg, K.; Eriksson, B.; Wiedenmann, B.; Rindi, G.; et al.	2006	Well-differentiated pancreatic tumor/carcinoma: Insulinoma	Neuroendocrinology	Design
47	Deeks, E. D. R., E.	2011	Sunitinib: in advanced, well differentiated pancreatic neuroendocrine tumors	Biodrugs	Design
48	Delaunoit, T. N., F.; Rubin, J.; Erlichman, C.; Hobday, T. J.	2008	Medical management of pancreatic neuroendocrine tumors	American Journal of Gastroenterology	No Data
49	Delavault, P. C., M. E.; Liyange, N.; Blumberg, J.	2012	The CLARINET study: Assessing the effect of lanreotide autogel on tumor progression-free survival in patients with nonfunctioning gastroenteropancreatic neuroendocrine tumors	Journal of Clinical Oncology	Treatment - Clarinet
50	Delpassand, E. M., H.; Thamake, S.; Broline, S.; Ranganathan, D.; Wagh, N.; Tworowska, I.; Delpassand, A.; Puentes, J.	2015	(177)Lutetium-DOTA-octreotate therapy in progressive somatostatin receptor-expressing neuroendocrine neoplasms	Journal of Nuclear Medicine	Design
51	Dreyer, C. H., O.; Zappa, M.; Hammel, P.; Bouattour, M.; Mateescu, C.; Faivre, S.; Ruszniewski, P.; Raymond, E.	2012	Response evaluation using recist and choi criteria in patients with well-differentiated pancreatic neuroendocrine tumors (pnet) treated with sunitinib or everolimus	Annals of Oncology	Design
52	Eberle, A. N. B., C.	2005	Does 177Lu-labeled octreotate improve the rate of remission of endocrine gastroenteropancreatic tumors?	Nature Clinical Practice Endocrinology & Metabolism	Design

53	Eriksson, B. K., G.; Krenning, E.; Ahlman, H.; Plockinger, U.; Wiedenmann, B.; Arnold, R.; Auernhammer, C.; Korner, M.; Rindi, G.; Wildi, S.; et al.	2008	Consensus guidelines for the management of patients with digestive neuroendocrine tumors - Well-differentiated jejunal-ileal tumor/carcinoma	Neuroendocrinology	Design
54	Eriksson, B. O., K.	2000	Neuroendocrine tumours of the pancreas	British Journal of Surgery	Design
55	Faggiano, A. M., P.; Modica, R.; Agrimi, D.; Aversano, M.; Bassi, V.; Giordano, E. A.; Guarnotta, V.; Logoluso, F. A.; Messina, E.; Nicastro, V.; Nuzzo, V.; Sciaraffia, M.; Colao, A.	2016	Efficacy and Safety of Everolimus in Extrapancreatic Neuroendocrine Tumor: A Comprehensive Review of Literature	Oncologist	Design
56	Faiss, S. R., E. O.; Wiedenmann, B.; Int Lanreotide Interferon-alpha study, grp	1998	Evaluation of the antiproliferative effect of lanreotide or interferon-alpha or the combination of both in the therapy of metastatic neuroendocrine tumors	Gastroenterology	Design
57	Faiss, S. S., H.; Riecken, E. O.; Wiedenmann, B.	1996	Interferon-alpha versus somatostatin or the combination of both in metastatic neuroendocrine gut and pancreatic tumours	Digestion	Design
58	Falconi, M. P., U.; Kwekkeboom, D. J.; Manfredi, R.; Korner, M.; Kvols, L.; Pape, U. F.; Ricke, J.; Goretzki, P. E.; Wildi, S.; Steinmuller, T.; et al.	2006	Well-differentiated pancreatic nonfunctioning tumors/carcinoma	Neuroendocrinology	Design
59	Fazio N, Granberg D, Grossman A, Saletan S, Klimovsky J, Panneerselvam A, et al.	2013	Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the phase 3, randomized, placebo-controlled RADIANT-2 study.	Chest	Design – RADIANT2
60	Fazio N, Granberg D, Grossman A, Saletan S, Winkler RE, Panneerselvam A, et al.	2011	Effect of everolimus + octreotide LAR in patients with advanced lung neuroendocrine tumours - Analysis from RADIANT-2.	European Journal of Cancer	Design – RADIANT2
61	Fazio, N. O., K.	2004	Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors	Journal of clinical oncology : official journal of the American Society of Clinical Oncology	Design
62	Fisher Jr, G. A. W., E. M.; Kunz, P.; Liyanage, N.; Gomez-Panzani, E.; Lowenthal, S. P.; Pommier, R. F.; Shaheen, M.; Vinik, A.	2015	Safety and efficacy of lanreotide depot versus placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy	American Journal of Gastroenterology	Treatment
63	Fisher, G. A. W., E. M.; Kunz, P.; Liyanage, N.; Gomez-Panzani, E.; Lowenthal, S. P.; Pommier, R. F.; Shaheen, M.; Vinik, A.	2016	Efficacy and Safety of Lanreotide Depot vs Placebo in Patients With Neuroendocrine Tumor and a History of Carcinoid Syndrome and Prior Octreotide Therapy	Pancreas	Treatment
64	Freeman, S.	2013	Lanreotide has benefit in nonfunctioning neuroendocrine tumors	Oncology Report	Design
65	Galli, L. R., S.; Antonuzzo, A.; Bengala, C.; Conte, P. F.	1998	The new long-acting somatostatin analogue Lanreotide in neuroendocrine tumors (NETs)	Annals of Oncology	Design
66	Gan, H. K. S., B.; Knox, J. J.	2009	Sunitinib in solid tumors	Expert Opinion on Investigational Drugs	Design
67	Ganetsky, A. B., V.	2012	Gastroenteropancreatic neuroendocrine tumors: Update on therapeutics	Annals of Pharmacotherapy	Design
68	Gilbert, J. A.	2014	Lanreotide delays progression of neuroendocrine tumours	Lancet Oncology	Design
69	Goldstein, R. M., T.	2011	Role of everolimus in pancreatic neuroendocrine tumors	Expert Review of Anticancer Therapy	Design

70	Gomez-Panzani, E. V., A.; Wolin, E.; Audry, H.	2014	Elect: A phase 3 study of efficacy and safety of lanreotide autogel (LAN) treatment for carcinoid syndrome (CS) in patients (Pts) with gastroenteropancreatic neuroendocrine tumors (gep-NETs)	Neuroendocrinology	Treatment
71	Gotthardt, M. L., D.; Wolf, D.; Lalyko, G.; Behr, T. M.; Behe, M.	2006	Increased therapeutic efficacy through combination of Lu-177-DOTATOC and chemotherapy in neuroendocrine tumours in vivo	European Journal of Nuclear Medicine and Molecular Imaging	Design
72	Granberg D, Fazio N, Grossman A, Saletan S, Pannnerselvam A, Wolin E.	2014	Everolimus plus octreotide LAR in patients with lung carcinoids.	Journal of thoracic oncology	Design – RADIANT2
73	Granberg, D. D. H., W.; O'Toole, D.; Kvols, L.	2012	Treatment of liver metastases in patients with neuroendocrine tumors	International Journal of Hepatology	Design
74	Grenader, T. R., P.; Pavel, M.; Cwikla, J.; Phan, A.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E.; Capdevila, J.; Wall, L.; Rindi, G.; Lang, A.; Gomez-Panzani, E.; Caplin, M.	2015	Prognostic value of neutrophil/lymphocyte ratio in intestinal and pancreatic neuroendocrine tumors: Exploratory analysis of data from the CLARINET trial of lanreotide depot/autogel	European Journal of Cancer	No Data
75	Gross D, Peeters M, Jehl V, Saletan S, Sideris L.	2011	A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus + octreotide lar vs. Placebo + octreotide lar in patients with advanced neuroendocrine tumors (NET) (RADIANT-2): Updated safety results.	Endocrine Reviews Conference: 93rd Annual Meeting and Expo of the Endocrine Society, ENDO	Design – RADIANT2
76	Gulenchyn, K. Y. Y., X.; Asa, S. L.; Singh, S.; Law, C.	2012	Radionuclide Therapy in Neuroendocrine Tumours: A Systematic Review	Clinical Oncology	Design
77	Guo, L. J. T., C. W.	2014	Somatostatin analogues do not prevent carcinoid crisis	Asian Pacific Journal of Cancer Prevention: Apjcp	Design
78	Guo, L. J. T., C. W.	2014	Somatostatin analogues for carcinoid syndrome	Journal of Digestive Diseases	No Data
79	Guo, L. T., C.	2014	Somatostatin analogues for carcinoid syndrome	Neuroendocrinology	Design
80	Guo, L. T., C.	2014	Somatostatin analogues for preventing carcinoid crisis	Neuroendocrinology	No Data
81	Hobday T, Becerra C, Yalcin S, Panneerselvam A, Saletan S, Hainsworth J.	2011	Post-progression therapies in patients with advanced neuroendocrine tumors (NET): Analysis from the RADIANT-2 trial.	American Journal of Gastroenterology	Design – RADIANT2
82	Hofman, M. S. H., R. J.	2014	Peptide receptor radionuclide therapy for neuroendocrine tumours: Standardized and randomized, or personalized?	European Journal of Nuclear Medicine and Molecular Imaging	Design
83	Hofman, M. S. K., R.; Kong, G.; Akhurst, T.; Pattison, D.; Eu, P.; Hicks, R. J.	2015	Improved survival of poor prognosis fdg-avid neuroendocrine tumours with lu-177 octreotate peptide receptor chemoradionuclide therapy (prcrt)	Internal Medicine Journal	Design
84	Horsch, D. S., J.	2014	Molecular Therapy of neuroendocrine neoplasia: Sunitinib (Sutent) and everolimus (Afinitor)	Verdauungskrankheiten	Language
85	Hosking, E. M., E.; Browne, E.; Thomas, D.; Liauw, W.; Morris, D.; Chu, F.; Hayes, A.; Butler, P.	2015	Lu-177 dotatate therapy in patients with nets	Internal Medicine Journal	Design
86	Hyrdel, R. N., G.; Krenning, E.; Vullierme, M. P.; Ahlman, H.; Arnold, R.; Bechstein, W. O.; Cadiot, G.; Caplin, M.; Christ, E.; Chung, D.; et al.	2006	Rare functioning pancreatic endocrine tumors	Neuroendocrinology	Design
87	Iwasaki, M. P., A.; Caplin, M.; Ruszniewski, P.; Pavel, M.; Gomez-Panzani, E.	2015	Quality of life (qol) with lanreotide depot (lan) vs placebo in patients with pancreatic and gastrointestinal neuroendocrine tumours: results from the clarinet phase iii study	Oncology Nursing Forum	Treatment - Clarinet
88	Iwasaki, M. W., E.; Dasari, A.; Liyanage, N.; Lowenthal, S. P.; Phan, A.	2016	Response rates in the phase 3 clarinet trial of lanreotide depot vs placebo in patients with metastatic gastroenteropancreatic neuroendocrine tumors (gep-nets)	Oncology Nursing Forum	Treatment - Clarinet

89	Jacobsen, M. B. d., E. G. E.; Eriksson, B.; Fiasse, R.; Wijmenga, M.; Salmela, P.; Valimaki, M.; Oberg, K.; Renstrup, J.	1996	Symptomatic effect of a long acting Lanreotide formulation in patients with gastrointestinal neuroendocrine tumours	Gastroenterology	Design
90	Joelle, B. N., L.; Martyn, C.	2012	The clarinet study y assessing the effect of lanreotide autogel on tumor progression-free survival in patients with non-functioning gastroenteropancreatic neuroendocrine tumors (GEP-NETS)	Pancreas	Treatment - Clarinet
91	Kaltsas, G. G., A. B.	2015	The expanding role of somatostatin analogues in the treatment of neuroendocrine tumours: the CLARINET study	Clinical Endocrinology	Design
92	Kim, S. J. P., K.; Koo, P. J.; Kwak, J. J.; Chang, S.	2015	The efficacy of (177)Lu-labelled peptide receptor radionuclide therapy in patients with neuroendocrine tumours: a meta-analysis	European Journal of Nuclear Medicine & Molecular Imaging	No Data
93	Koussis, H. S., A.; Cirillo, F.; Basso, U.; Ziampiri, S.; Casara, D.; Pelizzo, M. R.; Rebustello, F.; Behboo, R.; Jirillo, A.	2008	Alternating lanreotide and octreotide in the treatment of metastatic neuroendocrine tumors (NETs)	Journal of Clinical Oncology	Design
94	Krampitz, G. W. N., J. A.	2013	Pancreatic neuroendocrine tumors	Current Problems in Surgery	Design
95	Kuo, J. H. L., J. A.; Chabot, J. A.	2014	Nonfunctional Pancreatic Neuroendocrine Tumors	Surgical Clinics of North America	Design
96	Kwekkeboom, D. J. B., W. H.; Teunissen, J. J.; Kooij, P. P.; Krenning, E. P.	2003	Treatment with Lu-177-DOTA-Tyr3-octreotate in patients with neuroendocrine tumors: Interim results	Journal of Nuclear Medicine	Design
97	Lahner, H. D., Y.; Bojunga, J.	2014	Health-related Quality-of-Life in everolimus-treated patients with advanced neuroendocrine tumors: Results from an open-label, phase IIIb, multicenter, expanded access program (EVIDENT)	Oncology Research and Treatment	Design
98	Lahner, H. R., A.; Poppel, T. D.; Fuhrer, D.	2013	Sunitinib in pancreatic neuroendocrine tumours	Experimental and Clinical Endocrinology & Diabetes	Design
99	Lamberts, S. W. J. v. d. L., A. J.; Hofland, L. J.	2002	New somatostatin analogs: Will they fulfil old promises?	European Journal of Endocrinology	Design
100	Lee, Y. S. P., E. J.	2011	National formulary review of the drugs used in pancreatic neuroendocrine tumors in Korea	Value in Health	Design
101	Lu, C. C. L., H. F.; Feng, C. C.; Yu, C. Y.; Kao, W.	2008	Sunitinib malate as the salvage therapy in advanced rectal carcinoid tumor	International Journal of Colorectal Disease	Design
102	Mansour, J. C. C., H.	2004	Pancreatic endocrine tumors	Journal of Surgical Research	Design
103	Massironi, S. C., D.; Rossi, R. E.	2016	Somatostatin analogues in functioning gastroenteropancreatic neuroendocrine tumours: literature review, clinical recommendations and schedules	Scandinavian Journal of Gastroenterology	Design
104	Migliori, M. T., P.; Montini, G. C.; Lalli, S.; Corinaldesi, R.	1998	Treatment of gastro-entero-pancreatic (GEP) neuroendocrine tumors with lanreotide, a new-long-acting somatostatin analogue	Gastroenterology	Design
105	Mittendorf, E. A. I., W. B.; Libutti, S. K.; McHenry, C. R.; Demeure, M. J.	2006	Islet Cell Tumors	Current Problems in Surgery	Design
106	Modlin, I. M. B., L.; Kidd, M.	2014	A Historical Appreciation of Bronchopulmonary Neuroendocrine Neoplasia: Resolution of a Carcinoid Conundrum	Thoracic Surgery Clinics	Design

107	Modlin, I. M. K., M.; Drozdov, I.; Siddique, Z. L.; Gustafsson, B.	2008	Pharmacotherapy of neuroendocrine cancers	Expert Opinion on Pharmacotherapy	Design
108	Modlin, I. M. P., M.; Kidd, M.; Gustafsson, B. I.	2010	Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours	Alimentary Pharmacology & Therapeutics	Design
109	Motylewska, E. G., J.; Niedziela, A.; Melen-Mucha, G.; Lawnicka, H.; Komorowski, J.; Swietoslawski, J.; Stepien, H.	2016	Somatostatin Analogs and Tumor Localization Do Not Influence Vitamin D Concentration in Patients with Neuroendocrine Tumors	Nutrition and Cancer	Design
110	Muniraj, T. V., S.; Shetty, S.; Thiruvengadam, S.; Aslanian, H. R.	2013	Pancreatic neuroendocrine tumors	Disease-a-Month	Design
111	Niederhuber, J. E. F., T.	2006	Treatment of Metastatic Disease in Patients with Neuroendocrine Tumors	Surgical Oncology Clinics of North America	Design
112	Nihr, H. S. C.	2012	Everolimus (Afinitor) for advanced, unresectable or metastatic neuroendocrine tumours (Structured abstract)	Health Technology Assessment Database	Design
113	Nihr, H. S. C.	2014	Lanreotide for unresectable, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours – first line (Structured abstract)	Health Technology Assessment Database	Design
114	Nihr, H. S. C.	2014	Lutetium-177 for inoperable gastroenteropancreatic neuroendocrine tumours (Structured abstract)	Health Technology Assessment Database	Design
115	Oberg, K.	1994	Treatment of neuroendocrine tumors	Cancer Treatment Reviews	Design
116	Oberg, K.	2016	Universal everolimus for malignant neuroendocrine tumours?	Lancet	Design
117	Oberg, K. A., G.; Rindi, G.; Jelic, S.	2010	Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up	Annals of Oncology	Design
118	Oberg, K. A., L.; Sideris, L.; Chen, Lt; Cherfi, A.; Tsuchihashi, Z.; Winkler, R.; De Vries, E.	2011	Role of chromogranin a and neuron-specific enolase biomarkers in progression-free survival (PFS) with everolimus (EVE) versus placebo (PB) in patients with advanced pancreatic neuroendocrine tumors (pNET): Phase III radiant-3 results	Neuroendocrinology	No Data
119	Oberg, K. H., P.; Ferolla, P.; Papotti, M.	2012	Neuroendocrine bronchial and thymic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	Annals of Oncology	Design
120	Oberg, K. K., M.; Pavel, M.; Phan, A.; Hoosen, S.; St. Peter, J.; Cherfi, A.; Yao, J. C.	2010	Prognostic and predictive value of chromogranin a and neuron-specific enolase in patients (pts) with advanced pancreatic neuroendocrine tumors (pnet) treated with everolimus	Annals of Oncology	Design
121	Oberg, K. K., M.; Pavel, M.; Phan, A.; Hoosen, S.; St. Peter, J.; Cherfi, A.; Yao, J. C.	2011	Evaluation of chromogranin a and neuron-specific enolase as predictors of response to everolimus therapy in patients with advanced pancreatic neuroendocrine tumors (pNET)	Pancreas	Design
122	Oberg, K. K., U.; Kwekkeboom, D.; Perren, A.; Grp, Esmo Guidelines Working	2012	Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Annals of Oncology	Design

123	Ong, S. L. G., G.; Pollard, C. A.; Furness, P. N.; Steward, W. P.; Rajesh, A.; Spencer, L.; Lloyd, D. M.; Berry, D. P.; Dennison, A. R.	2009	A fuller understanding of pancreatic neuroendocrine tumours combined with aggressive management improves outcome	Pancreatology	Design
124	O'Toole, D. D., M.; Bommelaer, G.; Wemeau, J. L.; Bouché, O.; Catus, F.; Blumberg, J.; Ruszniewski, P.	2000	Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance	Cancer	Design
125	Ozdemir, N. Y., O.; Zengin, N.	2014	Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors	New England Journal of Medicine	Design
126	Pavel M, Hainsworth JD, Baudin E, Peeters M, Hoersch D, Anthony L, et al.	2010	A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus 1 octreotide lar vs placebo 1 octreotide lar in patients with advanced neuroendocrine tumors (net) (radiant-2).	Annals of Oncology	Design – RADIANT2
127	Pavel M, Oberg KE, Hainsworth JD, Lam D, Stergiopolos SG, Rouyrre N, et al.	2013	Everolimus plus octreotide long-acting release (LAR) for the treatment of advanced neuroendocrine tumors (NET) associated with carcinoid syndrome (RADIANT-2): Updated overall survival results.	European Journal of Cancer	Design – RADIANT2
128	Pavel M, Peeters M, Hoersch D, Van Cutsem E, Oberg K, Jehl V, et al.	2011	Everolimus plus Octreotide LAR versus Placebo plus Octreotide LAR in Patients with Advanced NET: Results of a Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial (RADIANT-2).	Neuroendocrinology	Design – RADIANT2
129	Pavel M, Singh N, Passos V, Oberg K.	2011	Impact of prior somatostatin analog (SSA) use on PFS in the multicenter, phase III trial of everolimus + octreotide LAR vs placebo + octreotide LAR in patients with advanced neuroendocrine tumours (radiant-2).	European Journal of Cancer	Design – RADIANT2
130	Pavel ME, Hainsworth JD, Baudin E, Peeters M, Horsch D, Winkler RE, et al.	2011	Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study.	Lancet	Design – RADIANT2
131	Pavel ME, Singh N, Passos V, Strosberg J.	2012	Progression-free survival by prior somatostatin analog use and primary tumor site and updated safety results in patients with advanced neuroendocrine tumors and a history of carcinoid syndrome: A radiant-2 analysis.	Neuroendocrinology	Design – RADIANT2
132	Pavel, M. D. V., E.; Oberg, K.; Lebrec, J.; Winkler, R.; Tsuchihashi, Z.; Yao, J.	2011	Everolimus improves progression-free survival (PFS) regardless of baseline chromogranin a (CGA) and neuron-specific enolase (NSE) levels in patients with advanced pancreatic neuroendocrine tumors (pNET) (RADIANT-3)	Annals of Oncology	No Data
133	Pavel, M. E. G., K.; Cheung, W.; Hasskarl, J.; Becerra, C.	2012	Effect of everolimus on the pharmacokinetics of octreotide LAR in patients with advanced neuroendocrine tumors: A RADIANT-2 analysis	Endocrine Reviews. Conference: 94th Annual Meeting and Expo of the Endocrine Society, ENDO	Design – RADIANT2
134	Pavel, M. E. G., K.; Cheung, W.; Hasskarl, J.; Becerra, C.	2012	Effect of everolimus on pharmacokinetics of octreotide LAR in patients with advanced neuroendocrine tumors: A radiant-2 analysis	Neuroendocrinology	Design – RADIANT2

135	Pavel, M. G., K.; Cheung, W.; Becerra, C.; Yao, J.	2012	Effect of everolimus on pharmacokinetics of octreotide LAR in patients with advanced neuroendocrine tumors: A RADIANT-2 analysis	American Journal of Gastroenterology	Design – RADIANT2
136	Pavel, M. G., K.; Cheung, W.; Becerra, C.; Yao, J.	2013	Pharmacokinetics of octreotide lar when administered with everolimus in patients with advanced neuroendocrine tumors: A radiant-2 analysis	Journal of Oncology Pharmacy Practice	Design – RADIANT2
137	Pavel, M. R., M.	2015	Antitumor activity of lanreotide autogel 120 mg in enteropancreatic Neuroendocrine Tumour (NET) patients: the clarinet open-label extension study	Oncology Research and Treatment	Design
138	Pavel, M. U., N.; Borbath, I.; Ricci, S.; Hwang, T. L.; Park, Y. S.; Tomasck, J.; Raef, H.; Laohavinij, S.; Sutradhar, S.; Jean-Louis, L.; Panneerselvam, A.; Saletan, S.; Stergiopoulos, S. G.; Bechter, O.	2014	Safety and Quality-Of-Life (QOL) Assessments in the Open-Label, Multicenter, Phase 3b, Expanded Access Study of Everolimus in Patients with Advanced Neuroendocrine Tumors (NET)	Pancreas	Design
139	Peeters, M. B., C.; Panneerselvam, A.; Saletan, S.; Yalcin, S.	2011	Post-study treatment options are limited in patients with advanced net: Analysis of postprogression therapies from the radiant-2 trial	Annals of Oncology	Design
140	Phan, A. C., M.; Pavel, M.; Cwikla, J.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P.	2015	Relative risk analysis of safety profile of lanreotide autogel/depot vs. placebo in patients with pancreatic and intestinal neuroendocrine tumours	European Journal of Cancer	Treatment - Clarinet
141	Phan, A. T.	2015	Lanreotide depot/autogel in neuroendocrine tumors: subgroup analyses from the CLARINET study	Clinical Advances in Hematology & Oncology	Design
142	Phan, A. T. C., M. E.; Pavel, M. E.; Cwikla, J. B.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Lanreotide depot/autogel (LAN) in pancreatic neuroendocrine tumors (pNETs): A subgroup analysis from the CLARINET study	Journal of Clinical Oncology	Treatment - Clarinet
143	Phan, A. T. C., M. E.; Pavel, M. E.; Cwikla, J. B.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Effects of lanreotide autogel/depot (LAN) in patients with neuroendocrine tumors (NETs) age 65 or younger versus older than age 65: Subgroup analyses from the CLARINET study	Journal of Clinical Oncology. Conference	Treatment - Clarinet
144	Phan, A. T. C., M. E.; Pavel, M. E.; Cwikla, J. B.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Relative risk of adverse events with lanreotide depot/autogel (LAN) vs. Placebo (PBO) in patients with intestinal and pancreatic neuroendocrine tumors (NETs)	Journal of Clinical Oncology. Conference	Treatment - Clarinet
145	Phan, A. T. C., M. E.; Pavel, M. E.; Jaroslaw, B. Cwikla; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wolin, E. M.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Effects of lanreotide autogel/depot (LAN) in pancreatic neuroendocrine tumors (pNETs): A subgroup analysis from the CLARINET study	Journal of Clinical Oncology. Conference	Treatment - Clarinet
146	Phan, A. T. D., A.; Liyanage, N.; Cox, D.; Lowenthal, S. P.; Wolin, E. M.	2016	Tumor response in the CLARINET study of lanreotide depot vs. placebo in patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs)	Journal of Clinical Oncology. Conference	Treatment - Clarinet
147	Pusceddu, S. D. B., F.; Festinese, F.; Bregant, C.; Lorenzoni, A.; Maccauro, M.; Milione, M.; Concas, L.; Formisano, B.; Leuzzi, L.; Mazzaferro, V.; Buzzoni, R.	2015	Evolution in the treatment of gastroenteropancreatic-neuroendocrine neoplasms, focus on systemic therapeutic options: a systematic review	Future Oncology	Design
148	Pusceddu, S. D. B., F.; Lo Russo, G.; Concas, L.; Femia, D.; Vernieri, C.; Indini, A.; Formisano, B.; Buzzoni, R.	2016	How do the results of the RADIANT trials impact on the management of NET patients? A systematic review of published studies	Oncotarget	Design

149	Qi, W. X. H., Y. J.; Yao, Y.; Shen, Z.; Min, D. L.	2013	Incidence and Risk of Treatment-Related Mortality with mTOR Inhibitors Everolimus and Temsirolimus in Cancer Patients: A Meta-Analysis	Plos One	Design
150	Ramage, J. K. A., A.; Ardill, J.; Bax, N.; Breen, D. J.; Caplin, M. E.; Corrie, P.; Davar, J.; Davies, A. H.; Lewington, V.; Meyer, T.; Newell-Price, J.; Poston, G.; Reed, N.; Rockall, A.; Steward, W.; Thakker, R. V.; Toubanakis, C.; Valle, J.; Verbeke, C.; Grossman, A. B.	2012	Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs)	Gut	Design
151	Ramundo, V. M., F.; Modica, R.; Marotta, V.; Pizza, G.; Camera, L.; Napolitano, V.; De Luca, L.; Colao, A.; Faggiano, A.	2015	Efficacy of lanreotide versus follow-up in early-stage duodeno-pancreatic neuroendocrine tumors (NETs) related to multiple endocrine neoplasia type 1 (MEN1): Preliminary data	Neuroendocrinology	Treatment
152	Raut, C. P. K., M. H.; Glickman, J. N.; Swanson, R. S.; Ashley, S. W.	2006	Carcinoid Tumors	Current Problems in Surgery	Design
153	Regnault, A. F., L.; Dinet, J.; Gabriel, S.; Pavel, M. E.; Ruszniewski, P. B.; Caplin, M. E.	2015	Health-related quality of life in CLARINET, a phase III trial of lanreotide autogel 120 mg in patients with non-functioning entero-pancreatic neuroendocrine tumour: analytical challenges and statistical solutions	Quality of Life Research	Treatment - Clarinet
154	Ricci S, Ruszniewski P, Tomasetti P, Jehl V, Saletan S, Yao JC, et al.	2011	Updated safety and efficacy results from radiant-2 - A randomized, double-blind, multicenter, phase III trial of everolimus + octreotide LAR vs placebo + octreotide LAR in pts with advanced neuroendocrine tumours (NET).	European journal of cancer	Design – RADIANT2
155	Ricci, S. C., C.; Cirillo, F.; De Angelis, C.; Galli, C.; Iannopollo, M.; Malagutti, A.; Palmieri, G.; Stivanello, M.; Tomassetti, P.; Besozzi, A.	2000	Efficacy of 1-month lanreotide in patients with neuroendocrine tumours: Preliminary results of a Italian multicenter study	Annals of Oncology	Design
156	Richards, C. J. J., Y.; Schutz, F. A.; Heng, D. Y.; Dallabrida, S. M.; Moslehi, J. J.; Choueiri, T. K.	2011	Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib	Journal of Clinical Oncology	Design
157	Rindi, G. C., M.	2011	MTOR inhibitor therapy for patients with carcinoid	The Lancet	Design
158	Rossi, R. E. M., S.; Spampatti, M. P.; Conte, D.; Ciafardini, C.; Cavalcoli, F.; Peracchi, M.	2012	Treatment of Liver Metastases in Patients with Digestive Neuroendocrine Tumors	Journal of Gastrointestinal Surgery	Design
159	Roth, I.	2010	Phase III Data in neuroendocrine Tumors show: RAD001 as Monotherapy and in Combination with Sandostatin (c) LAR (c) effectively	Viszeralmedizin	Language
160	Ruszniewski P, Tomassetti P, Saletan S, Panneerselvam A, Yao JC.	2011	Everolimus plus octreotide LAR versus placebo plus octreotide LAR in patients (pts) with advanced neuroendocrine tumors: Multivariate analysis of progression-free survival from the RADIANT-2 trial.	ASCO Annual Meeting	Design – RADIANT2
161	Ruszniewski, P. P., A. T.; Caplin, M. E.; Pavel, M. E.; Cwikla, J. B.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.	2015	Quality of Life (QoL) with Lanreotide Autogel/Depot (LAN) vs. Placebo in Patients with Enteropancreatic Neuroendocrine Tumors: Results From the CLARINET Core Study	Pancreas	Treatment - Clarinet
162	Ruszniewski, P. R., P.; Rampal, P.; Grange, J. D.; Jian, R.; Treffot, M. J.; Lesur, G.; Genestin, E.; Thomas, F.; Chayvialle, J. A.; Bernades, P.	1994	Does lanreotide influence the growth of metastatic carcinoid-tumors	Gastroenterology	Design
163	Schnirer, I. I. Y., J. C.; Ajani, J. A.	2003	Carcinoid: A Comprehensive Review	Acta Oncologica	Design
164	Sciandivasci, A. C., P.; Del Vecchio, M. T.; Marsili, S.; Pascucci, A.; Petrioli, R.; Ciliberto, D.; Savelli, V.;	2004	Chemo-hormone therapy of undifferentiated endocrine tumors from different anatomic sites with cisplatinum etoposide and long lasting release lanreotide	Annals of Oncology	Design

	Voltolini, L.; Di Bisceglie, M.; Guarnieri, A.; Gotti, G.; Francini, G.				
165	Siddall, R.	2010	Sunitinib use is justified for pancreatic neuroendocrine tumours	British Journal of Hospital Medicine	Design
166	Sideris, L. D., P.; Rinke, A.	2012	Antitumor effects of somatostatin analogs in neuroendocrine tumors	Oncologist	Design
167	Signorovitch, J. S., E.; Kantor, E.; Wang, X.; Klimovsky, J.; Haas, T.; Devine, B.; Metrakos, P.	2013	Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: A matching-adjusted indirect comparison	Experimental Hematology and Oncology	Design
168	Sjoquist, K. M.	2015	Control nets: Capecitabine on temozolomide radionuclide therapy octreotate lutetium-177 neuroendocrine tumours study	Asian Pacific Journal of Clinical Oncology	No Data
169	Slooter, G. D. M., A.; Breeman, W. A. P.; Marquet, R. L.; De Jong, M.; Krenning, E. P.; Van Eijck, C. H. J.	2001	Somatostatin receptor imaging, therapy and new strategies in patients with neuroendocrine tumours	British Journal of Surgery	Design
170	Srirajaskanthan, R. T., C.; Meyer, T.; Caplin, M. E.	2009	Review article: Future therapies for management of metastatic gastroenteropancreatic neuroendocrine tumours	Alimentary Pharmacology and Therapeutics	Design
171	Strosberg J, Ricci S, Ruszniewski P, Tomassetti P, Jehl V, Saletan S, et al.	2012	Radiant-2: A randomized, double-blind, multicenter, phase III trial of everolimus + octreotide lar vs placebo + octreotide lar in patients with advanced neuroendocrine tumors: Progression-free survival by primar tumor site and updated safety results.	Pancreas	Design – RADIANT2
172	Strosberg, J. A., L.; Sideris, L.; Lebrec, J.; Tsuchihashi, Z.; Winkler, R.; Yao, J.	2011	Prognostic value of chromogranin a and neuron-specific enolase in patients with advanced pancreatic neuroendocrine tumors (pNET): Phase III RADIANT-3 study results 2011 ACG presidential poster	American Journal of Gastroenterology	No Data
173	Strosberg, J. R. W., E. M.; Chasen, B.; Kulke, M. H.; Bushnell, D. L.; Caplin, M. E.; Baum, R. P.; Kunz, P. L.; Hobday, T. J.; Hendifar, A. E.; Oberg, K. E.; Sierra, M. L.; Kwekkeboom, D. J.; Ruszniewski, P. B.; Krenning, E.	2016	NETTER-1 phase III: Progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-Dotatate	Journal of Clinical Oncology. Conference	Treatment - NETTER
174	Strosberg, J. W., E.; Chasen, B.; Kulke, M.; Bushnell, D.; Caplin, M.; Baum, R. P.; Mittra, E.; Hobday, T.; Hendifar, A.; Oberg, K.; Lopera Sierra, M.; Ruszniewski, P.; Kwekkeboom, D.	2015	177-Lu-Dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: Results of the phase III NETTER-1 trial	European Journal of Cancer	Treatment - NETTER
175	Strosberg, J. W., E.; Chasen, B.; Kulke, M.; Bushnell, D.; Caplin, M.; Baum, R. P.; Mittra, E.; Hobday, T.; Hendifar, A.; Oberg, K.; Sierra, M. L.; Kwekkeboom, D.; Ruszniewski, P.; Krenning, E.	2016	177-Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumors: Results of the Phase III NETTER-1 Trial	Pancreas	Treatment - NETTER
176	Sutcliffe, R. M., D.; Ramage, J.; Rela, M.; Heaton, N.	2004	Management of neuroendocrine liver metastases	American Journal of Surgery	Design
177	Thompson, L. A. K., M.; Wenger, S. D.; O'Bryant, C. L.	2012	Everolimus: A New Treatment Option for Advanced Pancreatic Neuroendocrine Tumors	Annals of Pharmacotherapy	Design
178	Ujeyl, M.	2011	Everolimus for the treatment of unresectable or metastatic neuroendocrine tumours of pancreatic origin (Structured abstract)	Health Technology Assessment Database	Design
179	Van Essen, M. K., E. P.; Bakker, W. H.; Kooij, P. P.; Kwekkeboom, D. J.	2006	Peptide receptor radionuclide therapy with Lu-177-octreotate in foregut carcinoid tumours	European Journal of Nuclear Medicine and Molecular Imaging	Design

180	Vinik, A. I.	2014	Advances in diagnosis and treatment of pancreatic neuroendocrine tumors	Endocrine Practice	Design
181	Vinik, A. W., E. M.; Audry, H.; Gomez-Panzani, E. L.	2014	ELECT: A phase 3 study of efficacy and safety of lanreotide autogel/depot (LAN) treatment for carcinoid syndrome in patients with neuroendocrine tumors (NETs)	Journal of Clinical Oncology. Conference	Treatment
182	Vinik, A. W., E. M.; Audry, H.; Gomez-Panzani, E.; Fisher, G. A.	2015	Lanreotide depot/autogel (LAN) vs. placebo (PBO) for carcinoid syndrome (CS) in patients with neuroendocrine tumors (NETs): Subgroup analysis of the ELECT study	Journal of Clinical Oncology	Treatment
183	Volter, V. P., C.	2004	Is lanreotide and/or interferon alfa an adequate therapy for neuroendocrine tumors?	Journal of Clinical Oncology	Design
184	Vries, E. A., L. B.; Sideris, L.; Chen, L.; Lebrec, J.; Tsuchihashi, Z.; Winkler, R. E.; Yao, J. C.; Oberg, K. E.	2011	Effect of everolimus treatment on chromogranin A, neuron-specific enolase, gastrin, and glucagon levels in patients with advanced pancreatic neuroendocrine tumors (pNET): Phase III RADIANT-3 study results	Journal of Clinical Oncology	No Data
185	Wachter, K.	2010	Sunitinib doubles PFS of pancreatic neuroendocrine tumors	Oncology Report	Design
186	Walczak, W. J. J., J.; Lipinska, M.; PrzaDa-Machno, P.; Kroc, J.	2012	Clinical effectiveness analysis of sunitinib for the treatment of pancreatic neuroendocrine tumors	Value in Health	Design
187	Walker, P. R.	2009	Sunitinib in patients with advanced neuroendocrine tumors	American Journal of Hematology/ Oncology	Design
188	Wallace, D. M., S.	2012	Endocrine tumors of the pancreas	Practical Gastroenterology	Design
189	Wesolowski, R. A.-R., M.; Lustberg, M.; Paskell, M.; Shapiro, C. L.; Macrae, E. R.	2014	Treatment-Related Mortality With Everolimus in Cancer Patients	Oncologist	Design
190	Williams, D. V., A.; Wolin, E.; Kunz, P.; Lowenthal, S. P.; Fisher, G.	2016	Safety and efficacy of lanreotide depot vs placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy	Oncology Nursing Forum	Treatment
191	Wolin EM, Fazio N, Saletan S, Winkler RE, Panneerselvam A, Kvols L.	2011	Everolimus plus octreotide LAR versus placebo plus octreotide LAR in patients with advanced neuroendocrine tumors: Analysis by primary tumor site from RADIANT-2.	ASCO Annual Meeting	Design – RADIANT2
192	Wolin, E. C., D.; Kaltsas, G.; Gross, D.; Panneerselvam, A.; Klimovsky, J.; Saletan, S.; Yao, J.; Baudin, E.	2012	Correlation of progression-free survival (PFS) with early response of biomarkers chromogranin a (CGA) and 5-hhydroxyindoleacetic acid (5-HIAA) levels in patients with advanced neuroendocrine tumors: Phase III radiant-2 study results	Pancreas	No Data
193	Wolin, E. C., M.; Pavel, M.; Cwikla, J.; Phan, A.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P.	2015	Multivariate analysis of progression-free survival in the CLARINET study of lanreotide Autogel/Depot vs placebo identifies prognostic factors in neuroendocrine tumours	European Journal of Cancer	Treatment - Clarinet
194	Wolin, E. M.	2014	Long-term everolimus treatment of patients with pancreatic neuroendocrine tumors	Chemotherapy	Design
195	Wolin, E. M. C., M. E.; Pavel, M. E.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Prognostic factors for progression-free survival (PFS) in CLARINET study of lanreotide depot/autogel (LAN) vs placebo (PBO) in neuroendocrine tumors (NETs)	Journal of Clinical Oncology. Conference	Treatment - Clarinet
196	Wolin, E. M. C., M. E.; Pavel, M. E.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.	2015	Lanreotide depot/autogel (LAN) in intestinal and pancreatic neuroendocrine tumors (NETs) according to body mass index (BMI): Subgroup analyses from the CLARINET study	Journal of Clinical Oncology	Treatment - Clarinet

197	Wolin, E. M. C., M. E.; Pavel, M. E.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.; Grp, Clarinet Study	2016	Lanreotide Depot/Autogel in Intestinal and Pancreatic Neuroendocrine Tumors According to Body Mass Index: Subgroup Analyses From the CLARINET Study	Pancreas	Treatment - Clarinet
198	Wolin, E. M. C., M. E.; Pavel, M. E.; Cwikla, J. B.; Phan, A. T.; Raderer, M.; Sedlackova, E.; Cadiot, G.; Capdevila, J.; Wall, L.; Rindi, G.; Langley, A.; Gomez-Panzani, E.; Ruszniewski, P. B.; Grp, Clarinet Study	2016	Multivariate Analysis of Progression-Free Survival in the CLARINET Study of Lanreotide Autogel/Depot vs Placebo Identifies Prognostic Factors in Neuroendocrine Tumors	Pancreas	Treatment - Clarinet
199	Yang, F. J., C.; Fu, D. L.	2014	Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors	New England Journal of Medicine	Design
200	Yao JC, Hainsworth JD, Baudin E, Peeters M, Hoersch D, Anthony L, et al.	2011	Radiant-2: A phase III trial of everolimus + octreotide lar in patients with advanced neuroendocrine tumors (NET). Pancreas. 2011;40 (2):335.	Pancreas	Design – RADIANT2
201	Yao JC, Hainsworth JD, Baudin E, Peeters M, Hoersch D, Anthony LB, et al.	2011	Everolimus plus octreotide LAR (E+O) versus placebo plus octreotide LAR (P+O) in patients with advanced neuroendocrine tumors (NET): Updated results of a randomized, double-blind, placebo-controlled, multicenter phase III trial (RADIANT-2).	Journal of Clinical Oncology Conference	Design – RADIANT2
202	Yao JC, Hainsworth JD, Wolin EM, Pavel ME, Baudin E, Gross D, et al.	2012	Multivariate analysis including biomarkers in the phase III RADIANT-2 study of octreotide LAR plus everolimus (E+O) or placebo (P+O) among patients with advanced neuroendocrine tumors (NET).	Journal of Clinical Oncology Conference	Design – RADIANT2
203	Yao JC, Oberg KE, Hainsworth JD, Lam D, Stergiopolos SG, Rouyrre N, et al.	2014	Everolimus Plus Octreotide Long-Acting Repeatable (LAR) for the Treatment of Advanced Neuroendocrine Tumors (NET) Associated with Carcinoid Syndrome: Updated Overall Survival Results from RADIANT-2 Study.	Pancreas	Design – RADIANT2
204	Yao JC, Ricci S, Winkler RE, Jehl V, Pavel ME.	2011	Everolimus plus octreotide LAR versus placebo plus octreotide LAR in patients with advanced neuroendocrine tumors (NET): Updated safety and efficacy results from RADIANT-2.	ASCO Annual Meeting	Design – RADIANT2
205	Yao, J. C. B., R.; Carnaghi, C.; Fazio, N.; Singh, S.; Wolin, E. M.; Tomasek, J.; Raderer, M.; Lahner, H.; Lam, D. H.; Cauwel, H.; Valle, J. W.; Delle Fave, G.; Cutsem, E.; Strosberg, J. R.; Tesselaar, M. E.; Shimada, Y.; Oh, D. Y.; Kulke, M.; Pavel, M. E.	2015	Baseline demographics of the randomized, placebo-controlled, double-blind, phase III RADIANT-4 study of everolimus in nonfunctional gastrointestinal (GI) or lung neuroendocrine tumors (NET)	Journal of Clinical Oncology	No Data
206	Yao, J. C. P., A. T.; Chang, D. Z.; Wolff, R. A.; Hess, K.; Gupta, S.; Jacobs, C.; Mares, J. E.; Landgraf, A. N.; Rashid, A.; Meric-Bernstam, F.	2008	Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study.[Erratum appears in J Clin Oncol. 2008 Dec 1;26(34)5660.]	Journal of Clinical Oncology	Design
207	Yao, J. C. S., M.; Panneerselvam, A.; Chen, D.; Stergiopoulos, S.; Ito, T.; Pavel, M.	2013	The VEGF pathway in pancreatic neuroendocrine tumors: Prognostic and predictive capacity of baseline biomarker levels on efficacy of everolimus analyzed from the RADIANT-3 study	Pancreas	No Data
208	Yao, J. C. S., M.; Panneerselvam, A.; Stergiopoulos, S.; Chen, D.; Ito, T.; Pavel, M.	2012	The VEGF pathway in patients with pancreatic neuroendocrine tumors: Efficacy of everolimus by baseline marker level, and prognostic and predictive effect analyses from radiant-3	Annals of Oncology	No Data
209	Yao, J. C. T., Z.; Panneerselvam, A.; Winkler, R. E.; Bugarini, R.; Pavel, M.	2011	Effect of everolimus treatment on markers of angiogenesis in patients with advanced pancreatic neuroendocrine tumours (pNET) - Results from the phase III RADIANT-3 study	European Journal of Cancer	No Data

210	Yao, J. W., J. Y.; Liu, Y.; Wang, B.; Li, Y. X.; Zhang, R.; Wang, L. S.; Liu, L.	2014	A randomized phase II study of everolimus for advanced pancreatic neuroendocrine tumors in Chinese patients.[Retraction in Med Oncol. 2015 Aug;32(8):221; PMID: 26195291]	Medical Oncology	Retracted
211		2007	Off-label uses of Sorafenib and Sunitinib (Structured abstract)	Health Technology Assessment Database	Design
212		2008	Everolimus (RAD-001) for advanced gastroenteropancreatic neuroendocrine tumours (Structured abstract)	Health Technology Assessment Database	Design
213		2010	Sunitinib for advanced and/or metastatic pancreatic neuroendocrine tumours (Structured abstract)	Health Technology Assessment Database	Design
214		2011	Sunitinib (Sutent®) (Structured abstract)	Health Technology Assessment Database	Design
215		2012	Everolimus (Afinitor®) (Structured abstract)	Health Technology Assessment Database	Design
216		2009	Neuro-endocrine tumor. New study on tumor growth control with Sandostatin LAR and high efficacy or oral mTOR-Inhibitor RAD 001	Viszeralmedizin	Language
217		2011	Advanced pancreatic Neuroendocrine Tumors: mTOR Inhibitor Afinitor (R) (Everolimus) receives EU Approval	Viszeralmedizin	Language

Appendix 5. Additional clinical effectiveness data

NB: all cost-effectiveness results that include ACIC information such as confidential Patient Access Schemes (PAS), must be reported in a separate appendix and NOT in this document.

Table 166: AEs reported in at least 10% of patients regardless of study drug relationship (safety population) RADIANT-4

	Everolimus plus BSC (n=202)		Placebo plus BSC (n=98)	
	All grades n (%)	**Grade 3 or 4 n (%)**	**All grades n (%)**	**Grade 3 or 4 n (%)**
All AEs	200 (99.0)	140 (69.3)	87 (88.8)	28 (28.6)
Stomatitis*	111 (55.0)	15 (7.4)	19 (19.4)	0 (0.0)
Diarrhoea	83 (41.1)	18 (8.9)	30 (30.6)	2 (2.0)
Peripheral oedema	78 (38.6)	6 (3.0)	6 (6.1)	1 (1.0)
Fatigue	75 (37.1)	9 (4.5)	35 (35.7)	1 (1.0)
Rash	61 (30.2)	1 (0.5)	9 (9.2)	0 (0.0)
Cough	55 (27.2)	0 (0.0)	20 (20.4)	0 (0.0)
Nausea	53 (26.2)	6 (3.0)	17 (17.3)	1 (1.0)
Asthenia	47 (23.3)	5 (2.5)	8 (8.2)	0 (0.0)
Pyrexia	47 (23.3)	4 (2.0)	8 (8.2)	0 (0.0)
Anaemia	45 (22.3)	11 (5.4)	9 (9.2)	2 (2.0)
Decreased appetite	45 (22.3)	2 (1.0)	17 (17.3)	1 (1.0)
Weight decreased	44 (21.8)	3 (1.5)	11 (11.2)	1 (1.0)
Dyspnoea	40 (19.8)	5 (2.5)	11 (11.2)	2 (2.0)
Abdominal pain	39 (19.3)	10 (5.0)	19 (19.4)	5 (5.1)
Dysguesia	37 (18.3)	1 (0.5)	4 (4.1)	0 (0.0)
Pruritis	35 (17.3)	1 (0.5)	9 (9.2)	0 (0.0)
Vomiting	30 (14.9)	7 (3.5)	12 (12.2)	2 (2.0)
Back pain	27 (13.4)	3 (1.5)	14 (14.3)	0 (0.0)
Pneumonitis	27 (13.4)	3 (1.5)	2 (2.0)	0 (0.0)
Epistaxis	26 (12.9)	1 (0.5)	3 (3.1)	0 (0.0)
Headache	25 (12.4)	0 (0.0)	15 (15.3)	0 (0.0)
Arthralgia	24 (11.9)	1 (0.5)	8 (8.2)	0 (0.0)
Hyperglycaemia	24 (11.9)	9 (4.5)	3 (3.1)	0 (0.0)
Hypertension	24 (11.9)	8 (4.0)	8 (8.2)	3 (3.1)
Urinary tract infection	22 (10.9)	4 (2.0)	5 (5.1)	0 (0.0)
Constipation	21 (10.4)	0 (0.0)	18 (18.4)	0 (0.0)
Upper abdominal pain	19 (9.4)	0 (0.0)	11 (11.2)	0 (0.0)

*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

†All types of infections are included.
‡Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.
AE: adverse event, BSC: best supportive care.
Source: Novartis company submission

Table 167: Most common (≥ 5% sunitinib-treated subjects) treatment-related adverse events A6181111

Number (%) of subjects with preferred term AE	Sunitinib (N = 83)		Placebo (N = 82)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhoea	44 (53.0)	4 (4.8)	25 (30.5)	1 (1.2)
Nausea	32 (38.6)	1 (1.2)	18 (22.0)	0 (0.0)
Asthenia	26 (31.3)	3 (3.6)	18 (22.0)	2 (2.4)
Fatigue	24 (28.9)	4 (4.8)	14 (17.1)	3 (3.7)
Hair colour changes	24 (28.9)	1 (1.2)	1 (1.2)	0 (0.0)
Neutropenia	24 (28.9)	10 (12.0)	3 (3.7)	0 (0.0)
Vomiting	21 (25.3)	0 (0.0)	14 (17.1)	0 (0.0)
Hypertension	19 (22.9)	8 (9.6)	3 (3.7)	0 (0.0)
Palmar-plantar erythordysaesthesia syndrome	19 (22.9)	5 (6.0)	2 (2.4)	0 (0.0)
Stomatitis	18 (21.7)	3 (3.6)	2 (2.4)	0 (0.0)
Anorexia	17 (20.5)	2 (2.4)	11 (13.4)	0 (0.0)
Dysgeusia	16 (19.3)	0 (0.0)	3 (3.7)	0 (0.0)
Epistaxis	16 (19.3)	1 (1.2)	2 (2.4)	0 (0.0)
Thrombocytopenia	14 (16.9)	3 (3.6)	4 (4.9)	0 (0.0)
Mucosal inflammation	13 (15.7)	1 (1.2)	6 (7.3)	0 (0.0)
Rash	13 (15.7)	0 (0.0)	4 (4.9)	0 (0.0)
Abdominal pain	12 (14.5)	1 (1.2)	10 (12.2)	3 (3.7)
Dyspepsia	12 (14.5)	0 (0.0)	1 (1.2)	0 (0.0)
Weight decreased	11 (13.3)	1 (1.2)	6 (7.3)	0 (0.0)
Dry skin	11 (13.3)	0 (0.0)	9 (11.0)	0 (0.0)
Headache	10 (12.0)	0 (0.0)	5 (6.1)	1 (1.2)
Constipation	8 (9.6)	0 (0.0)	8 (9.8)	1 (1.2)
Leukopenia	8 (9.6)	5 (6.0)	1 (1.2)	0 (0.0)
Nail disorder	8 (9.6)	0 (0.0)	1 (1.2)	0 (0.0)
Dry mouth	7 (8.4)	0 (0.0)	4 (4.9)	0 (0.0)
Erythema	7 (8.4)	0 (0.0)	3 (3.7)	0 (0.0)
Insomnia	7 (8.4)	0 (0.0)	5 (6.1)	0 (0.0)
Pain in extremity	7 (8.4)	0 (0.0)	3 (3.7)	0 (0.0)
Abdominal pain upper	6 (7.2)	1 (1.2)	1 (1.2)	0 (0.0)
Arthralgia	6 (7.2)	0 (0.0)	2 (2.4)	0 (0.0)
Dyspnoea	6 (7.2)	1 (1.2)	8 (9.8)	0 (0.0)
Yellow skin	6 (7.2)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	5 (6.0)	0 (0.0)	1 (1.2)	0 (0.0)
Aphthous stomatitis	5 (6.0)	0 (0.0)	2 (2.4)	0 (0.0)
Decreased appetite	5 (6.0)	0 (0.0)	3 (3.7)	0 (0.0)
Dizziness	5 (6.0)	1 (1.2)	3 (3.7)	0 (0.0)
Eyelid oedema	5 (6.0)	1 (1.2)	0 (0.0)	0 (0.0)
Flatulence	5 (6.0)	0 (0.0)	1 (1.2)	0 (0.0)
Gingival bleeding	5 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	5 (6.0)	0 (0.0)	1 (1.2)	0 (0.0)

Source: Pfizer Company Submission – their source being the CSR

Table 168: Drug-related adverse events in ≥10% in any treatment group (safety set) RADIANT-3

	Everolimus plus BSC (n=204) n events (%)		Placebo plus BSC (n=203) n events (%)		Open-label everolimus (n=225) n events (%)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Anaemia	34 (16.7)	10 (4.9)	7 (3.4)	0	32 (14.2)	0

Asthenia	26 (12.7)	2 (1.0)	17 (8.4)	2 (1.0)	22 (9.8)	2 (<1)
Cough	26 (12.7)	0	3 (1.5)	0	22 (9.8)	0
Decreased appetite	41 (20.1)	0	14 (6.9)	2 (1.0)	35 (15.6)	0
Diarrhoea	69 (33.8)	7 (3.4)	21 (10.3)	0	59 (26.2)	4 (1.8)
Dry skin	21 (10.3)	0	9 (4.4)	0	18 (8.0)	2 (<1)
Dysgeusia	34 (16.7)	0	8 (3.9)	0	30 (13.3)	0
Epistaxis	37 (18.1)	0	0	0	34 (15.1)	5 (2.2)
Fatigue	66 (32.4)	3 (1.5)	29 (14.3)	1 (<1)	44 (19.6)	7 (3.1)
Headache	39 (19.1)	0	13 (6.4)	0	35 (15.6)	8 (3.6)
Hyperglycaemia	29 (14.2)	12 (5.9)	10 (4.9)	5 (2.5)	23 (10.2)	7 (3.1)
Infections[b]	57 (27.9)	5 (2.5)	15 (7.4)	1 (0.5)	62 (27.6)	11 (4.9)
Nail Disorder	25 (12.3)	1 (<1)	2 (1.0)	0	22 (9.8)	0
Nausea	42 (20.6)	2 (1.0)	37 (18.2)	0	38 (16.9)	0
Non-infectious pneumonitis[c]	34 (16.7)	5 (2.5)	0	0	23 (10.2)	1 (<1)
Oedema peripheral	44 (21.6)	1 (<1)	6 (3.0)	0	42 (18.7)	1 (<1)
Pruritus	31 (15.2)	0	18 (8.9)	0	26 (11.6)	0
Pyrexia	24 (11.8)	0	0	0	21 (9.8)	4 (1.8)
Rash	98 (48.0)	1 (<1)	21 (10.3)	0	84 (37.3)	3 (1.3)
Stomatitis[a]	137 (67.2)	15 (7.4)	36 (17.7)	0	134 (59.6)	8 (3.6)
Thrombocytopenia	26 (12.7)	8 (3.9)	1 (<1)	0	22 (9.8)	10 (4.4)
Vomiting	30 (14.7)	0	13 (6.4)	0	24 (10.7)	0
Weight decreased	34 (16.7)	0	11 (5.4)	0	31 (13.8)	0

Notes: a,, included in this category are stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration; b, all types of infections are included; c, included in this category are pneumonitis, interstitial lung disease, lung infiltration and pulmonary fibrosis

Source: Yao et al., J of Clin Oncol, 2016 (RADIANT-3)

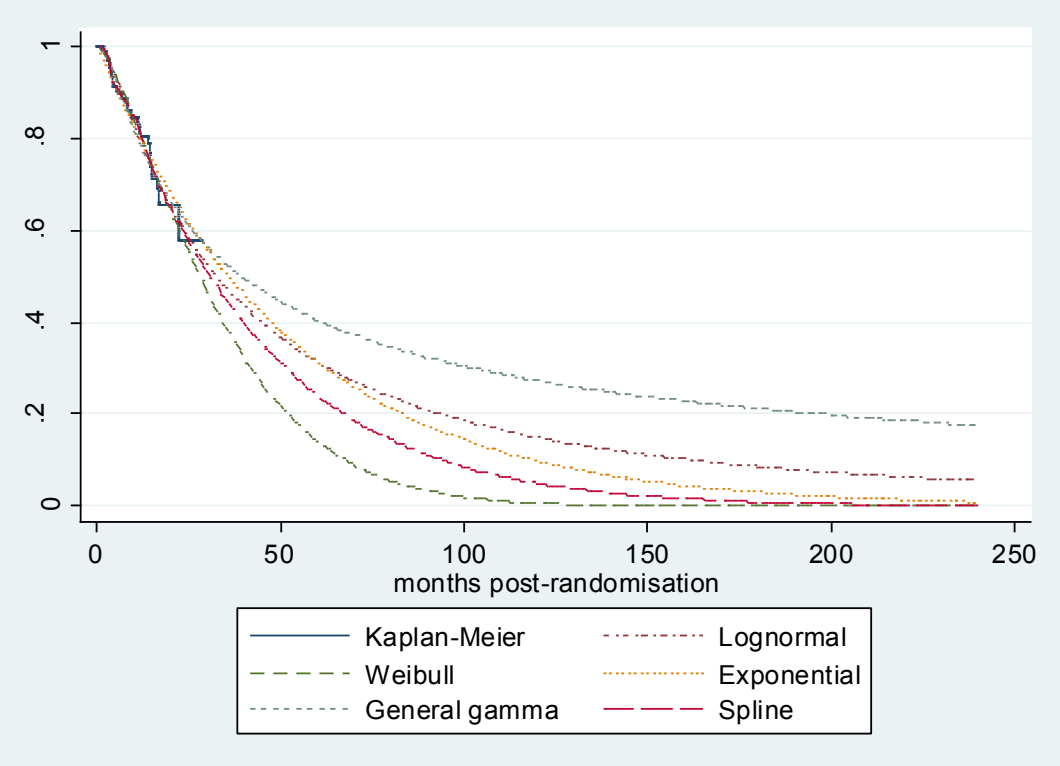
Appendix 6. PFS and OS extrapolation of 177Lu-DOTATATE in NETTER-1

A6.1 177Lu-DOTATATE in NETTER-1 (AAA submission to NICE)

A6.1.1 Progression Free Survival

While the models did not differ in their goodness of fit to the PFS outcomes of 177Lu-DOTATE in NETTER-1 (Table 117), the Weibull model exhibited the closest fit to its associated risk of death or disease progression (Figure 76). The exponential fell in the middle of the range of PFS rates of the candidate distributions (Figure 62).

Figure 62 PFS in 177Lu-DOTATE arm of NETTER-1: Extrapolation to 20 years



The parameter of the PFS distribution was adjusted for the difference in expected PFS between the Octreotide 60mg arm of the NETTER-1 and the placebo arm of RADIANT-4 (midgut population), following the method described above for the analysis of pNETs (Section 7.1.5). This indirect comparative analysis implicitly assumes that these two arms would be expected to produce the same PFS and OS outcomes, and are thus subject to the reservations discussed in section 7.1.5. Restricting the mean area under the Kaplan-Meier curve of the placebo arm in RADIANT-4 to the maximum length of follow-up of OS in the octreotide 60 mg arm in NETTER-1 (which had a shorter follow-up than RADIANT-4), that is, 25.18 months, led to a restricted mean PFS 9.97 months in the placebo arm of RADIANT-4 and 13.23 months with octreotide 60 in NETTER-1. In terms of Eq. 1 above, the adjusted hazard and exponential survival functions with 177Lu-DOTATATE are

$$\hat{\lambda} = \left(\frac{1}{0.019341} * \frac{13.23}{9.97}\right)^{-1} = 0.014576$$

and

$S(\hat{\lambda}) = exp^{-0.014576t}$.

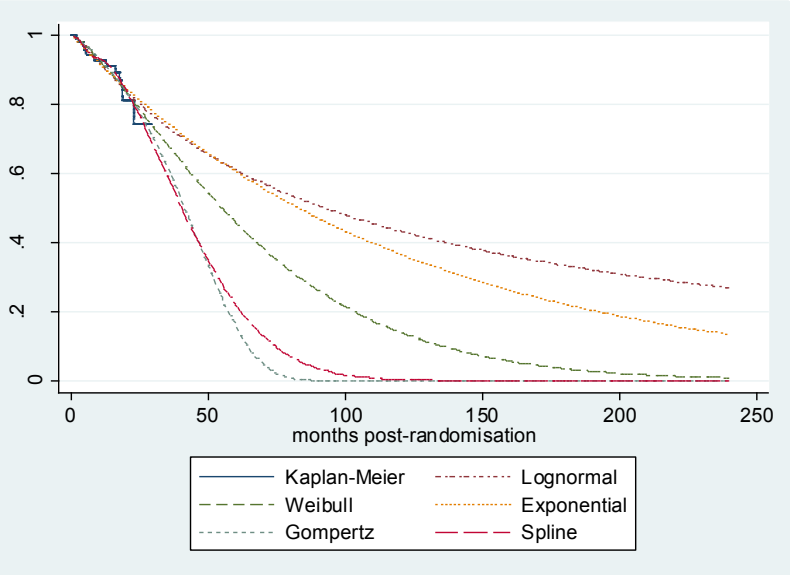
In scenario analyses, the log-normal distribution was used instead of the exponential to model PFS experience of patients in the placebo arm, given the results presented below.

The OS curve of the lutetium arm of NETTER-1 adopted for the base case on the basis of the diagnostic results was the exponential (Table 117).The parametric OS curve of lutetium was adjusted for the 9.1% shorter expected OS in the octreotide 60mg arm of NETTER-1 than that in the placebo arm of RADIANT-4 (midgut population), using the methods described above for pNETs (section 7.1.5.)

A6.1.2 Overall Survival

The 15-year OS rate with 177Lu-DOTATATE with the exponential distribution is 22%. After adjusting for the differences in the control arms of NETTER-1 and RADIANT-4 (midgut only), this rate becomes 25%. In contrast, the respective unadjusted rate for the Weibull function (Figure 63) is 3%. In any case, the available OS data from NETTER-1 is extremely immature, making the comparison of 177Lu-DOTATATE with everolimus very uncertain.

Figure 63: OS in lutetium arm of NETTER-1: Extrapolation to 20 years



Appendix 7. Visual fit to (instantaneous) survival event risk

Figure 64: Everolimus arm in RADIANT-3: Observed and predicted PFS hazard functions

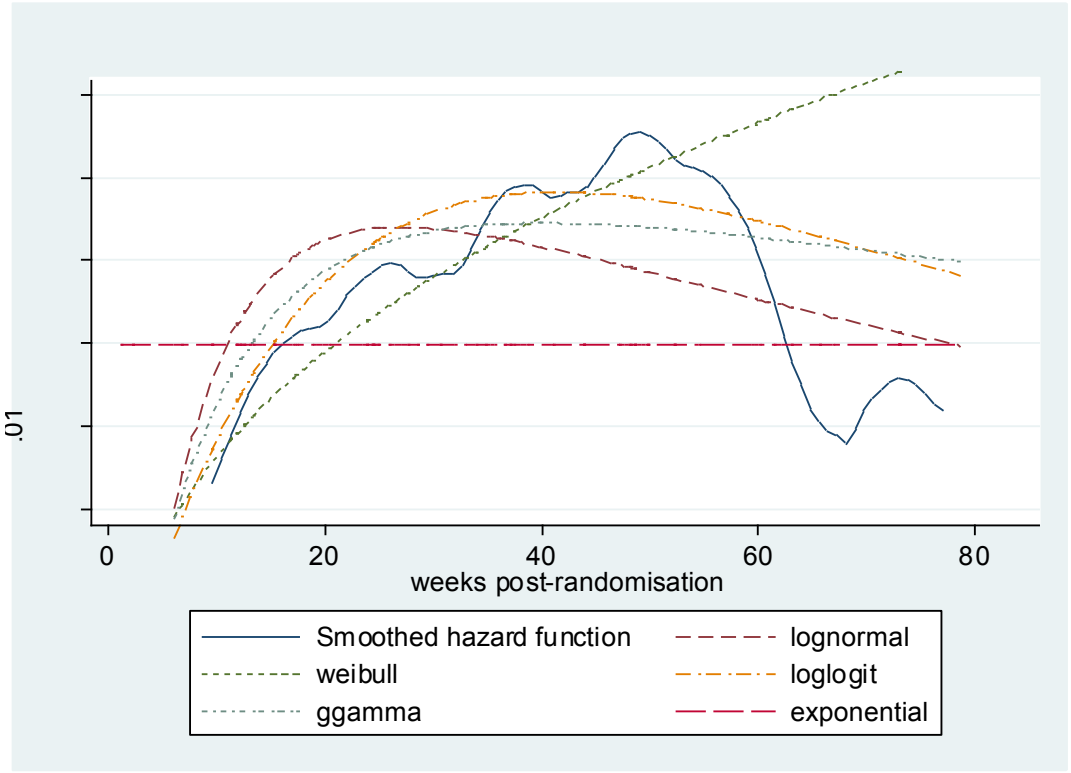


Figure 65: Placebo arm: Observed and predicted PFS hazard functions by the best fitting models

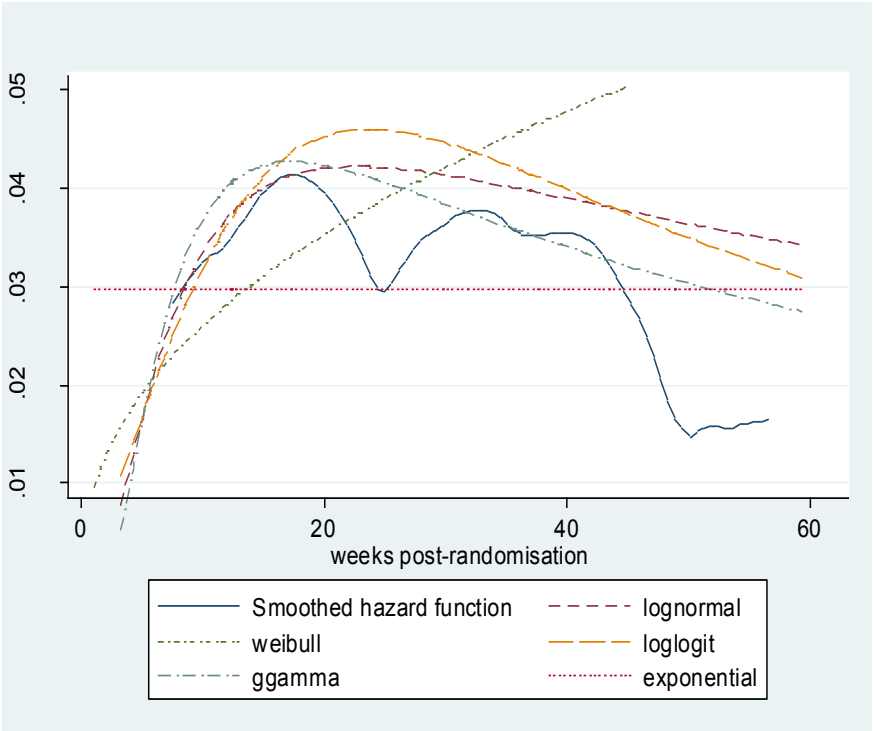


Figure 66: Sunitinib arm: Observed and predicted PFS hazard functions by the best fitting models

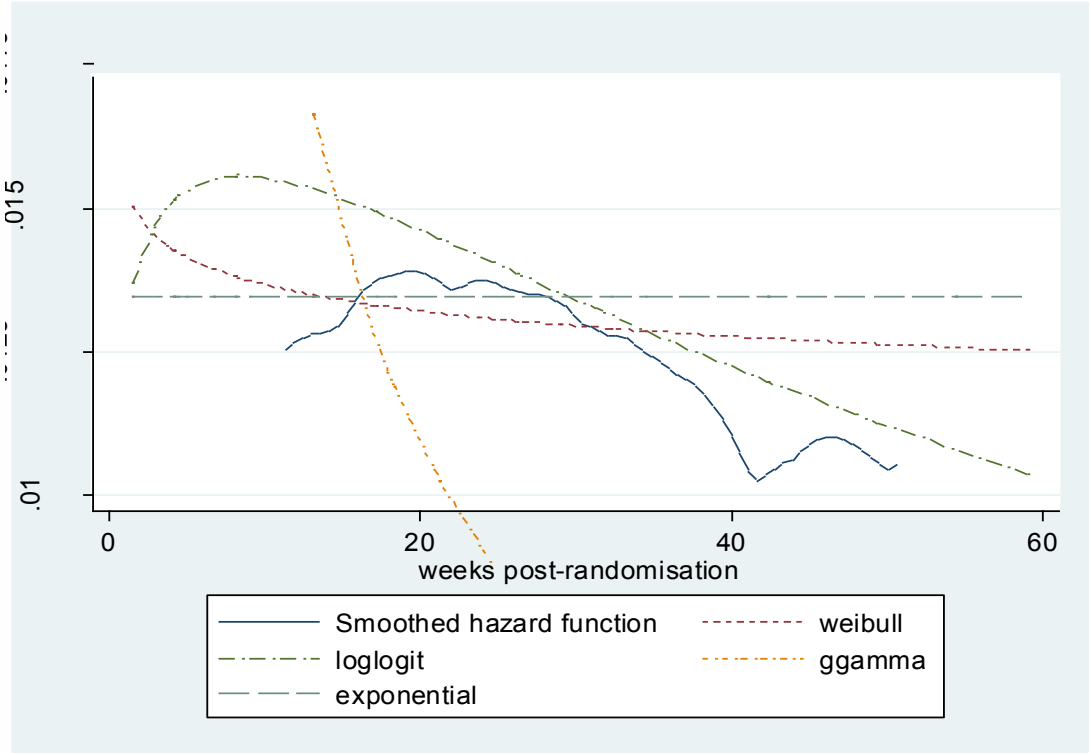


Figure 67: Everolimus arm: Observed and predicted PFS hazard functions by the best fitting models

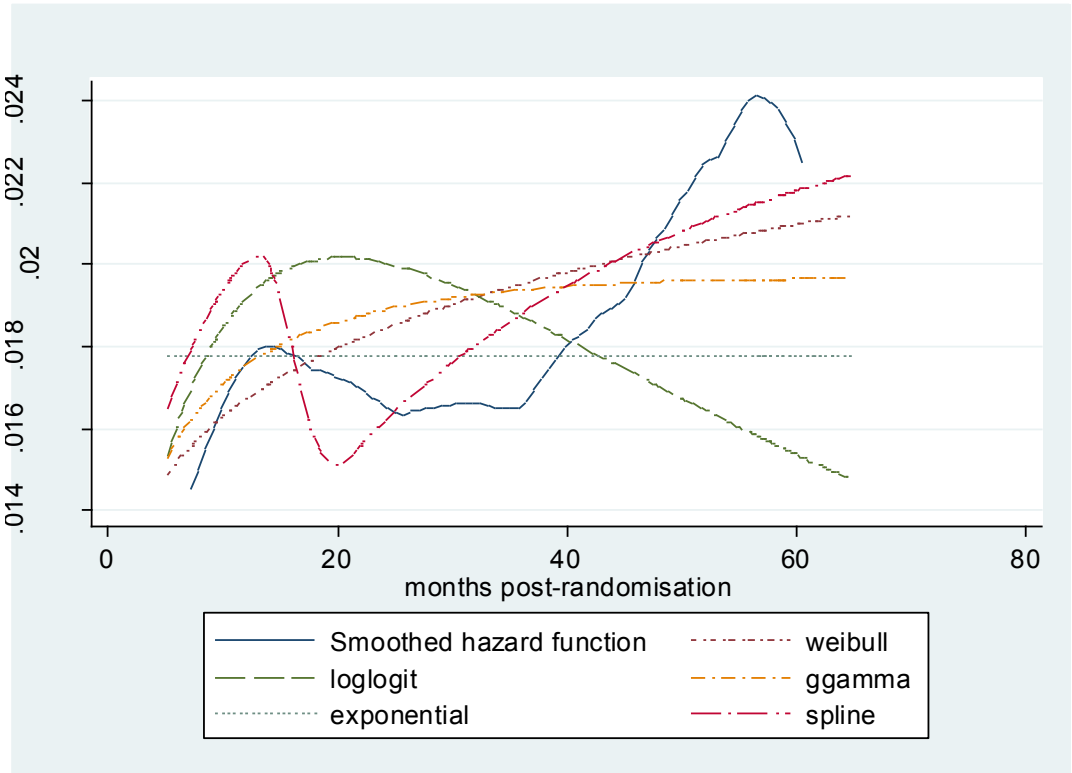


Figure 68: Placebo arm in RADIANT-3: Observed and predicted OS hazard functions by the best fitting models

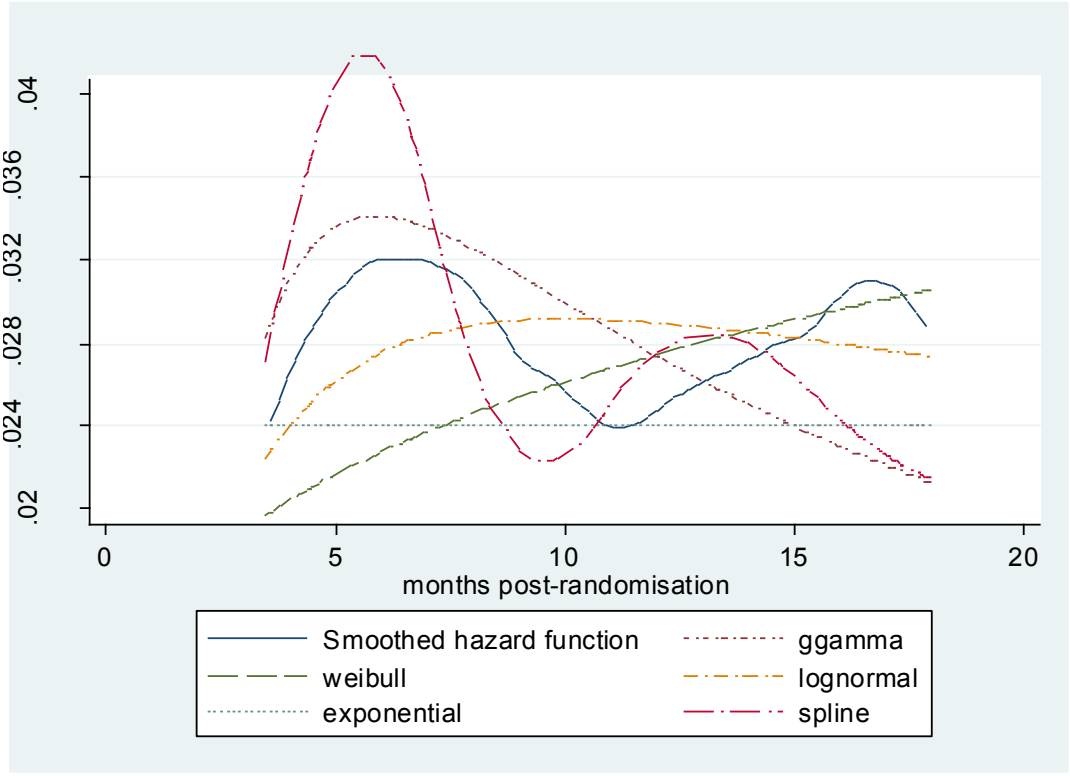


Figure 69: Sunitinib arm in A6181111: Observed and predicted OS hazard functions by the best fitting models

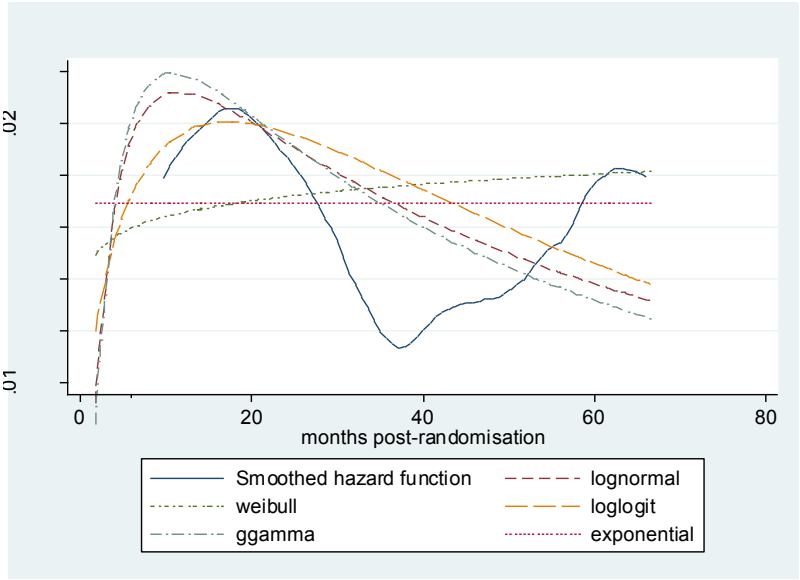


Figure 70: Everolimus arm in RADIANT-4: Observed and predicted PFS hazard functions by the best fitting models

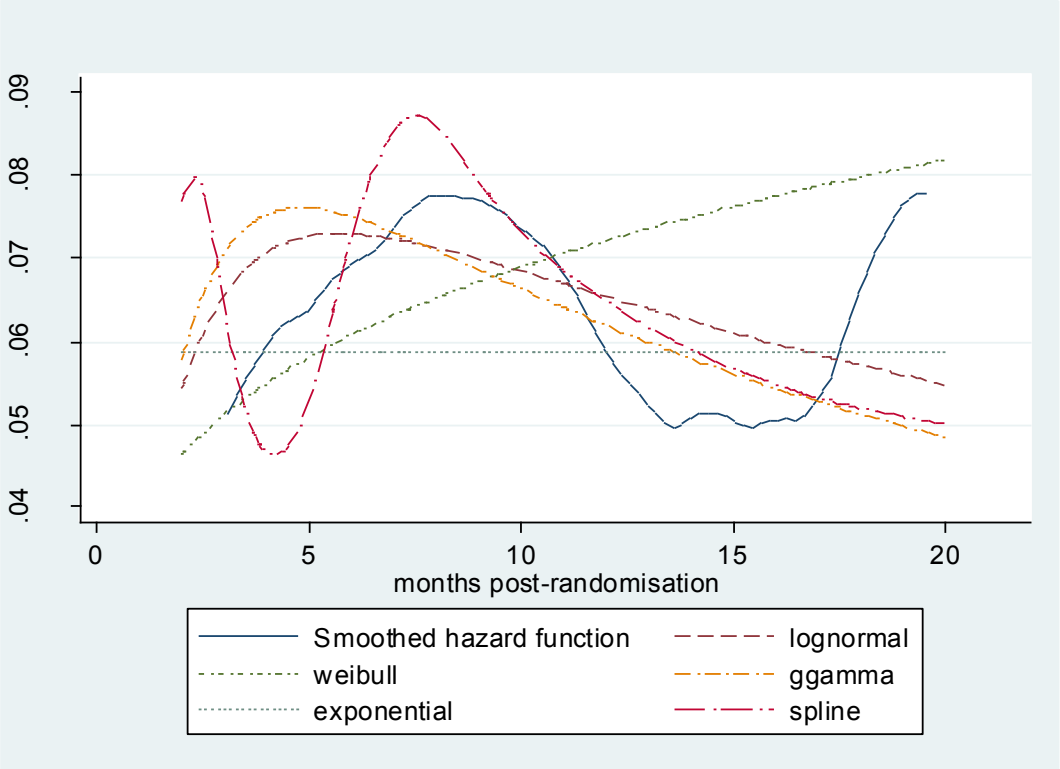


Figure 71: Placebo arm in RADIANT-4: Observed and predicted PFS hazard functions by the best fitting models

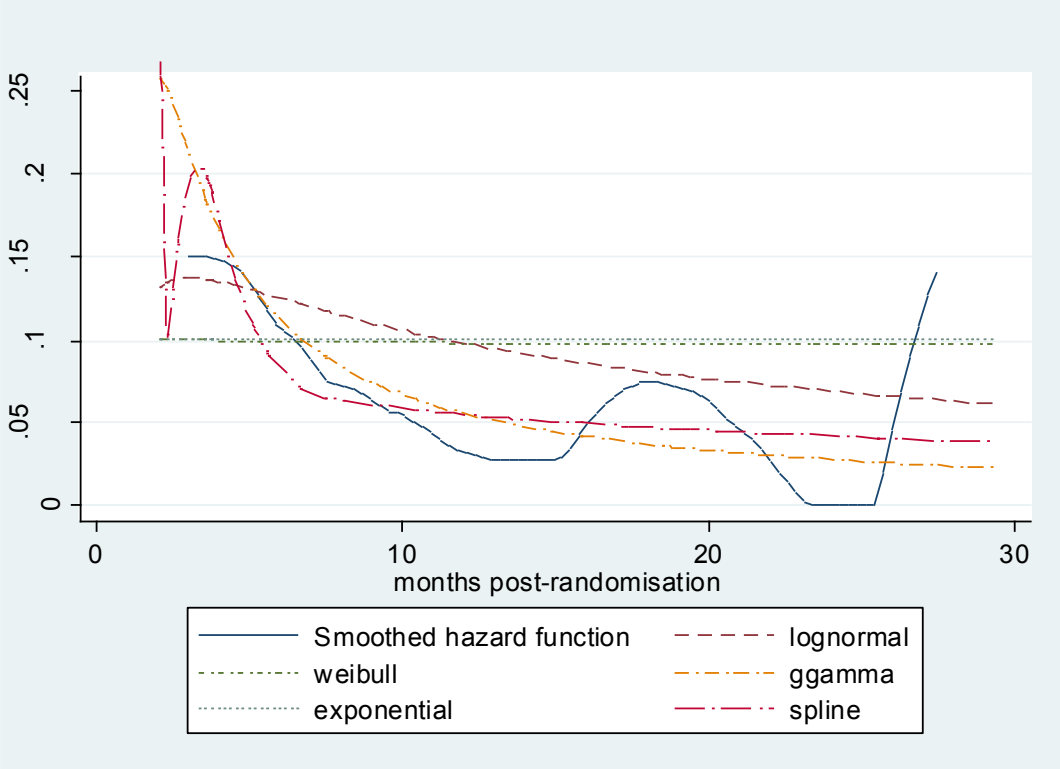


Figure 72: Everolimus arm in RADIANT-4: Observed and predicted OS hazard functions by the best fitting models

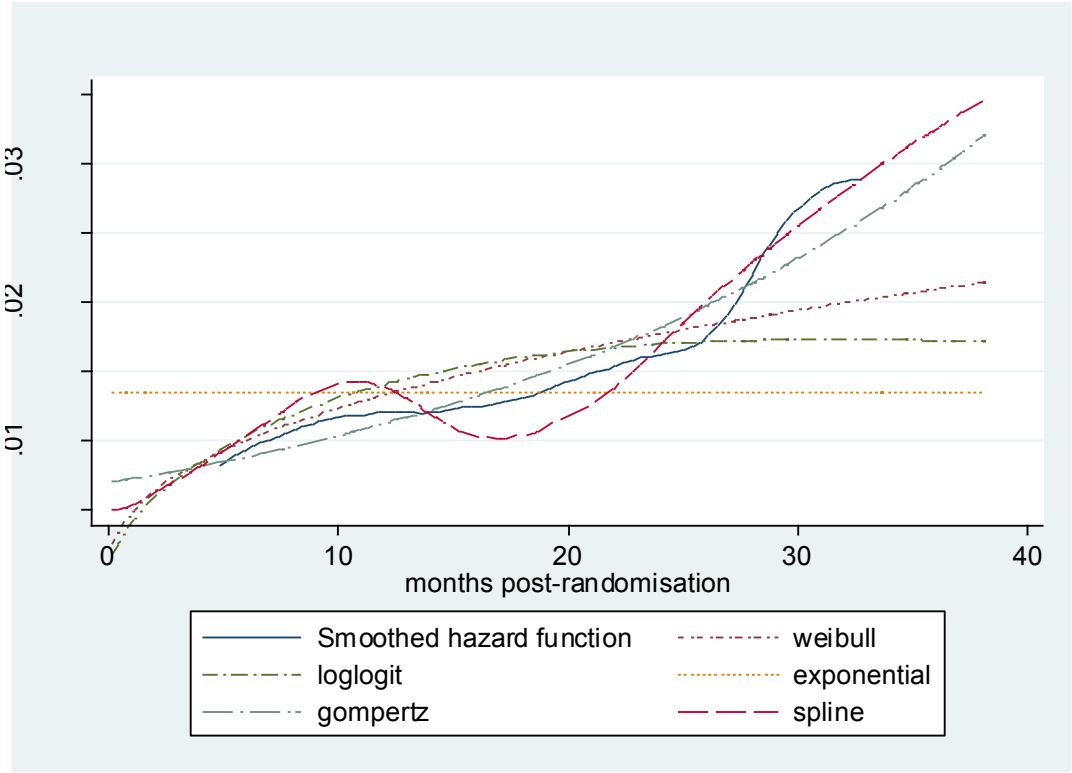


Figure 73: Placebo arm in RADIANT-4: Observed and predicted OS hazard functions by the best fitting models

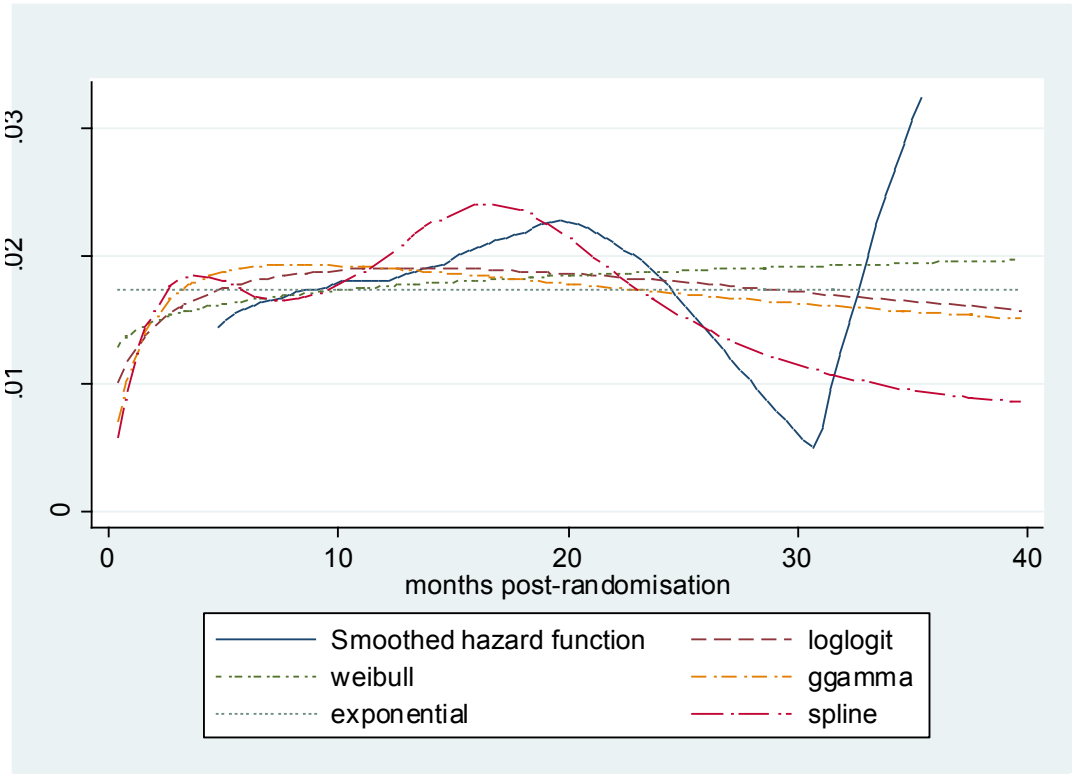


Figure 74: Everolimus arm in RADIANT-4 (midgut): Observed and predicted PFS hazard functions by the best fitting models

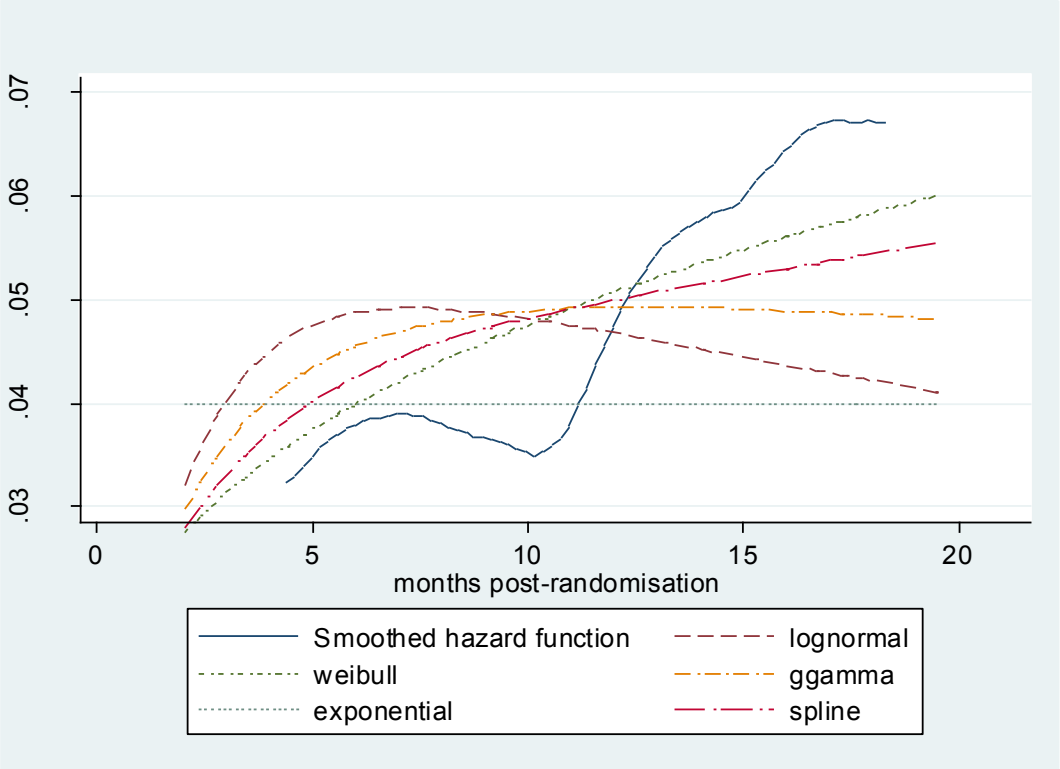


Figure 75: Placebo arm in RADIANT-4 (midgut): Observed and predicted PFS hazard functions by the best fitting models

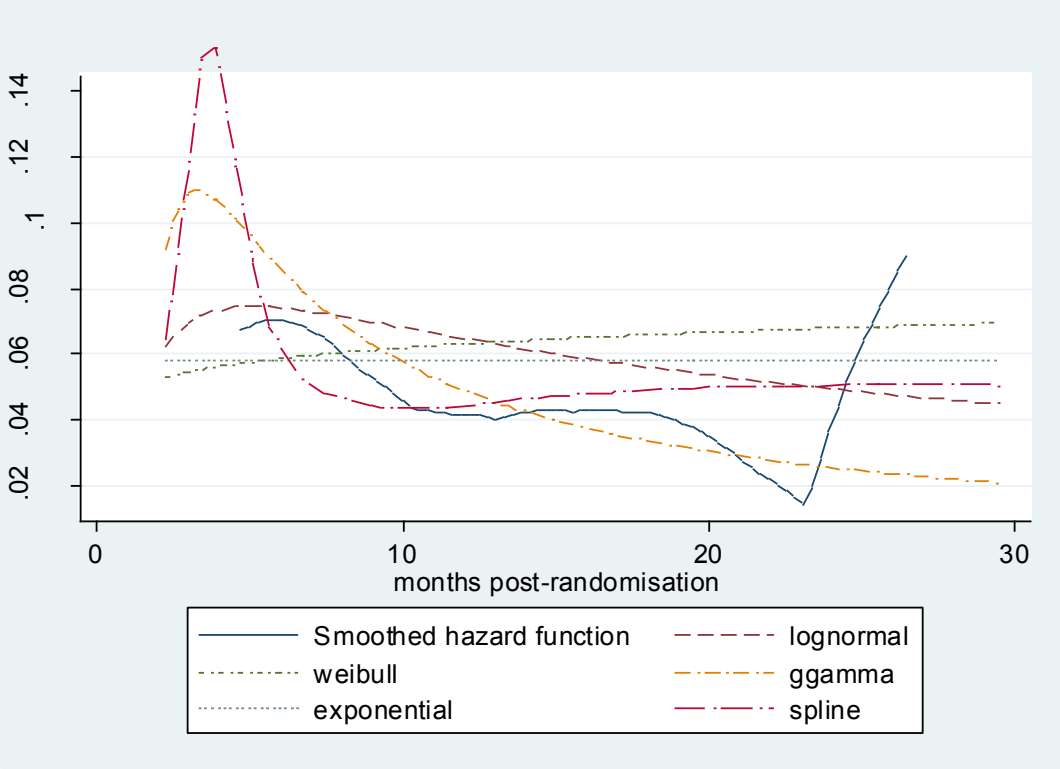


Figure 76: Lutetium arm in NETTER-1: Observed and predicted PFS hazard functions by the best fitting models

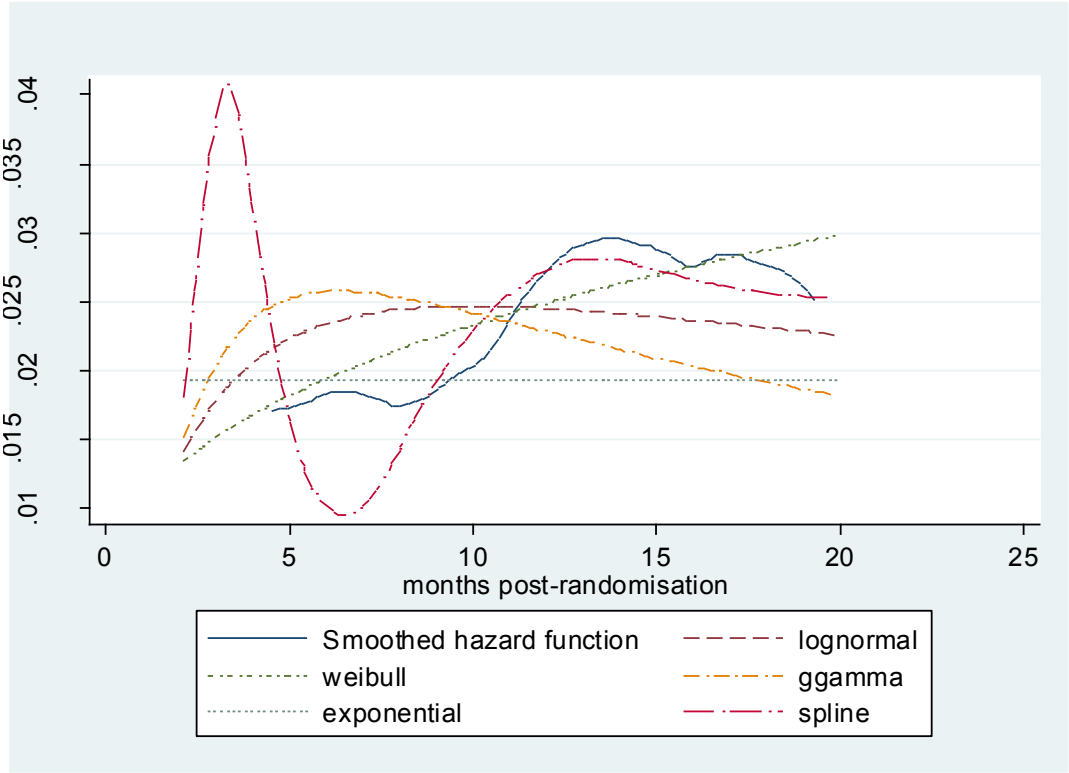
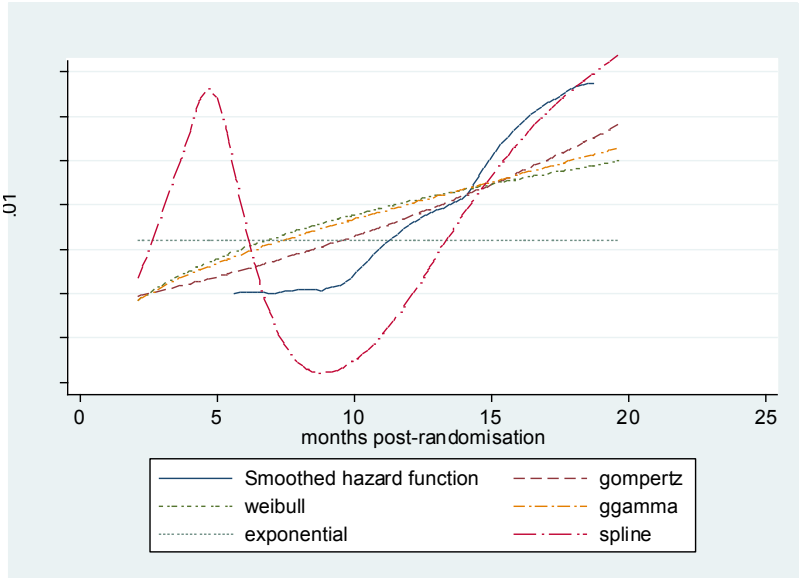


Figure 77: Lutetium arm in NETTER-1: Observed and predicted OS hazard functions by the best fitting models



Appendix 8. Reference Case

Table 169: Summary of reference case characteristics of industry submissions

Element of health technology assessment	Reference case	Novartis pNETs	Novartis GI & Lung	AAA pNETs	AAA GI
Defining the decision problem	The scope developed by NICE	Yes	Yes	Yes	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes	Yes	Yes	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes	Yes	Yes	Yes
Perspective on costs	NHS and PSS	Yes	Yes	Yes	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes	Yes	Yes	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	Yes	Yes	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes	Yes	Yes	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs.The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes	Yes	Yes	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No	Yes	Yes	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes	Yes	Yes	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	Yes	Yes	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	Yes	Yes	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes	Yes	Yes	Yes

Key: NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.

Appendix 9. Adverse Events Indirect Comparison

Event	RADIANT-3								A6181111								Eve vs. PBO	Sun vs. PBO	Bucher IC
	N		n		%		Odds*		N		n		%		Odds		OR	OR	OR
	EVE	PBO	EVE	PBO	EVE	PBO	EVE	PBO	SUN	PBO	SUN	PBO	SUN	PBO	SUN	PBO			
Neutropenia	204	203	0	0	0.25%	0.25%	0.002	0.002	83	82	10	0	12.70%	0.60%	0.145	0.006	1.00	23.61	23.723
Hypertension	204	203	0	0	0.25%	0.25%	0.002	0.002	83	82	8	0	10.20%	0.60%	0.114	0.006	1.00	18.60	18.689
PPE syndrome	204	203	0	0	0.25%	0.25%	0.002	0.002	83	82	5	0	6.60%	0.60%	0.071	0.006	1.00	11.57	11.625
Leukopenia	204	203	0	0	0.25%	0.25%	0.002	0.002	83	82	5	0	6.60%	0.60%	0.071	0.006	1.00	11.57	11.625
Diarrhoea	204	203	7	1 1	3.43%	0.49%	0.036	0.005	83	82	4	1	4.80%	1.20%	0.051	0.012	7.18	4.10	0.571
Stomatitis	204	203	14 2	0	7.11%	0.25%	0.077	0.002	83	82	3	0	4.20%	0.60%	0.044	0.006	30.99	7.18	0.232
Thrombocytopenia	204	203	8	0	4.17%	0.25%	0.043	0.002	83	82	3	0	4.20%	0.60%	0.044	0.006	17.61	7.18	0.408
Anaemia	204	203	12 3	0	6.13%	0.25%	0.065	0.002	83	82	0	0	0.60%	0.60%	0.006	0.006	26.44	0.99	0.037
Hyperglycaemia	204	203	11 4	4 5	5.39%	1.97%	0.057	0.02	83	82	0	0	0.60%	0.60%	0.006	0.006	2.84	0.99	0.348
Fatigue	204	203	5 6	1	2.45%	0.49%	0.025	0.005	83	82	4 8	3 9	4.80%	3.70%	0.051	0.038	5.08	1.33	0.263
Infections	204	203	5	1	2.45%	0.49%	0.025	0.005	83	82	0	0	0.60%	0.60%	0.006	0.006	5.08	0.99	0.195
Pneumonitis	204	203	5	0	2.70%	0.25%	0.028	0.002	83	82	0	0	0.60%	0.60%	0.006	0.006	11.22	0.99	0.088
Nausea	204	203	5 7	0	2.70%	0.25%	0.028	0.002	83	82	1 10	0	1.80%	0.60%	0.018	0.006	11.22	3.00	0.267
Sum	204	203	72	7	35.30%	3.45%	0.545	0.036	83	82	4311	4 12	51.80%	4.90%	1.075	0.051	15.27	20.96	1.372 13

Key: EVE, everolimus; PBO, placebo; PPE, palmar-plantar erythrodysesthesia SUN, sunitinib; N total number of participants; n, number of events; vs, verses;

Notes: 1. Latest figure is 0 (Singh et al. 2016). 2. Latest figure is 15 (Singh et al. 2016). 3. Latest figure is 10 (Singh et al. 2016). 4. Latest figure is 12 (Singh et al. 2016). 5. Latest figure is 5 (Singh et al. 2016). 6. Latest figure is 3 (Singh et al. 2016). 7. Latest figure is 2 (Singh et al. 2016). 8. Updated with data from Pfizer submission; Novartis submission used a figure of 0. 9. Updated with data from Pfizer submission; Novartis submission used a figure of 0. 10. Updated with data from Pfizer submission; Novartis submission used a figure of 0. 11. Updated with data from Pfizer submission; Novartis submission used a figure of 38. 12. Updated with data from Pfizer submission; Novartis submission used a figure of 1. 13. Updated with data from Pfizer submission; Novartis submission used a figure of 4.479.

Appendix 10. Mapping FACT-G to EQ-5D

A10.1 The best-fitting algorithm by Longworth et al. (2014)

Summary statistics and model performance test	Mobility		Self-care		Usual activities		Pain		Anxiety/depression	
	Some problems	Extreme problems	Some problems	Extreme problems	Some problems	Extreme problems	Some problems	Extreme problems	Some problems	Extreme problems
Physical	−0.111	N/A	−0.100	−0.244	−0.237	−0.285	−0.206	−0.319		
	(0.023)***		(0.024)***	(-2.191)	(0.044)***	(0.056)***	(0.030)***	(0.051)***		
Emotional		N/A							−0.331	−0.607
									(0.036)***	(5.147)
Functional	−0.074	N/A	−0.104	−0.307	−0.124	−0.266	−0.057	0.01	-0.047	−0.197
	(0.020)***		(0.027)***	(-6.663)	(0.030)***	(0.053)***	(0.023)*	(0.053)	(0.021)*	(1.465)
Constant	3.089	N/A	1.633	2.017	7.737	8.239	5.499	3.51	6.773	8.839
	(0.418)***		(0.427)***	(60.731)	(0.895)***	(1.210)***	(0.574)***	(1.045)**	(0.660)***	(47.729)
Log-likelihood	−310.22		−189.70		−338.3		−346.92		−302.08	
Pseudo R2	0.132		0.151		0.263		0.191		0.263	
AIC	626.44		391.39		688.27		705.84		616.16	
BIC	639.26		417.03		713.91		731.48		641.8	

* Statistically significant at the 10% level

** Statistically significant at the 5% level

*** Statistically significant at the 1% level

N/A, not applicable as there is no one with extreme problems for mobility

Values in brackets are the standard errors of regression coefficients

A10.2 Linearised version of the best-fitting mapping algorithm by Longworth et al., (2014)

The best fitting algorithm for FACT-G estimated by Longworth and colleagues (Longworth et al. 2014) maps the domain scores of that tool into each dimension of EQ-5D-3L by fitting a multinomial logit model to response data for each dimension separately.

The EQ-5D index score equation (Dolan 1997) is

EQ-5D Index= 1- 0.081* D1 - 0.069 * Mob_m - 0.314*Mob_s - 0.104*$Selfcare_m$ - 0.214*$Selfcare_s$ - 0.036* $Usualact_m$ - 0.094* $Usualact_s$ - 0.123*$Pain_m$ - 0.386*$Pain_s$ - 0.071*Anx_m - 0.236*Anx_s - 0.269*D2

Eq. 1

where D1 equals 1 if the person had any problems in any dimension, and D2 if he had any severe problems in any dimension; Mob is a binary indicator of reporting problems in the mobility dimension; Self-care a binary indicator of problems in self-care; Pain a binary indicator of problems in Pain/Discomfort; Anx is an indicator of problems in Axiety/Depression. Separate indicators are used for moderate and severe problems, denoted by subscripts m and s respectively.

The mapping algorithm substitutes the binary indicators by the corresponding predicted probabilities of reporting the problem in question. Since in EQ-5D-3L there is two levels of problem that a person can choose as response, the politomous regression model is required to calculate the predicted probabilities of reporting a given level of problem (moderate or severe) for a given dimension. As for the predicted probabilities of reporting any problems across all dimensions (corresponding to D1) and of reporting any severe problems across all dimensions, these could be obtained from running separate regression analyses for dichotomous variables or it may be simply obtained from assuming that the probabilities of reporting problems in a dimension is independent of doing so in any other dimension. In the latter case, the predicted probability of reporting any severe problems (D2=1), i.e. is simply equal to

$$\widehat{D2} = 1 - \left(1 - \widehat{Mob_s}\right) * \left(1 - \widehat{Selfcare_s}\right) * \left(1 - \widehat{Usualact_s}\right) * \left(1 - \widehat{Pain_s}\right) * \left(1 - \widehat{Anxiety_s}\right)$$

Eq. 2

where the hat symbols denote predicted probabilities that the respective variable takes thevalue of 1. The value of $\widehat{D1}$ is similarly obtained with the difference that the expressions within brackets in Eq. 2 now include the predicted probability of reporting moderate problems:

$$\widehat{D1} = 1 - \left(1 - \widehat{Mob_s} - \widehat{Mob_m}\right) * \left(1 - \widehat{Selfcare_s} - \widehat{Selfcare_m}\right) * \left(1 - \widehat{Usualact_s} - \widehat{Usualact_m}\right) * \left(1 - \widehat{Pain_s} - Pain_m\right) * \left(1 - \widehat{Anxiety_s} - \widehat{Anxiety_m}\right)$$

Eq. 3.

The Longworth response mapping algorithm (Longworth et al. 2014, p. 220) is then used to estimate the predicted probabilities of D1, D2 and the ten probabilities of reporting problem levels for the EQ-5D dimensions on the right hand side of Eq. 2 and Eq. 3. In the case of $\widehat{Mob_m}$ this is obtained by

$$\widehat{Mob_{mj}} = P_{m2j}(PW_j, EW_j, FW_j) \equiv P(D_{mj} = 2 | PW_j, EW_j, FW_j) = \frac{\exp(\alpha_2 + \beta_{m2} PW_j + \gamma_{m2} EW_j + \delta_{m2} FW_j)}{1 + \exp(\alpha_2 + \beta_{m2} PW_j + \gamma_{m2} EW_j + \delta_{m2} FW_j) + \exp(\alpha_3 + \beta_{m3} PW_j + \gamma_{m3} EW_j + \delta_{m3} FW_j)}$$

Eq. 4.

where P_{m2j} is the probability of a person j responding 'moderate problems' for EQ-5D dimension m (mobility) and the greek symbols represent coefficients estimated by Longworth and colleagues from a multinomial regression of a dependent variable D, taking the value of 1 for 'no problems', 2 for 'moderate' problems and 3 for 'severe' problems, against the three FACT-G domains of Physical (PW), emotional (EW) and Functional (FW) well-being. The predicted probability of choosing level 3 for the dimension m is given by the same formula but with the subscripts 2 and 3 reversed. In the same way predicted probabilities for the other eight domain predictions in Eq. 2 and Eq. 3 are obtained, based on the coefficients of the multinomial regression for the respective dimension.

With individual patient data on FACT-G available, the predicted probabilities for Eq. 2 and Eq. 3, which are then used to derive EQ-5D utilities using Eq. 1 are obtained by first substituting the FACT-G scores for each person in Eq. 4, and then taking the mean of those predictions across the whole sample. Repeating this process using the corresponding equation of P for 'severe' mobility and all other eight possible responses, provides the required probabilities to obtain mapped FCAT_G data into EQ-5D utilities using Eq. 1.

When, as is common in multiple technology assessment reviews or economic modelling studies, only aggregate data are available in the form of mean FACT-G scores for a sample of patients, one cannot directly use those values in Eq. 4 and the other nine multinomial equations for obtaining the required predicted response probabilities because their nonlinear form means the resulting predictions will have systematic errors. To solve this issue it is proposed that each of Eq. 4 and the other 9 multinomial probability equations be approximated using a first order Taylor series expansion around the midpoint of the FCAT-G mean covariate scores that we had available for the two health states (before progression and after progression) in the RADIANT-4 RCT (Singh et al. 2016). Thus, the linearised predictor of the probability of response in Eq. 4 is:

$$\widehat{Mob_{mj}} \approx P_{m2}(PW_o, EW_o, FW_o) + \frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} * (PW - PW_o) + \frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} * (EW - EW_o) + \frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} * (FW - FW_o)$$

Eq. 5

where $P_{m2}(PW_o, EW_o, FW_o)$ represents Eq. 4 evaluated at the mid-point value between the mean scores of FACT-G domains PW, EW, and FW for observations in the stable disease and disease progression states. (Here the issue of missing data or informative lost to follow-

up is ignored but a pertinent issue to address in further research). The derivatives are of the P_{m2} function are also evaluated also at the midpoint, and have the following expressions:

$$\frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} = \beta_{m2} * P_{m2}(1 - P_{m2}\left(P_{m2} + \frac{\beta_{m3}}{\beta_{m2}} * P_{m3}\right))$$

Eq. 6

Similar expressions are used for the other derivatives in Eq. 5 and in the corresponding equations for other EQ-5D dimensions and levels. Note that Eq. 5 and the corresponding equations for other dimensions and levels are linear in the FACT-G scores, which is convenient as they may be used to approximate mean EQ-5D scores in a group of patients when only aggregate FACT-G data are available by substituting the mean FACT-G domain scores $\overline{PW}, \overline{EW}, \overline{FW}$.

Finally, substituting expressions such as Eq. 5 (after substituting Eq. 6 into Eq. 5) for all arguments in Eq. 1, leads to the linearised mapped EQ-5D score. This linearised mapped FACT-G function was used to approximate utilities for Stable Disease and Disease Progression using only data points on $\overline{PW}, \overline{EW}, \overline{FW}$ for the two phases, reported in Singh et al. 2016, to reproduce their reported mapped utilities, which used the original best-fitting response mapping nonlinear Longworth algorithm their unpublished individual patient data.

A10.3 Comparison of utilities obtained from the mapping of FACT-G mean domain scores using the linearised best-fitting algorithm by Longworth and the utilities obtained by Yao et al. (2016) based on mapping individual patient data using the same algorithm.

	Statistics	Unadjusted model including response status (pre- vs post-progression) as a single categorical fixed-effects covariate			
		Response status – pooled analysis		Response status – pooled analysis linearised algorithm + summary domain scores	
		Pre-progression	Post-progression	Pre-progression	Post-progression
Young mapping algorithm (n=1499)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	****		[redacted]	
	[redacted]				

Appendix 11. Old and New scope

A11.1 Old Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of everolimus, , lutetium-177 DOTATATE and sunitinib within their marketing authorisation for treating unresectable or metastatic neuroendocrine tumours with disease progression.

Background

Neuroendocrine tumours constitute a heterogeneous group of rare tumours. These tumours develop from neuroendocrine cells of the pancreas, gastrointestinal tissue (from diffuse neuroendocrine cells distributed throughout the gut), the lung (neuroendocrine cells within the respiratory epithelium) and thyroid. Depending on the data source used, approximately 45-65 % of neuroendocrine tumours occur in the gastrointestinal tissue, approximately 3-7 % in the pancreas and 10% in the lungs. Neuroendocrine tumours can be broadly subdivided into those with and those without a clinical syndrome and are accordingly termed 'functional' or 'non-functional' neuroendocrine tumours, respectively.

Neuroendocrine tumours can be graded as low (grade 1), moderate (grade 2) or high grade tumours (grade 3) based upon how the tumour cells look under the microscope. The grade of tumour gives an idea of how quickly the tumour may develop. The tumours can also be referred to as 'well differentiated' (corresponding to grades 1 and 2), and poorly differentiated tumours (grade 3). Ki-67 proliferative index (Ki-67 index) is also used as a prognostic measure for grading parameters for neuroendocrine tumours. Grade 1 is equivalent to a Ki67 index of up to 3%, Grade 2 is equivalent to a 3-20%. Ki67 index beyond a score of 20% is equivalent to grade 3. The stage of the tumour describes its size, with advanced neuroendocrine tumours falling within stages III (locally advanced and/or has spread to regional lymph nodes) and IV (distant metastasis has occurred). The 5 year survival rate for stages III and IV range from 55% to 79%[1].

Neuroendocrine tumours of the gastrointestinal tissue are classified according to their point of origin, into tumours of the foregut (stomach, gall bladder, and proximal duodenum), midgut (distal duodenum, jejunum, ileum, caecum and appendix, ascending, and right two thirds of transverse colon) and hindgut (left one third of transverse colon, rectum). The incidence of neuroendocrine tumours of the gastrointestinal tissue may be between 2 and 3 per 100,000 of the population per year[1]. Most neuroendocrine tumours of the gastrointestinal

tissue are non-functioning and are associated with non-specific symptoms such as intestinal or bronchial obstruction and abdominal pain. A specific clinical syndrome related to these tumours is carcinoid syndrome which is caused by the tumour secreting serotonin. Symptoms include flushing, diarrhoea, heart palpitations and congestive heart failure. Neuroendocrine tumours of the gastrointestinal tissue are usually slow growing and survival depends on a number of factors such as histological type, degree of differentiation, tumour size and presence of liver or lymph node metastases.

Pancreatic neuroendocrine tumours (also known as pancreatic islet cells tumours) develop from pancreatic islet cells. The incidence of pancreatic neuroendocrine tumours is estimated to be less than 0.2 per 100,000 of the population per year[1]. The incidence of pancreatic neuroendocrine tumours is age-related. Functioning tumours constitute approximately 25-50 % of all pancreatic neuroendocrine tumours, with insulinoma (produces too much insulin) and gastrinoma (produces too much gastrin) as the most common. Presentation and symptoms of functioning pancreatic neuroendocrine tumours include severe peptic ulceration, diarrhoea, confusion, sweating, dizziness, weakness, high blood pressure, skin rashes, anaemia and mouth ulcers. Non-functioning tumours generally present with mass effects of the primary tumour or metastases of the liver.

Neuroendocrine tumours of the lung are classified according to their histology and clinical outcome into typical carcinoid lung tumour and atypical carcinoid lung tumour. Typical carcinoid lung tumours grow slowly and rarely spread beyond the lungs. Atypical carcinoid lung tumours grow faster than typical tumours and are more likely to spread to other organs. Most neuroendocrine tumours of the lung are non-functioning and common symptoms are those associated with bronchial obstruction, such as persistent cough, coughing up blood, and recurrent or obstructive pneumonitis.

Surgery is the only curative treatment for neuroendocrine tumours. For people who are unable to have surgery, or where surgery has been unsuccessful or curative surgery was not an option because of the advance stage of the disease, the choice of treatment depends on the symptoms, stage of disease, and histological features of the tumour. Options for treating neuroendocrine tumours that have progressed include somastatin analogues, radionuclides, chemotherapy regimens (using combinations of streptozocin, 5-fluorouracil, doxorubicin, temozolomide and capecitabine), everolimus and sunitinib. Sunitinib is available on the cancer drugs fund.

This technology appraisal only considers lutetium-177 DOTATATE for the treatment of unresectable or metastatic gastroenteropancreatic neuroendocrine tumours with disease progression. Lutetium-177 DOTATATE for the treatment of unresectable or metastatic gastroenteropancreatic neuroendocrine tumours without disease progression is outside the scope of this appraisal and is subject to ongoing NICE appraisal (ID857).

The technologies

Everolimus (Afinitor, Novartis), is an oral inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. It has a marketing authorisation in the UK for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. It does not currently have a marketing authorisation in the UK for the treatment of advanced neuroendocrine tumours of gastrointestinal or lung origin. It has been studied in clinical trials compared with placebo in adults with advanced unresectable or metastatic neuroendocrine tumours of gastrointestinal or lung origin.

Lutetium-177 DOTATATE (Lutathera, Imaging Equipment) is a radio-labelled analogue of somatostatin designed to deliver radiation to the cells. It kills tumour cells by binding to a specific type of somatostatin receptor, called sst2 receptors, which are overexpressed by the malignant cells. It does not currently have marketing authorisation in the UK for any indication. It has been studied in a clinical trial in people with inoperable, locally advanced or metastatic somastostatin receptor positive midgut neuroendocrine tumours (Ki67 index ≤ 20%) with or without disease progression compared with octreotide long acting release (LAR). It has also been studied in a single arm study in people with gastrointestinal or pancreatic neuroendocrine tumours with or without disease progression. Lutetium-177 DOTATATE is administered by intravenous infusion.

Sunitinib (Sutent, Pfizer) is a protein kinase inhibitor that works by preventing tumour proliferation and inhibiting blood vessel growth, leading to cancer cell death. It has a marketing authorisation for treating unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Sunitinib is administered orally.

Intervention(s)	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • Lutetium-177 DOTATATE (neuroendeocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)
Population(s)	People with progressed unresectable or metastatic neuroendocrine tumours • according to the specific locations covered by the existing and anticipated marketing authorisations of the interventions

Comparators	• the technologies listed above will be compared with each other where appropriate. • octreotide (long-acting release formulation) • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows the following subgroups will be considered: • location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s) Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Appraisals in development: 'Lanreotide for treating unresectable locally advanced or

and NICE Pathways	metastatic gastroenteropancreatic neuroendocrine tumours without disease progression' [ID 961]. Publication date to be confirmed Lutetium-177 DOTATATE for treating inoperable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression'. [ID 857]. Publication date to be confirmed. Related Guidelines: 'Diagnosis and management of metastatic malignant disease of unknown primary origin' (2010) NICE guideline 104. Static guidance Related NICE Pathways: Metastatic malignant disease of unknown primary origin overview (2010) NICE pathway http://pathways.nice.org.uk/metastatic-malignant-disease-of-unknown-primary-origin
Related National Policy	NHS England commissions adult specialist endocrine services from Adult Specialist Endocrinology Centres for specified condition, including the management of neuro-endocrine tumours of the gut and elsewhere (see section 10. Adult specialist endocrinology services, pages 37-38) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Questions for consultation

Is the proposed approach of amending the remit to remove lanreotide appropriate?

Is octreotide an appropriate comparator for this appraisal?

Reference

1. Ramage J et al. (2012). Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs) Gut 61: 6–32.

A11.2 New Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

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

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of everolimus, lutetium-177 DOTATATE and sunitinib within their marketing authorisation for treating unresectable or metastatic neuroendocrine tumours with disease progression.

Background

Neuroendocrine tumours constitute a heterogeneous group of rare tumours. These tumours develop from neuroendocrine cells of the pancreas, gastrointestinal tissue (from diffuse neuroendocrine cells distributed throughout the gut), the lung (neuroendocrine cells within the respiratory epithelium) and thyroid. Depending on the data source used, approximately 45-65 % of neuroendocrine tumours occur in the gastrointestinal tissue, approximately 3-7 % in the pancreas and 10% in the lungs. Neuroendocrine tumours can be broadly subdivided into those with and those without a clinical syndrome and are accordingly termed 'functional' or 'non-functional' neuroendocrine tumours, respectively.

Neuroendocrine tumours can be graded as low (grade 1), moderate (grade 2) or high grade tumours (grade 3) based upon how the tumour cells look under the microscope. The grade of tumour gives an idea of how quickly the tumour may develop. The tumours can also be referred to as 'well differentiated' (corresponding to grades 1 and 2), and poorly differentiated tumours (grade 3). Ki-67 proliferative index (Ki-67 index) is also used as a prognostic measure for grading parameters for neuroendocrine tumours. Grade 1 is equivalent to a Ki67 index of up to 3%, Grade 2 is equivalent to a 3-20%. Ki67 index beyond a score of 20% is equivalent to grade 3. The stage of the tumour describes its size, with advanced neuroendocrine tumours falling within stages III (locally advanced and/or has spread to regional lymph nodes) and IV (distant metastasis has occurred). The 5 year survival rate for stages III and IV range from 55% to 79%[1].

Neuroendocrine tumours of the gastrointestinal tissue are classified according to their point of origin, into tumours of the foregut (stomach, gall bladder, and proximal duodenum), midgut (distal duodenum, jejunum, ileum, caecum and appendix, ascending, and right two thirds of transverse colon) and hindgut (left one third of transverse colon, rectum). The incidence of neuroendocrine tumours of the gastrointestinal tissue may be between 2 and 3 per 100,000 of the population per year[1]. Most neuroendocrine tumours of the gastrointestinal

tissue are non-functioning and are associated with non-specific symptoms such as intestinal or bronchial obstruction and abdominal pain. A specific clinical syndrome related to these tumours is carcinoid syndrome which is caused by the tumour secreting serotonin. Symptoms include flushing, diarrhoea, heart palpitations and congestive heart failure. Neuroendocrine tumours of the gastrointestinal tissue are usually slow growing and survival depends on a number of factors such as histological type, degree of differentiation, tumour size and presence of liver or lymph node metastases.

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Surgery is the only curative treatment for neuroendocrine tumours. For people who are unable to have surgery, or where surgery has been unsuccessful or curative surgery was not an option because of the advance stage of the disease, the choice of treatment depends on the symptoms, stage of disease, and histological features of the tumour. Options for treating neuroendocrine tumours that have progressed include radionuclides, chemotherapy regimens (using combinations of streptozocin, 5-fluorouracil, doxorubicin, temozolomide and capecitabine), everolimus and sunitinib. Sunitinib is available on the cancer drugs fund.

This technology appraisal only considers lutetium-177 DOTATATE for the treatment of unresectable or metastatic gastroenteropancreatic neuroendocrine tumours with disease progression. Lutetium-177 DOTATATE for the treatment of unresectable or metastatic gastroenteropancreatic neuroendocrine tumours without disease progression is outside the scope of this appraisal and is subject to ongoing NICE appraisal (ID857).

The technologies

Everolimus (Afinitor, Novartis), is an oral inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. It has a marketing authorisation in the UK for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. It does not currently have a marketing authorisation in the UK for the treatment of advanced neuroendocrine tumours of gastrointestinal or lung origin. It has been studied in clinical trials compared with placebo in adults with advanced unresectable or metastatic neuroendocrine tumours of gastrointestinal or lung origin.

Lutetium-177 DOTATATE (Lutathera, Imaging Equipment) is a radio-labelled analogue of somatostatin designed to deliver radiation to the cells. It kills tumour cells by binding to a specific type of somatostatin receptor, called sst2 receptors, which are overexpressed by the malignant cells. It does not currently have marketing authorisation in the UK for any indication. It has been studied in a clinical trial in people with inoperable, locally advanced or metastatic somastostatin receptor positive midgut neuroendocrine tumours (Ki67 index ≤ 20%) with or without disease progression compared with octreotide long acting release (LAR). It has also been studied in a single arm study in people with gastrointestinal or pancreatic neuroendocrine tumours with or without disease progression. Lutetium-177 DOTATATE is administered by intravenous infusion.

Sunitinib (Sutent, Pfizer) is a protein kinase inhibitor that works by preventing tumour proliferation and inhibiting blood vessel growth, leading to cancer cell death. It has a marketing authorisation for treating unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Sunitinib is administered orally.

Intervention(s)	• Everolimus (neuroendocrine tumours of gastrointestinal, pancreatic or lung origin) • Lutetium-177 DOTATATE (neuroendeocrine tumours of gastrointestinal or pancreatic origin) • Sunitinib (pancreatic neuroendocrine tumours)
Population(s)	People with progressed unresectable or metastatic neuroendocrine tumours • according to the specific locations covered by the existing and anticipated marketing authorisations of the interventions

Comparators	• the technologies listed above will be compared with each other where appropriate. • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows the following subgroups will be considered: • location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s) Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE	Appraisals in development: 'Lanreotide for treating unresectable locally advanced or metastatic gastroenteropancreatic neuroendocrine

Pathways	tumours without disease progression' [ID 961]. Publication date to be confirmed Lutetium-177 DOTATATE for treating inoperable, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours without disease progression'. [ID 857]. Publication date to be confirmed. Related Guidelines: 'Diagnosis and management of metastatic malignant disease of unknown primary origin' (2010) NICE guideline 104. Static guidance Related NICE Pathways: Metastatic malignant disease of unknown primary origin overview (2010) NICE pathway http://pathways.nice.org.uk/metastatic-malignant-disease-of-unknown-primary-origin
Related National Policy	NHS England commissions adult specialist endocrine services from Adult Specialist Endocrinology Centres for specified condition, including the management of neuro-endocrine tumours of the gut and elsewhere (see section 10. Adult specialist endocrinology services, pages 37-38) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Reference

1. Ramage J et al. (2012). Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs) Gut 61: 6–32.

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

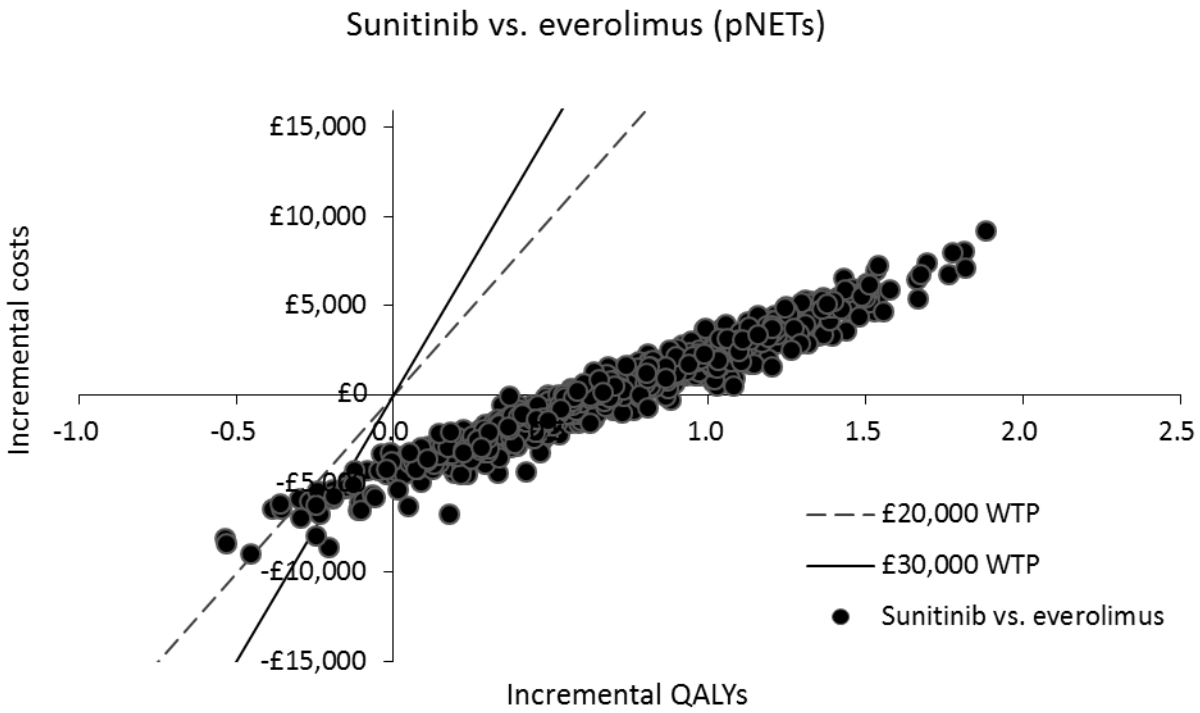
Errata

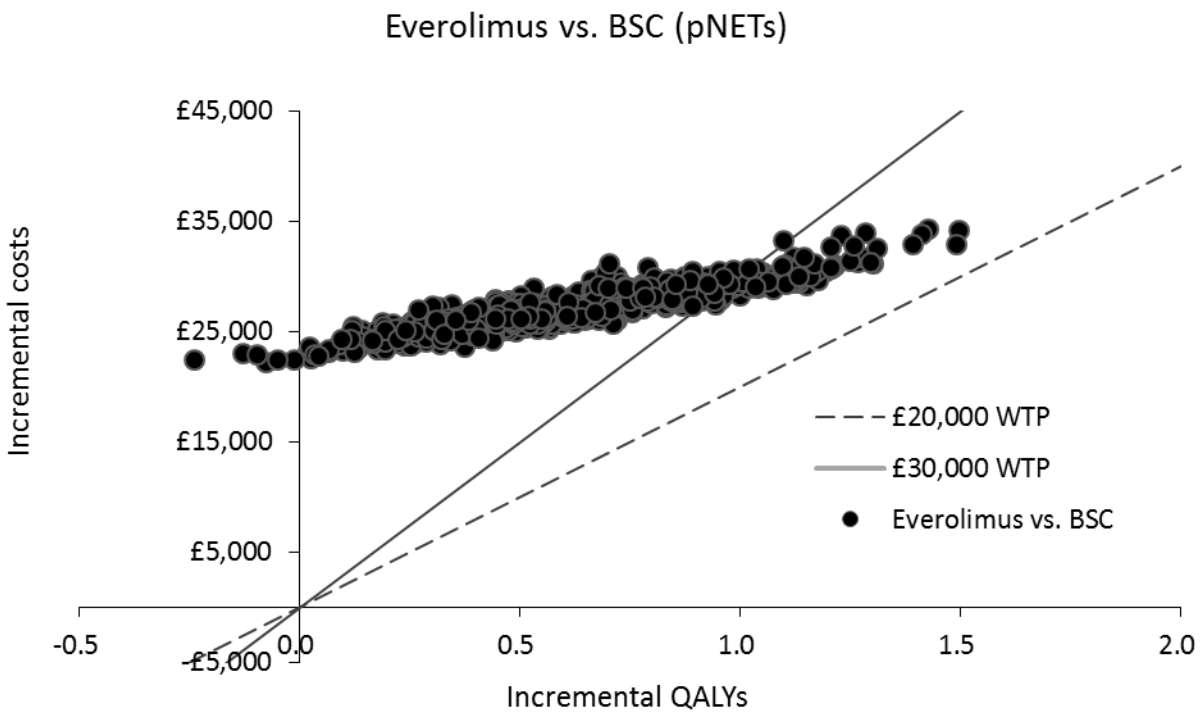
Location in report	Original text	Corrected text
Section 7.2.4.1, pNETs, p.279		The mean ICER for everolimus vs. BSC for pNETs, obtained in the probabilistic sensitivity analysis, is £44,133; the mean ICER for sunitinib vs. everolimus is £434; and the mean ICER for sunitinib vs. BSC is £20,698.
	The probability that everolimus for pNETs is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 0% and 0.6%, respectively. The probability of being the most cost-effective treatment of sunitinib for pNETs at a willingness-to-pay threshold of £20,000 per QALY is 21.2%; at £30,000/QALY, sunitinib is the most cost-effective treatment with probability of 44.8%.	The probabilities that everolimus is the most cost-effective treatment for pNETs at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY are 0% and 0.8%, respectively. The probability of sunitinib being the most cost-effective treatment for pNETs at a willingness-to-pay threshold of £20,000 per QALY is 43.7%; at £30,000/QALY, sunitinib is the most cost-effective treatment with probability of 90.5%.
Section 7.2.4.2, GI and lung NETs, p. 280		For GI and lung NETs, the probabilistic mean ICER is £46,611. The probability that everolimus for GI and lung is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 1.6% and 20.2%, respectively.
	The probability that everolimus for GI and lung is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 0.9% and 10.5%, respectively.	

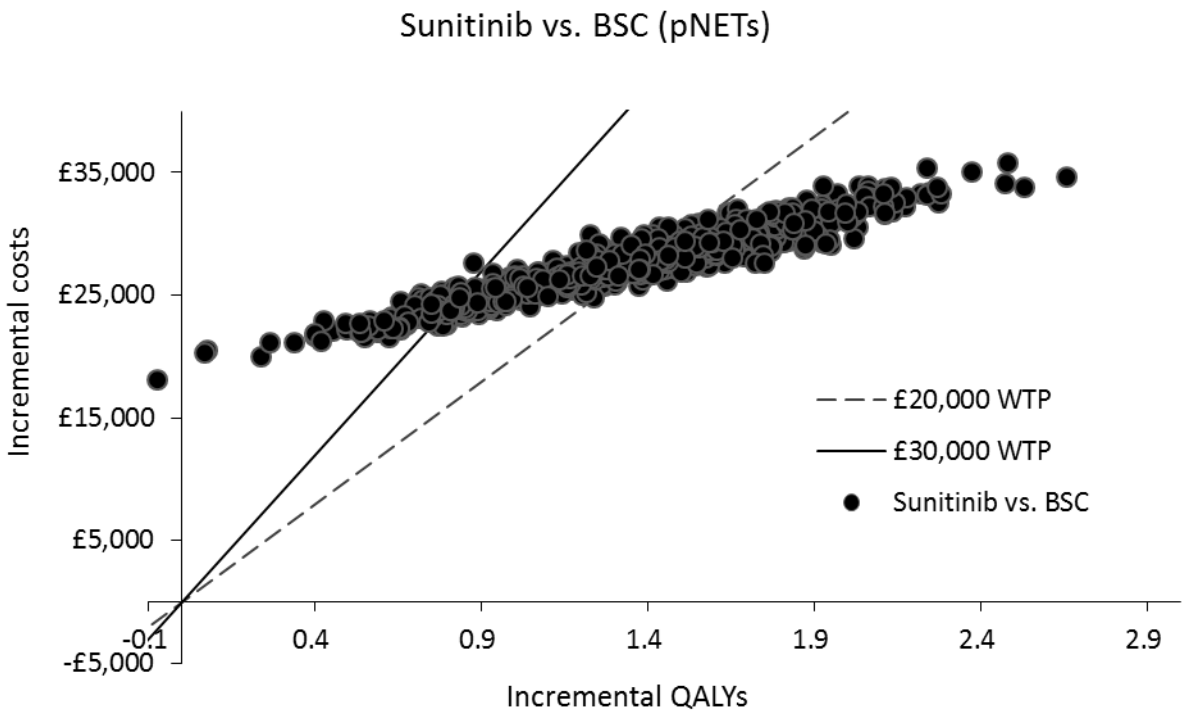
Section 7.2.4.3, GI midgut NETs, p. 281	The probability that everolimus for GI (midgut) is the most cost-effective treatment at the willingness to pay thresholds of £20,000 per QALY and £30,000 per QALY is 0.1% and 2.5%, respectively.	The probabilistic mean ICER for GI (midgut) is £193,049.The probability that everolimus for GI (midgut) is the most cost-effective treatment at the willingness to pay thresholds of £20,000 per QALY and £30,000 per QALY is 0% and 5.1%, respectively.

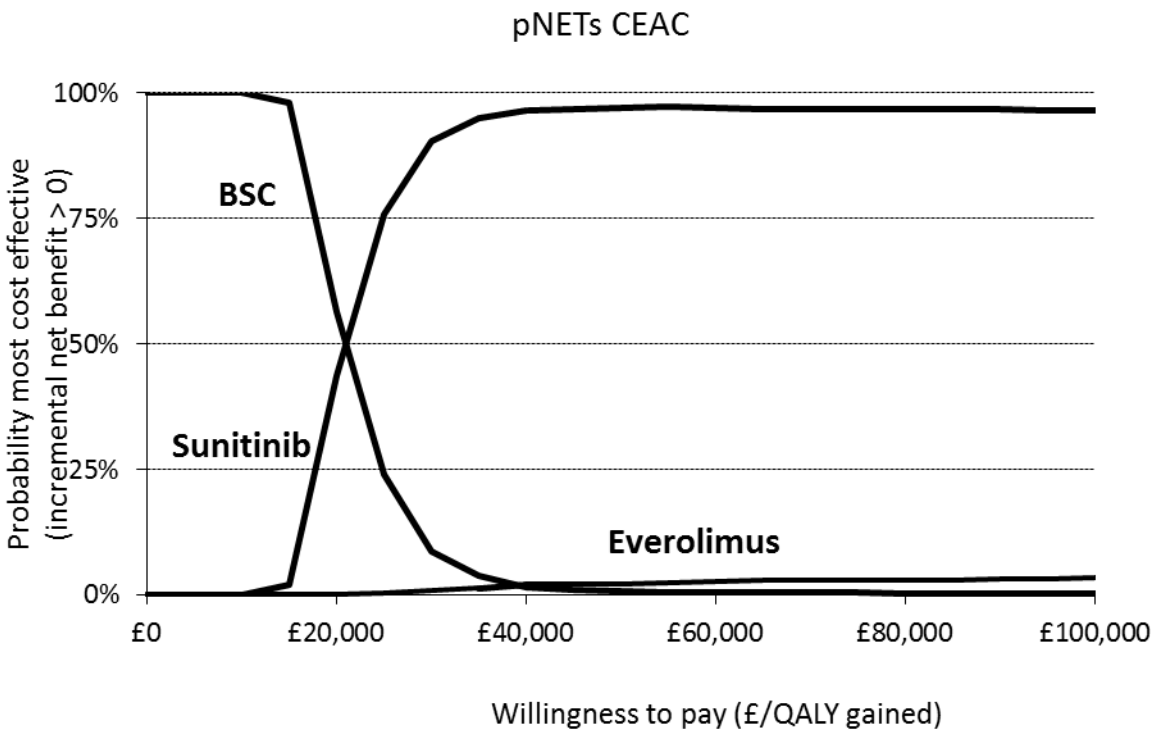
7.2.4 Probabilistic sensitivity analyses

7.2.4.1 Pancreatic NETs




Everolimus vs. BSC (pNETs)
£45,000
£35,000
£25,000
£15,000
£5,000
-£5,000
Incremental costs
-0.5
0.0
0.5
1.0
1.5
2.0
Incremental QALYs
£20,000 WTP
£30,000 WTP
Everolimus vs. BSC

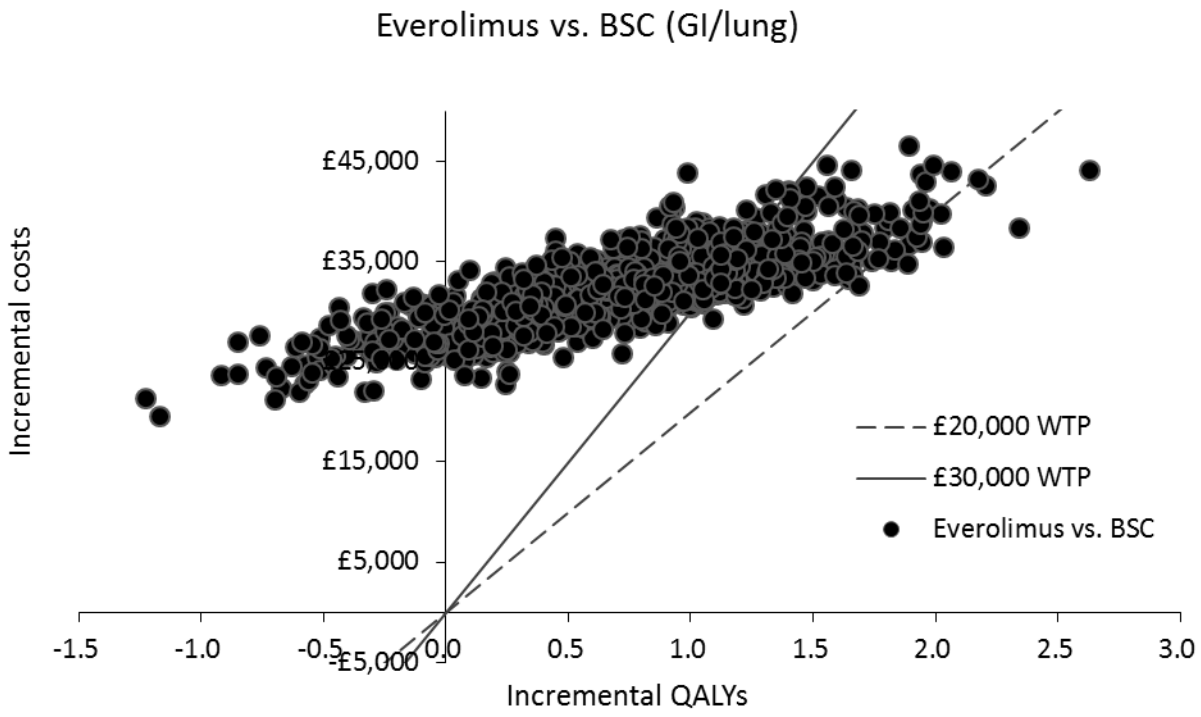

Sunitinib vs. BSC (pNETs)
£35,000
£25,000
£15,000
£5,000
-£5,000
Incremental costs
-0.1
0.4
0.9
1.4
1.9
2.4
2.9
Incremental QALYs
£20,000 WTP
£30,000 WTP
Sunitinib vs. BSC

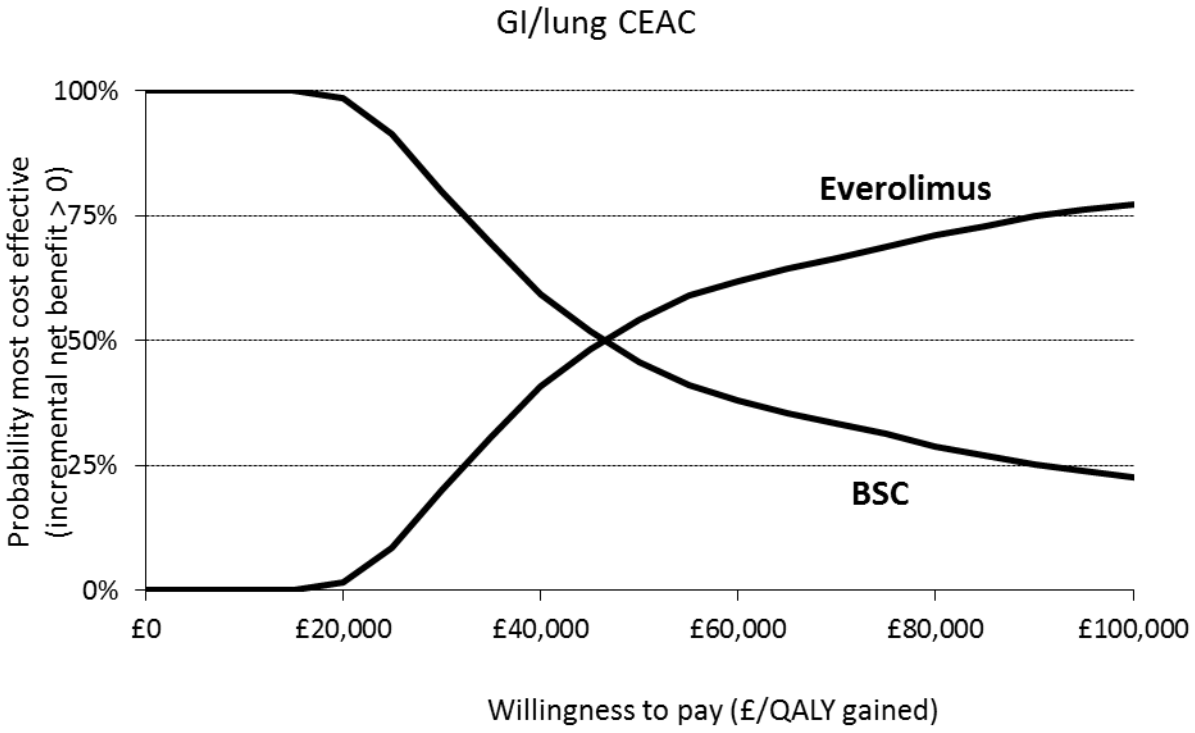


The mean ICER for everolimus vs. BSC for pNETs, obtained in the probabilistic sensitivity analysis, is £44,133; the mean ICER for sunitinib vs. everolimus is £434; and the mean ICER for sunitinib vs. BSC is £20,698.

The probabilities that everolimus is the most cost-effective treatment for pNETs at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY are 0% and 0.8%, respectively. The probability of sunitinib being the most cost-effective treatment for pNETs at a willingness-to-pay threshold of £20,000 per QALY is 43.7%; at £30,000/QALY, sunitinib is the most cost-effective treatment with probability of 90.5%.

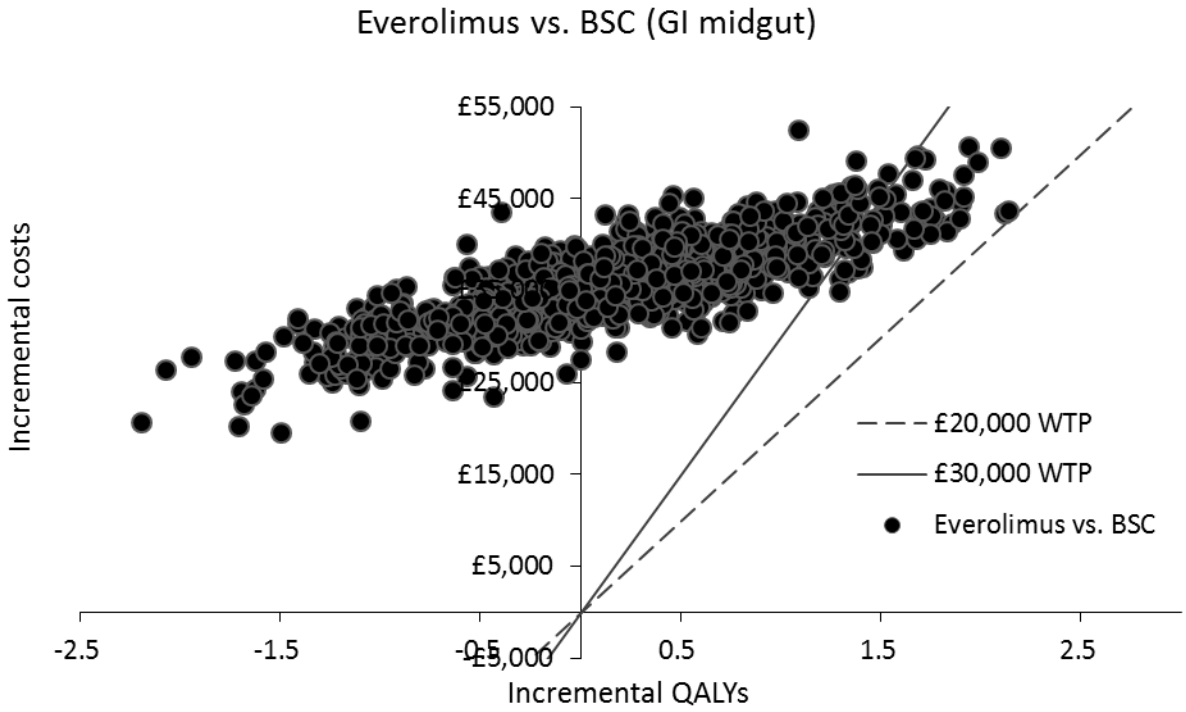
7.2.4.2 GI and lung NETs

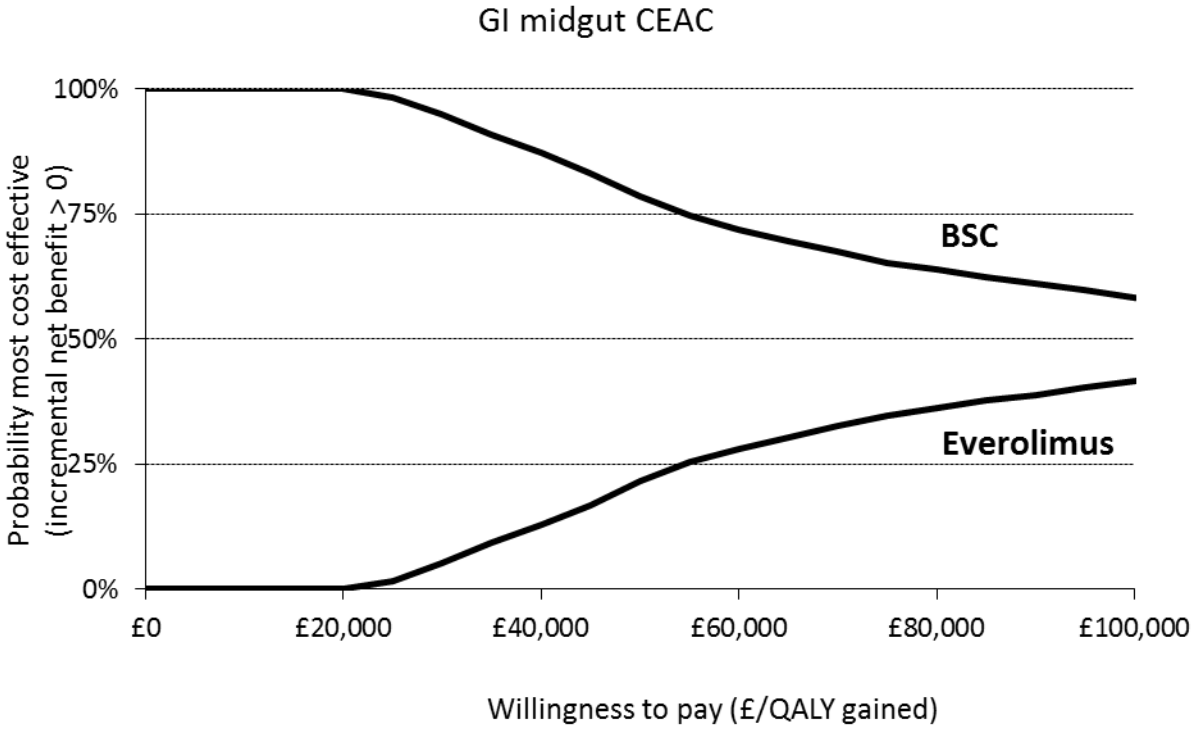




For GI and lung NETs, the probabilistic mean ICER is £46,611. The probability that everolimus for GI and lung is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 1.6% and 20.2%, respectively.

7.2.4.3 GI midgut NETs





The probabilistic mean ICER for GI (midgut) is £193,049.The probability that everolimus for GI (midgut) is the most cost-effective treatment at the willingness to pay thresholds of £20,000 per QALY and £30,000 per QALY is 0% and 5.1%, respectively.

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

Addendum

27 Feb 2017

Produced by

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7.2.4.1 Lung NETs

The comparison between treatment with everolimus and BSC for lung NETs patient subpopulation yielded an ICER of £31,016 (**Error! Reference source not found.**). Treatment of these patients with everolimus results in better survival (5.12 years vs. 2.96 for BSC). Likewise, the treatment costs in everolimus arm are higher; they are driven by the drug acquisition costs in pre-progression health state.

It must be noted that these analyses were derived using

- mean treatment durations from exponential extrapolations of median treatment durations reported for the lung subgroup in the CSR Appendices provided by Novartis
- Exponential curves fitted to individual patient data (IPD) derived from OS Kaplan-Meier (KM) curves and number of patients at risk data provided by Novartis in the Lung subgroup of RADIANT-4,
- Exponential curves fitted to IPD on lung KM PFS survival curves derived from the ASCO poster by Singh et al. 2016 (from PFS curves for all, non-prior SSA, and prior SSA subgroups in RADIANT-4 and validated by comparing the resulting HR 0.48 [95% CI: 0.27-0.85] with the Lung HR of 0.50 [0.28-0.88] reported in the RADIANT-4 CSR)
- All other parameters were assumed to be the same as for GI/Lung patient population in RADIANT-4

Table 1: PenTAG base-case results for lung NETs

	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	5.12	2.96	2.16
QALYs (mean, discounted)	3.18	1.99	1.19
Total costs (mean, discounted)	£49,168	£12,249	£36,920
ICER (Cost / QALY)			£31,016

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 2: PenTAG base-case detailed results for lung NETs

	Everolimus	BSC	Everolimus vs.BSC
Life years (mean, undiscounted)			
Pre-progression	1.13	0.61	0.52
Post-progression	3.98	2.35	1.64
Total	5.12	2.96	2.16
QALYs (mean, discounted)			
Pre-progression	0.84	0.48	0.35
Post-progression	2.34	1.50	0.84
Total	3.18	1.99	1.19
Costs (mean, discounted)			
Pre-progression			
Drug acquisition	£30,332	£278	£30,054
Drug administration	£172	£2	£170
Medical management	£3,338	£1,509	£1,830
AEs	£171	£34	£137
Total (pre-progression)	£34,013	£1,822	£32,191
Post-progression			
Drug acquisition	£3,748	£1,572	£2,175
Drug administration	£18	£6	£12
Medical management	£7,689	£4,898	£2,791
End-of-life care	£3,700	£3,950	-£250
Total (post-progression)	£15,155	£10,426	£4,729
Total	£49,168	£12,249	£36,920
ICER (Cost / QALY)			£31,016

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

7.2.4.2 Alternative set of utility values

Table 3: PenTAG scenario analysis results with different utility values

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£41,246
	Sunitinib	BSC	£19,411
GI	Everolimus	BSC	£352,801
	177Lu-DOTATATE	BSC	£57,745
GI and lung	Everolimus	BSC	£49,949
Lung	Everolimus	BSC	£32,413

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.4.3 Analysis limited to PFS

Table 4: PenTAG scenario analysis results limiting analytical horizon to PFS

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£57,493
	Sunitinib	BSC	£35,448
GI (midgut)	Everolimus	BSC	£88,801
	177Lu-DOTATATE	BSC	£30,115
GI and lung	Everolimus	BSC	£73,086
Lung	Everolimus	BSC	£91,202

7.2.4.4 Background mortality adjustments to OS and PFS curves

Table 5: PenTAG scenario analysis results on background mortality

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£44,032
	Sunitinib	BSC	£21,594
GI (midgut)	Everolimus	BSC	£78,330
	177Lu-DOTATATE (no mortality adjustment)	BSC	£43,348
GI and lung	Everolimus	BSC	£46,687
Lung	Everolimus	BSC	£33,908

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

1.1..4.1 First-cycle costs and disease monitoring

Table 6: PenTAG scenario analysis results on first-cycle costs

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£45,288
	Sunitinib	BSC	£20,624
GI (midgut)	Everolimus	BSC	£208,095
	177Lu-DOTATATE	BSC	£61,619
GI and lung	Everolimus	BSC	£47,205
Lung	Everolimus	BSC	£32,744

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

Table 7: PenTAG scenario analysis results for disease monitoring

Tumour location	Treatment	Comparator	ICER
GI (midgut)	Everolimus	BSC	£205,437
	177Lu-DOTATATE	BSC	£64,513
GI and lung	Everolimus	BSC	£46,249
Lung	Everolimus	BSC	£32,221

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

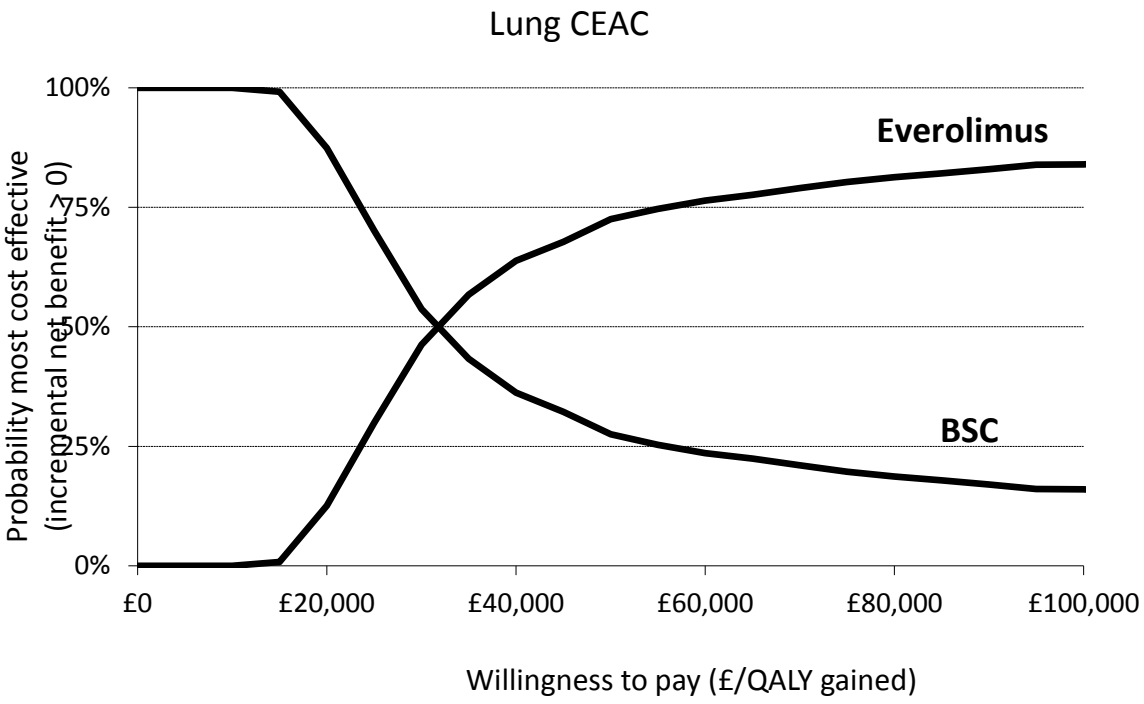
1.1..4.2 Scenario analysis with 0% discount rate

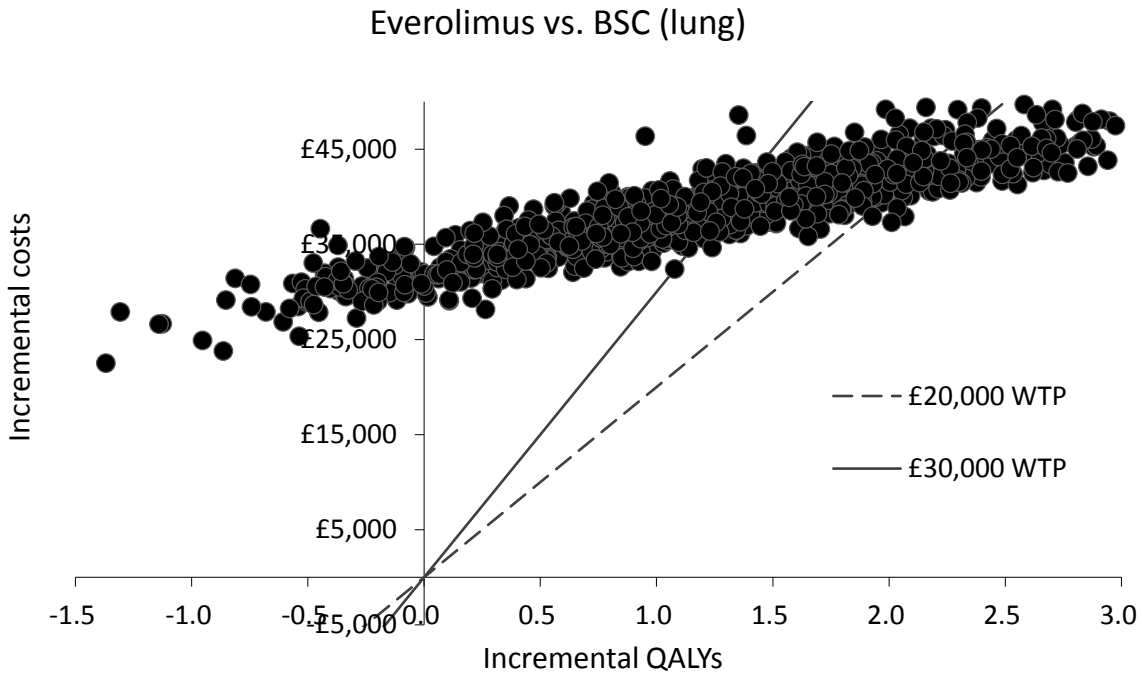
Table 8: PenTAG scenario analysis results without discounting

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£38,021
	Sunitinib	BSC	£17,605
GI (midgut)	Everolimus	BSC	£131,512
	177Lu-DOTATATE	BSC	£49,907
GI and lung	Everolimus	BSC	£34,367
Lung	Everolimus	BSC	£26,114

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.4 Probabilistic sensitivity analyses





For lung NETs, the probabilistic mean ICER is £31,987. The probability that everolimus for lung is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 12.6% and 46.3%, respectively.

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

Addendum II

10 March 2017

Produced by

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Background and summary to this addendum

The analyses produced in the Assessment Report comparing everolimus plus BSC vs. BSC alone in the GI subgroup was restricted to midgut GI patients, as opposed to the overall GI NETs population. After the Appraisal Committee meeting NICE requested that the AG conducted analysis for the overall GI NETs patient population. The results of the additional analyses are presented below.

According to these analyses, everolimus plus BSC has much lower ICERs relative to BSC alone than those found in the previous analyses for the GI midgut population. The new analyses employ overall survival data from Kaplan and Meier curves provided by the Novartis in their comments to the Assessment Report. Further, the whole GI subgroup was not a pre-specified stratification factor in the source trial (RADIANT-4) and thus these results may be biased.

7.2.4.1 GI NETs

The comparison between treatment with everolimus and BSC for the whole GI NETs patient subpopulation in RADIANT-4 yielded an ICER of £26,383 (**Error! Reference source not found.**). Treatment of these patients with everolimus results in better survival (8.25 years vs. 5.19 for BSC). Likewise, the treatment costs in everolimus arm are higher; they are driven by the drug acquisition costs in pre-progression health state.

It must be noted that these analyses were derived using

- mean treatment durations from exponential extrapolations of median everolimus treatment duration (40 weeks) reported for the GI subgroup provided by Novartis on November 11 2016, in response to a data request by the AG
- Exponential curves fitted to individual patient data (IPD) derived from OS Kaplan-Meier (KM) curves and number of patients at risk data provided by Novartis for the GI subgroup of RADIANT-4 in response to the AR (data cut-off 30 November 2015, resulting in HR 0.65 [95% CI: 0.37-1.13]; the GI HR of 0.57 [95% CI: 0.28-1.16] was provided by Novartis on November 11 2016 in response to a data request by AG)
- Exponential curves fitted to IPD derived from PFS KM survival curves for GI subgroup reported in the ASCO poster by Singh et al. 2016 (data cut-off date 28 Nov 2014; from PFS curves for midgut and non-midgut subgroups in RADIANT-4; resulting HR 0.54 [95% CI: 0.36-0.82]; the GI HR of 0.56 [0.37-0.84] was provided by Novartis on November 11 2016, in response to a data request by AG)
- All other parameters were assumed to be the same as for GI/Lung patient population in RADIANT-4, as presented in the Assessment Report. In particular, our base case analysis does not apply background mortality adjustment to our survival model extrapolations. Scenario analyses applying background mortality adjustment are presented in Table 162.

Table 1: PenTAG base-case results for GI NETs

	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	8.25	5.19	3.06
QALYs (mean, discounted)	4.69	3.24	1.45
Total costs (mean, discounted)	£55,499	£17,305	£38,193
ICER (Cost / QALY)			£26,383

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Note: estimated assuming background mortality

Table 2: PenTAG base-case detailed results for GI NETs

	Everolimus	BSC	Everolimus vs.BSC
Life years (mean, undiscounted)			
Pre-progression	1.65	0.90	0.75
Post-progression	6.59	4.28	2.31
Total	8.25	5.19	3.06
QALYs (mean, discounted)			
Pre-progression	1.20	0.71	0.49
Post-progression	3.49	2.53	0.96
Total	4.69	3.24	1.45
Costs (mean, discounted)			
Pre-progression			
Drug acquisition	£29,823	£406	£29,417
Drug administration	£168	£3	£165
Medical management	£4,779	£2,202	£2,577
AEs	£171	£34	£137
Total (pre-progression)	£34,940	£2,644	£32,296
Post-progression			
Drug acquisition	£5,621	£2,663	£2,958
Drug administration	£27	£10	£17
Medical management	£11,533	£8,296	£3,237
End-of-life care	£3,377	£3,692	-£315
Total (post-progression)	£20,558	£14,661	£5,897
Total	£55,499	£17,305	£38,193
ICER (Cost / QALY)			£26,383

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

7.2.4.2 Alternative set of utility values

Table 3: PenTAG scenario analysis results with different utility values

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£41,246
	Sunitinib	BSC	£19,411
GI (midgut)	Everolimus	BSC	£352,801
	177Lu-DOTATATE	BSC	£57,745
GI and lung	Everolimus	BSC	£49,949
Lung	Everolimus	BSC	£32,413
GI	Everolimus	BSC	£28,063

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

7.2.4.3 Analysis limited to PFS

Table 4: PenTAG scenario analysis results limiting analytical horizon to PFS

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£57,493
	Sunitinib	BSC	£35,448
GI (midgut)	Everolimus	BSC	£88,801
	177Lu-DOTATATE	BSC	£30,115
GI and lung	Everolimus	BSC	£73,086
Lung	Everolimus	BSC	£91,202
GI	Everolimus	BSC	£65,775

7.2.4.4 Background mortality adjustments to OS and PFS curves

Table 5: PenTAG scenario analysis results on background mortality

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£44,032
	Sunitinib	BSC	£21,594
GI (midgut)	Everolimus	BSC	£78,330
	177Lu-DOTATATE (no mortality adjustment)	BSC	£43,348
GI and lung	Everolimus	BSC	£46,687
Lung	Everolimus	BSC	£33,908
GI	Everolimus	BSC	£31,353

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

1.1..4.1 First-cycle costs and disease monitoring

Table 6: PenTAG scenario analysis results on first-cycle costs

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£45,288
	Sunitinib	BSC	£20,624
GI (midgut)	Everolimus	BSC	£208,095
	177Lu-DOTATATE	BSC	£61,619
GI and lung	Everolimus	BSC	£47,205

Tumour location	Treatment	Comparator	ICER
Lung	Everolimus	BSC	£32,744
GI	Everolimus	BSC	£27,834

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

Table 7: PenTAG scenario analysis results for disease monitoring

Tumour location	Treatment	Comparator	ICER
GI (midgut)	Everolimus	BSC	£205,437
	177Lu-DOTATATE	BSC	£64,513
GI and lung	Everolimus	BSC	£46,249
Lung	Everolimus	BSC	£32,221
GI	Everolimus	BSC	£27,669

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

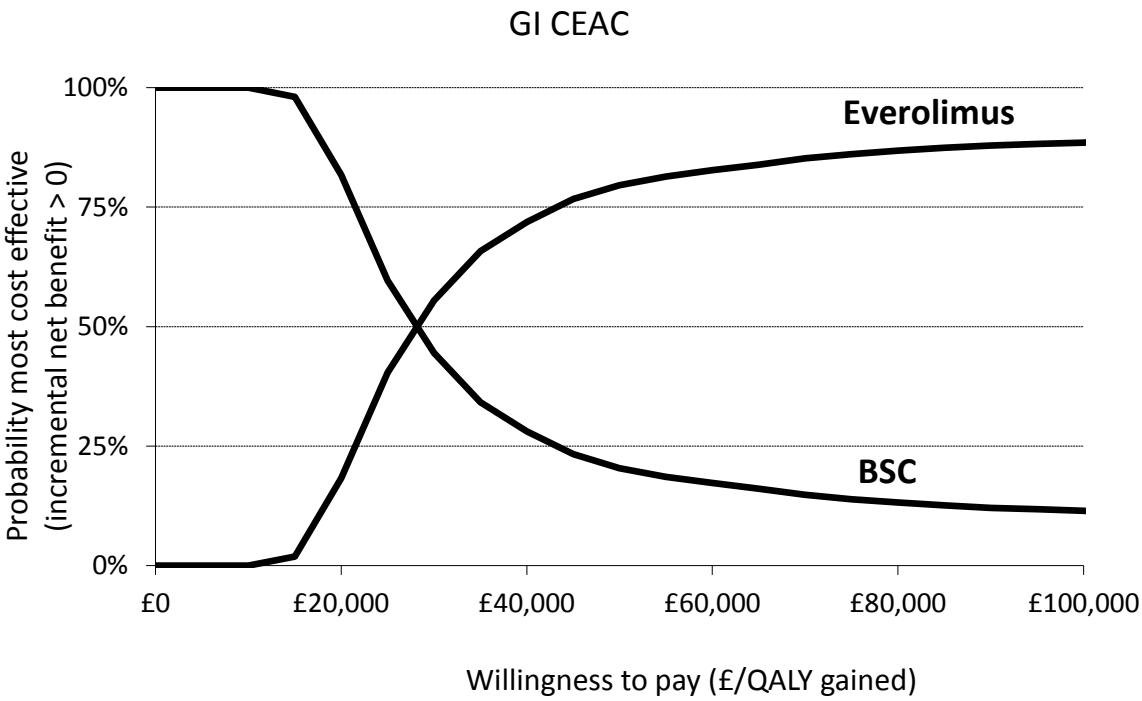
1.1..4.2 Scenario analysis with 0% discount rate

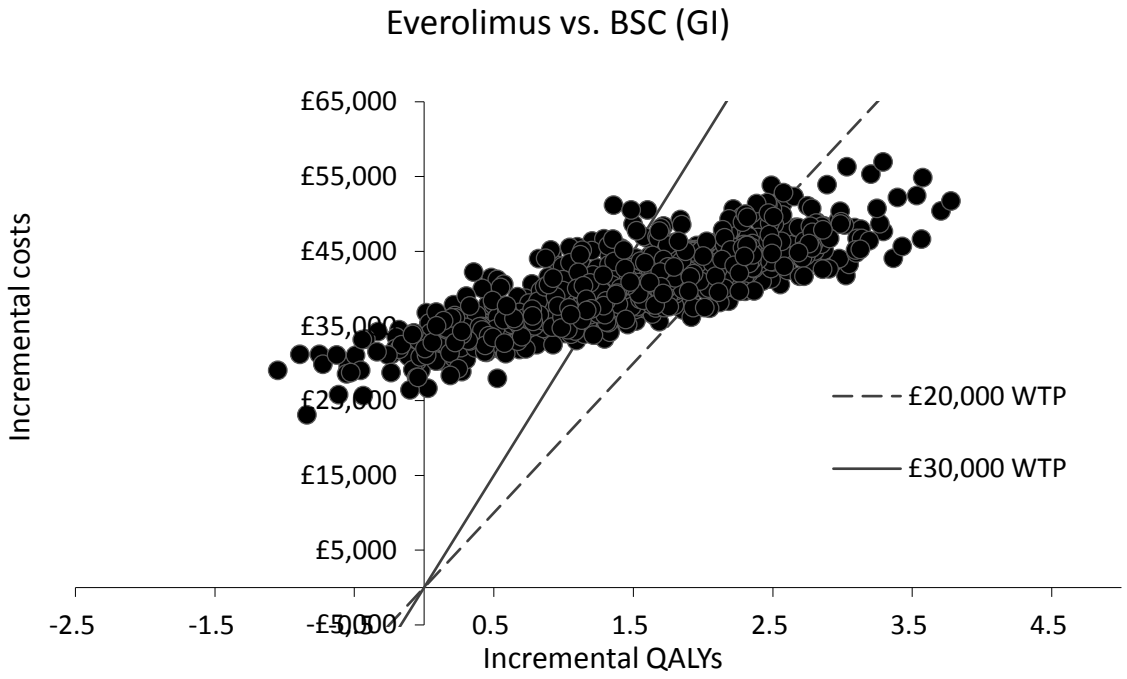
Table 8: PenTAG scenario analysis results without discounting

Tumour location	Treatment	Comparator	ICER
Pancreas	Everolimus	BSC	£38,021
	Sunitinib	BSC	£17,605
GI (midgut)	Everolimus	BSC	£131,512
	177Lu-DOTATATE	BSC	£49,907
GI and lung	Everolimus	BSC	£34,367
Lung	Everolimus	BSC	£26,114
GI	Everolimus	BSC	£20,184

Key: BSC, best supportive care; GI, gastrointestinal; ICER, incremental cost-effectiveness ratio

1.1..4.3 Probabilistic sensitivity analyses





For GI NETs, the probabilistic mean ICER is £27,582. The probability that everolimus for GI is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY is 18.3% and 55.5%, respectively.

Everolimus, 177Lu-DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression

Advanced Accelerator Applications: comments on the PenTAG Assessment Report

We would like to thank NICE for the opportunity to comment on the Assessment Report produced by PenTAG. Whilst we appreciate the considerable effort that has gone into the production of the Assessment Report, we are concerned that the Assessment Group has misunderstood key elements of the pathway of care for this complex and rare disease.

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) have a profound impact on patients' lives. The condition significantly affects patients' quality of life and, approximately 50% of patients present with distant metastases at diagnosis when curative treatments are usually no longer possible. GEP-NETs are rare; it is estimated that there will be only 3,287 patients with GI-NETs or P-NETs in 2017. 177Lu-DOTATATE is an innovative treatment for this rare disease and has been granted orphan drug designation by the EMA.

177Lu-DOTATATE has previously been made available to patients through the Cancer Drugs Fund in both the PNET and entire GI NET population. There is considerable experience of its use in England, with 729 patients treated in 20 centres outside of a clinical trial context and five centres involved in the pivotal Phase III NETTER-1 study.

We have categorised our key comments on the Assessment Report into the following issues:

1. The design of the NETTER-1 trial
2. The failure to consider the whole anticipated marketing authorisation for 177Lu-DOTATATE
3. The place and role of somatostatin analogues in the pathway of care
4. Serious flaws in the Assessment Group's economic analysis
5. The Assessment Group's critique of the systematic review submitted by AAA.

We would also like to highlight our concern that much of the information included in our submission has not been given full consideration by the Assessment Group. Firstly, the pivotal phase III trial of 177Lu-DOTATATE, the NETTER-1 study, has been excluded from the Assessment Group's systematic review. Secondly, the Assessment Group's economic analysis limits consideration of 177Lu-DOTATATE to a scenario analysis. In doing so, the Assessment Group has not given the same degree of consideration to the cost-effectiveness of 177Lu-DOTATATE compared to the other treatments included in the report. Finally, the Assessment Group has not given full consideration to our submitted economic analysis on the use of 177Lu-DOTATATE to treat patients with pancreatic neuroendocrine tumours (P-NETs).

1. The NETTER-1 study is a well-designed clinical study that has been designed to meet regulatory requirements and has been peer-reviewed and published in the New England Journal of Medicine

The Assessment Report (AR) states that '*NETTER-1 is a poorly designed study, as there is no control arm.*' (AR, Page 11). Furthermore, the Assessment Group has excluded the NETTER-1 study from their systematic review.

The NETTER-1 study has been subject to extensive peer review and has been published in one of the most prestigious medical journals, the *New England Journal of Medicine* (NEJM) (Strosberg et al, 2017a). It is a controlled study which fulfils the requirements of the Food and Drug Agency (FDA) and European Medicines Agency (EMA) for pivotal confirmatory trials for marketing authorisation applications.

- It is a multicentre, stratified, randomised, controlled, parallel-group phase III study, prepared in collaboration with internationally recognised experts in treating NETs.

The study design and the choice of comparator for the study were finalised with the requirements from the EMA and the FDA. A key inclusion criterion for the NETTER-1 study was that patients had to have progressed on somatostatin analogues (SSAs). The regulatory agencies decided it was unethical to maintain the dose for patients in the control arm who had progressed on octreotide 30mg, and at the time of designing the trial, they thought that a double dose of octreotide LAR, i.e. 60 mg, could have had better efficacy, and was included in the comparator arm.

As per the discussions with the FDA and EMA, the NETTER-1 was designed to confirm the findings obtained in the Erasmus Phase I/II trial. This is also indicated in the recent publication of NETTER-1 in NEJM (Strosberg et al, 2017a). Midgut carcinoid tumour was considered as the most suitable study population for the pivotal NETTER-1 trial. Conclusions of the NETTER-1 study confirm the results from the Phase I-II Erasmus trial, which supported the therapeutic benefit of 177Lu-DOTATATE for the key efficacy endpoints of progression-free survival and overall survival.

The NETTER-1 study therefore represents key clinical evidence demonstrating the efficacy of 177Lu-DOTATATE. The median progression free survival (PFS) for 177Lu-DOTATATE was not reached at the time of analysis of the NETTER-1 data, whereas the PFS of octreotide LAR was 8.4 months.

- The hazard ratio for 177Lu-DOTATATE was 0.21 (95% CI: 0.13 to 0.33), indicating a 79% reduction in the risk of disease progression or death with 177Lu-DOTATATE compared to octreotide LAR.

As indicated in the recent publication in NEJM, at the time of the analysis of the primary endpoint, progression-free survival (PFS), a planned interim analysis of overall survival (OS) was conducted. A total of 14 deaths in the 177Lu-DOTATATE group and 26 deaths in the control group were observed, which represented an estimated risk of death that was 60% lower in the 177Lu-DOTATATE group than in the control group (hazard ratio for death with 177Lu-DOTATATE group versus control, 0.40; p=0.004). The O'Brien–Fleming threshold for significance at the first interim analysis was 0.000085, i.e. a tremendously high threshold for significance. Nevertheless, the level of significance was already 0.004 in this interim analysis, supporting a therapeutic benefit in overall survival.

Feedback from UK clinicians shows that progressive gastrointestinal (GI) midgut patients in the UK are administered a dose of between 1.4 – 1.6 times the recommended dose of SSA.

- Of all the trials considered by the Assessment Group in establishing the cost effectiveness of 177Lu-DOTATATE vs best supportive care (BSC) and everolimus, the NETTER-1 study is the only study which closely reflects UK clinical practice. This has been confirmed by expert clinical opinion (See Appendix 1).

In conducting their evaluation, the Assessment Group has misunderstood the pathway of care for this group of patients. This has led them to excluding the NETTER-1 and therefore 177Lu-DOTATATE from their main analysis. By relegating 177Lu-DOTATATE to a scenario analysis, the Assessment Group has not given 177Lu-DOTATATE fair consideration in its analysis.

Further misunderstandings are highlighted in descriptions of the NETTER-1 study, for example, the Assessment Group states that 177Lu-DOTATATE "has been studied in a clinical trial in people with inoperable, locally advanced or metastatic somatostatin receptor positive mid-gut neuroendocrine tumours (Ki67 index ≤ 20%) with or without disease progression compared with octreotide long acting release (LAR)." (AR, page 65). However, the Phase III NETTER-1 study enrolled only patients with confirmed disease progression.

We would like to highlight the challenge of conducting clinical studies in rare diseases such as GEP-NETs. Despite this, we have submitted a well-designed, controlled, randomised study, which has been peer reviewed by experts and published in the NEJM.

2. The Assessment Group's analysis has failed to take into consideration the anticipated marketing authorisation for 177Lu-DOTATATE

The Assessment Group has failed to take into consideration the anticipated marketing authorisation for 177Lu-DOTATATE. The intended 177Lu-DOTATATE label is [redacted].

Gastrointestinal neuroendocrine tumours (GI-NETs)

The evaluation of 177Lu-DOTATATE by the Assessment Group is restricted to patients with midgut NETs; however, the marketing authorisation is anticipated to be for all GEP-NETs. The evidence available shows that the response to treatment by midgut patients is equivalent to response by all GI NET patients.

This has been recognised by the regulatory agencies in communication exchange regarding the marketing authorisation application and the supporting clinical trial program design.

Midgut carcinoid tumour was considered as the most suitable study population for the pivotal NETTER-1 trial because of the following:

- Midgut carcinoid tumours are the most prevalent carcinoid tumour type, accounting for 40% of all types of GEP-NETs;
- Like most GEP-NETs, midgut carcinoid tumours are frequently metastatic and progressive at diagnosis, therefore, this subgroup is likely to be representative of the entire GEP-NET population;
- Midgut carcinoid tumours share similar features with other GEP-NETs, such as a common cell type origin (Mamikunian 2009) and the overexpression of somatostatin receptors (Reubi 2003).

In addition, considering that GEP-NET is, by definition, an orphan disease, most of the subpopulations are too small to conduct separate adequately powered randomised controlled trials within reasonable time spans, especially considering the high level of unmet medical need.

Pancreatic neuroendocrine tumours (P-NETs)

The Assessment Group has not fully considered the evidence submitted by AAA on the use of 177Lu-DOTATATE for treating patients with P-NETs. In the description of the interventions, the Assessment Group fails to recognise that 177Lu-DOTATATE has been studied in patients with P-NETs (AR, page 65).

In the Phase I/II Erasmus trial, which forms a key source of evidence supporting the regulatory submission to the EMA, substantial efficacy improvement in progression-free survival, time to disease progression and overall survival was achieved for GEP-NET patients receiving treatment with 177Lu-DOTATATE. This was found to be the case in all tumour classes examined which included GEP-NET, bronchial, pancreatic, foregut, midgut, hindgut, progressive GEP-NET, progressive pancreatic NET and progressive midgut NET. Most recent results were presented at the recent North American Neuroendocrine Tumor Society (NANETS) conference in 2016. Despite the inherent difficulty in conducting clinical trials in designated orphan diseases such as GEP-NETs, the Erasmus study is a well-designed, large, single-arm study with a substantial period of follow-up (mean follow up in the Dutch population 41.1 months, SD: 36.9). The overall response rate from the study was 44% (95% CI 38% - 49%) (full analysis dataset; n=360). The overall median PFS across all tumour subtypes was 29.8 months (95% CI 25.4 - 33.0 months) and overall median overall survival (OS) across all tumour subtypes was 64.4 months (95% CI 57.0 - 75.3).

- The evidence from the Erasmus clinical study shows that the benefits of 177Lu-DOTATATE are at least as good for patients with P-NETs as they are for midgut NET patients.

Established survival rates in the absence of an active treatment for patients with P-NETs are similar to that for midgut NETs, and on average worse compared to GI-NETs: 60% for midgut; 75% GI-NETs; and 60% P-NETs (Oberg et al, 2012). The evidence from the Erasmus study demonstrates that patients with P-NETs had the longest median PFS, 30.5 months, compared to 29.8 months for all GEP-NETs.

3. Somatostatin analogues (SSAs - octreotide LAR) are an established part of the care pathway in UK clinical practice for progressive and advanced patients with unresectable or metastatic gastrointestinal neuroendocrine tumours (GI-NET).

The NICE reference case states that the perspective for all evidence submissions should be that of the National Health Service (NHS) and personal social services (PSS). The analysis carried out by the Assessment Group) is not reflective of clinical practice in the NHS as it does not include the use of SSAs (octreotide LAR) in patients at this stage of the treatment pathway in England and Wales.

- Based on evidence from UK clinical practice SSAs are an important part of the pathway of care, and are used for symptomatic relief in GI-NET patients who have progressive or advanced disease.

Experience from UK clinical practice and expert opinion shows that dose escalation (or frequency of administration) of SSAs is often required following disease progression; typically at 1.6 times the average dose they received pre-progression. In the absence of an active recommended treatment, all patients receive SSAs for symptomatic relief as part of BSC.

Despite recognising the role of SSAs in various sections of the AR, the Assessment Group fails to adequately reflect this in their own economic analysis or in their critique of the submission by AAA. The treatment guidelines included in the AR clearly show that SSAs, such as octreotide LAR, are a key part of the clinical pathway for patients with disease progression. Figures 7 and 8 of the AR show their place in the pathway of care for patients with progressive GEP-NETs from established European Guidelines, published in 2016 and including several leading UK clinical experts as co-authors. Figure 6 of the AR presents guidelines from a UK NHS Trust also citing the use of SSAs (Norfolk and Norwich University Trust); however it is unclear why this specific centre has been selected and the figure cited is not included in the reference provided by the Assessment Group (Swords et al, 2010).

The Assessment Group also acknowledges the use of SSAs in the care pathway for the treatment of NETs 'Symptom control is often with a somatostatin analogue, e.g., octreotide or lanreotide' (AR, page 50). Despite these acknowledgements, the Assessment Group fails to adequately reflect the use of SSAs in this part of the care pathway in their critical appraisal of the evidence submitted by AAA or in their economic evaluation performed.

Furthermore, most clinical trials included in the submission reflect the use of SSAs in this part of the care pathway. In the RADIANT-3 trial, where patients were randomised to receive everolimus plus BSC or placebo plus BSC, approximately 40% of patients received octreotide LAR as part of BSC (Yao, 2011). In the randomised controlled trial of sunitinib plus BSC compared to placebo plus BSC over 30% of patients received SSAs (Raymond, 2011). The use of octreotide for symptomatic relief as part of BSC is demonstrated in the evidence from the RADIANT-2 trial. Furthermore, another study which stratified patients according to ongoing treatment with octreotide LAR found that co-administration of octreotide LAR did not have a clinically significant effect on the exposure of everolimus, and co-administration of everolimus did not have clinically significant effects on the exposure of octreotide LAR (Yao, 2010).

The Assessment Group fail to define BSC. They appear to have selected the control arm of RADIANT-4 to represent BSC, but the rationale for this selection is unclear given that the BSC arm of the RADIANT-4 study does not represent UK clinical practice.

- Review of the Assessment Group analysis suggests that only 1% of BSC patients receive the treatment that is the key component of BSC (SSAs). This assumption is incorrect and not in line with UK clinical practice.

The analysis performed by the Assessment Group does therefore not represent UK clinical practise and should be revised to take this into consideration.

4. There are serious flaws in the Assessment Group's analysis of the cost-effectiveness of 177Lu-DOTATATE

i. Drug acquisition cost in the progression-free state for best supportive care (BSC).

The Assessment Group's analysis underestimates the costs of best supportive care and does not reflect UK clinical practice. The analysis assumes that patients allocated to BSC receive the following treatments in the PFS health state:

- Octreotide LAR 30mg (1% of GI NET patients)
- Lidocaine
- Dexamethasone
- Prednisone
- Prochlorperazine
- Biofermin
- Sacchromyces boulardii
- External beam radiation therapy.

The analysis wrongly assumes that only 1% of patients allocated to BSC will receive octreotide LAR. Evidence from UK clinical practise shows that, in the absence of an active treatment for progressive GI-NETs, patients at this stage of treatment will <u>all</u> receive SSAs (octreotide LAR). See response point 3 for further details. The analysis performed by the Assessment Group does therefore not reflect UK

clinical practice. This assumption underestimates the cost of BSC treatment and biases the analysis against 177Lu-DOTATATE in favour of BSC.

ii. Drug acquisition cost in the progression free health state for 177Lu-DOTATATE.

In calculating the cost per cycle in the progression-free health state for patients in the 177Lu-DOTATATE group, the Assessment Group assumes that patients will receive a combination of the following treatments in addition to active treatment (177Lu-DOTATATE):

- Lidocaine
- Dexamethasone
- Prednisone
- Prochlorperazine
- Biofermin
- Sacchromyces boulardii
- External beam radiation therapy.

It is inappropriate to include these costs alongside of 177Lu-DOTATATE treatment as patients would not receive these treatments in clinical practice. Patients did not receive any of the treatments listed above either in the NETTER-1 study or at any of the 20 treatment centres in the UK at which 177Lu-DOTATATE is administered. The impact of this in the Assessment Group analysis is to overestimate the costs of 177Lu-DOTATATE.

iii. Post-progression treatment for patients who progress on active treatment in the model.

Post progression treatment for GI-NET patients in the analysis performed should be SSAs, external beam radiation therapy or liver embolisation, as these represent current clinical practice.

There are currently no recommended treatments for GI (midgut)-NET patients who have progressive or advanced disease in the UK. Feedback from clinicians in the UK suggests that once patients' disease has progressed /advanced (and in the absence of any recommended treatments), they will receive SSAs indefinitely. Depending on individual circumstances of the patients, they may undergo external beam radiation therapy or liver embolization or a combination of both in addition to SSAs.

In addition to SSAs, external beam radiation therapy and liver embolisation, the Assessment Group assumes that patients who progress on treatment in the UK will receive one or a combination of the following:

- Everolimus
- 177Lu-DOTATATE
- 5-FU
- Streptozocyn
- Interferon - 5 million units
- Lidocaine
- Dexamethasone
- Prednisone
- Prochlorperazine
- Biofermin
- Sacchromyces boulardii
- Hepatic artery embolisation
- Radiofrequency ablation

- Selective internal radiation therapy (SIRT)
- Temozolomide
- Capecitabine

There is no evidence to show that these treatments are administered to patients in the UK and this does not reflect current clinical practice. GI-NET patients in the UK are not treated with chemotherapy.

In addition to modelling an inappropriate combination of treatments post-disease progression, the Assessment Group assumes that the frequency of these treatments differs between the comparators considered, which biases against 177Lu-DOTATATE. For example, the Assessment Group assumes that substantially more patients allocated to the 177Lu-DOTATATE group will receive retreatment with 177Lu-DOTATATE post disease progression, compared to patients allocated to the other treatments. In the Assessment Group's economic model, it is assumed that 5% of patients allocated to and treated with 177Lu-DOTATATE, will go on to receive further treatment with 177Lu-DOTATATE post-progression. Whereas, the model assumes that only 3% of patients in the BSC arm will receive 177Lu-DOTATATE post-progression. Furthermore, these figures have been multiplied by an 'adjustment factor' in the model.

- This assumes that patients receiving 177Lu-DOTATATE post-progression will get 5.74 cycles of therapy if they have previously received 177Lu-DOTATATE, and only 0.03 cycles of therapy if they have previously received BSC. These estimates are implausible and do not reflect clinical practice.

There are several other differences in the assumptions made regarding the treatments that constitute BSC, depending on what treatments have previously been received. The assumptions regarding BSC should be standardised across all treatment arms as there is no evidence to justify a difference in the way patients will be treated once they have progressed. In addition, there is no evidence to suggest that retreatment with 177Lu-DOTATATE is effective or used in clinical practice. This assumption biases the analysis in favour of BSC as the post progression cost per cycle accrued by patients on 177Lu-DOTATATE is significantly higher than the cost per cycle of patients on BSC.

iv. Choice of model for extrapolation of the data.

In choosing a model for extrapolation of the data from the NETTER-1 trial, the Assessment Group has focussed exclusively on the fit of the data and not considered the clinical and biological plausibility of the inferred outcome. The Assessment Group has inappropriately chosen an exponential model as the best fit to the data. Given the nature of the disease, an exponential model is not a clinically plausible choice for GI-NET patients. Patients with GEP-NETs typically have 60-75% 5 year survival rate (Oberg et al, 2012).

- The exponential model assumes a constant rate of death over time and inherently assumes a high rate of death over time which is not the case for these patients.

In choosing the best fitted curve for the data, the Assessment Group used the results from the BIC instead of the results from the AIC. The AIC results presented by the Assessment Group show that the lognormal is the best fitting curve for the NETTER-1 data. Although the Assessment Group chose to fit both lognormal and exponential curves to all other groups in their analysis, they have only fitted the exponential model to the NETTER-1 data. The Assessment Group has not given any explanation for not fitting both models (exponential and log normal) to the data in the same way they have done for P-NET and lung/GI NET patients in the other analyses. The only logical explanation for this omission is the fact that 177Lu-DOTATATE has been relegated to a scenario analysis. We believe that the choice

of the exponential model as the best fitting model is not clinically plausible. This model assumes a constant rate of death over a patient's lifetime and it therefore underestimates the treatment benefit of 177Lu-DOTATATE.

v. Comparing 177Lu-DOTATATE to a non-prespecified subgroup of the RADIANT-4 study.

The Assessment Group analysis compares 177Lu-DOTATATE in GI patients from the NETTER-1 study to GI patients from the RADIANT-4 study. In the RADIANT-4 study: Yao et al,2016 'Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study' GI (midgut) was not a prespecified subgroup. It can therefore only be assumed that the Assessment Group were only able to perform this analysis because they had access to individual patient level data from the RADIANT-4 study. The sub groups which has been chosen by the Assessment Group does not match the group of patients in the NETTER-1 study. The midgut patient population in the NETTER-1 study are somatostatin receptor positive (SSR+) patients while the population from the RADIANT-4 study is a combination of SSR+ and SSR- patients. Therefore, we do not believe that the analysis presented by the Assessment Group reflects the true treatment difference between 177Lu-DOTATATE, everolimus and BSC. The indirect comparison performed by the Assessment Group for this subgroup of patients is therefore subject to considerable uncertainty.

vi. The Assessment Group analysis overestimates the cost of 177Lu-DOTATATE administration.

The Assessment Group analysis assumes that an overnight stay is required for the administration of 177Lu-DOTATATE in 90% of patients. However, 177Lu-DOTATATE can be administered as a day case in the majority of patients and an overnight stay is not required in most cases. In UK clinical practice approximately 65% of patients could receive 177Lu-DOTATATE as day case patients (see letter from Clinical specialist [redacted]

vii. There are inconsistencies in the way that the Assessment Group has modelled the cost-effectiveness of 177Lu-DOTATATE compared to other treatments.

There have been several inconsistencies in the way the Assessment Group has modelled the cost-effectiveness of 177Lu-DOTATATE compared to the other treatments included in the appraisal. In addition to the differences in the approach taken to identifying the most appropriate model for extrapolation (see point 4.iv), differences in assumptions around post-progression treatments (see point 4.iii) and differences in the extent and type of sensitivity analysis performed, there are also significant differences in how the Assessment Group has included all-cause mortality for 177Lu-DOTATATE.

- The Assessment Group exclude all-cause mortality in their basecase analyses for everolimus and sunitinib, but include it in their analysis of 177Lu-DOTATATE.

We suggest that a consistent approach should be taken to all treatments included in the evaluation.

viii. Selection of utility data.

Utility data (mapped from EORTC-QLQ C30 to EQ-5D) from the NETTER-1 trial are shown in Table 50 of our submission, along with further information on the health-related quality of life (HRQL) data from the NETTER-1 study presented in pages 53-54. These highlight that patients in the 177Lu-DOTATATE group had a statistically significantly greater improvement in HRQL from baseline at 36 and 60 weeks compared to the octreotide group. Mean global health status improved in 28% of patients in the 177Lu-DOTATATE arm compared to 15% in the comparator, and worsened in 18% of patients in

the 177Lu-DOTATATE arm compared to 26% in the comparator group. Diarrhoea improved in 39% of 177Lu-DOTATATE patients compared to 23% in the comparator, and worsened in 19% of patients for 177Lu-DOTATATE compared to 23% in the comparator. There was also a trend towards improvement in pain that was not statistically significant. Flushing appeared to improve compared to baseline in both arms of the study with no clear advantage to treatment with 177Lu-DOTATATE relative to the comparator. The results were presented at the ASCO GI conference in January 2017 and will be presented at the forthcoming ASCO conference in June 2017 (Strosberg et al, 2017b)

In the economic analysis we employed the conservative assumption that there were no differences in HRQL between treatments within each of the health states. Given this conservative assumption, it was not necessary to restrict the selection of utility to comparative studies and we were able to select the best available evidence. As stated on page 146 of the manufacturers submission, the best available evidence for the economic model came from a patient registry at the Guys and St Thomas hospital where UK patients with GEP-NETs are being treated with 177Lu-DOTATATE.

This is HRQL data collected from UK GEP-NET patients treated with 177Lu-DOTATATE in a real-world setting and is more generalisable to the UK clinical practice than data from the clinical trials. Analysis of these data found that few patients who were treated with 177Lu-DOTATATE had disease progression during the course of the study and therefore was used only for the GI-NET progression free health state.

The Assessment Group criticise trials of targeted treatments (everolimus and sunitinib), as their "outcomes tend to cover only the phase when patients are on treatment and it is therefore not known how health related quality of life evolves over time, or towards the end of life." (AR, page 21). AAA have provided evidence on HRQL from a real-world setting in the UK (Guys and St Thomas NHS hospital) for patients following treatment with 177Lu-DOTATATE. This has however not been fully considered by the Assessment Group.

The next best source of evidence came from the large observational study of 177Lu-DOTATATE, which included patients with GI-NETs and P-NETs. The mapped utility data from the NETTER-1 trial were presented in a scenario analysis in our submission (page 179) and demonstrated that this has little impact on the basecase ICER.

We note that the difference in utility estimates between the stable and progressive disease states provided in the submission for patients with PNETs is small. However, we note that if this difference was larger it would reduce the ICER for 177Lu-DOTATATE.

5. Response to criticisms of the systematic review submitted by AAA

i. The Assessment Group suggest that the RADIANT-2 trial should be excluded from the ITC. We included data for a subgroup of patients with colorectal NETs (n=39) reported in a post hoc analysis of the RADIANT-2 trial in our submitted ITC (Castellano et al., 2013). Colorectal patients fall under the definition of GI-NET patients used in the RADIANT-4 and NETTER-1 trials. Therefore, this subgroup was included in our analysis. AAA considers that the exclusion of these data, particularly given the limited data available for this orphan condition, is an oversight on the part of the Assessment Group.

ii. Data on adverse events for the GI-NET subgroup were not available in the RADANT-4 publication. As we did not have access to the patient level data from this study, adverse events were not included in the ITC analysis submitted by AAA.

iii. AAA performed a systematic review of non-randomised studies of P-NETs. We would like to highlight that the additional 28 trials identified by Assessment Group were not considered to meet the eligibility criteria of the systematic review we performed. Interventional studies (phase II to phase IV) or randomised studies were included if they reported at least one outcome of interest (OS, PFS, PFS2 or AEs) for more than 15 patients treated with pharmacological interventions of interest for inoperable GEP-NETs. Studies were excluded if they did not present data specifically for patients with GEP-NETs (either as a subgroup analysis or as the main trial cohort). Therefore, not all publications relating to the identified trials were included in the systematic review because they did not report outcomes of interest for the target population which was a requirement of our systematic review.

Summary

In summary, we consider that the Assessment Group's misunderstandings about the complexities of the management and treatment of patients with GEP-NETs have hindered their assessment of the clinical and cost-effectiveness of 177Lu-DOTATATE. In particular, a lack of appropriate treatments given to patients with progressed disease at this point in the pathway of care. SSAs, such as octreotide, are a key component in the management of patients, particularly for providing symptom relief, and form a key component of BSC. Also, the Assessment Group have not accurately reflected treatments given to GEP-NET patients pre- and post- disease progression, and the assumptions made around concomitant and post-progression treatments in the AR bias against 177Lu-DOTATATE. Furthermore, we note that the approach taken to extrapolating data from the NETTER-1 study are inappropriate, are not fully justified and not clinically plausible. Finally, we would like to reiterate that 177Lu-DOTATATE is an innovative treatment that offers patients a statistically and clinically meaningful increase in PFS. This has been demonstrated in the NETTER-1 study, a controlled, randomised trial which has been fully peer-reviewed and published in one of the most prestigious clinical journals.

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APPENDIX 1: Letter from clinical specialist [redacted]

(next page)

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Dr Claude Hariton, Global Head of Research and Development
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6th February 2016

Dear Claude,

This letter is a summary of our clinical practice and experience both with and without the availability of 177Lu-Dotatate in the treatment of progressive Neuroendocrine Tumours of GEPNET origin. We began treating with this therapy in 2010 and have successfully treated over 80 patients. The therapy has been well tolerated and has had a step change effect in the management of patients in relation to progression free survival and quality of life.

- We found the treatment of patients as out-patients very successful patients with Performance Status of 1 or 2. This is often a patient preference, reduces internal costs and has no determent to patient outcomes or care. Over 65% of our patients are treated as day cases.

- As part of Best Supportive Care (BSC) patients receive opioid based pain control such as codeine or morphine, loperamide for control of diarrhoea, dexamethasone for those patients with appetite suppression and somatostatin analogues (SSA).

- SSA is a critical part of BSC for those patients with symptomatic disease due to functional syndrome, such as carcinoid syndrome. Approximately 40% of patients, those with disease from midgut origin, often require an escalation of SSA doses to remain non-symptomatic.

- SSA are provided for over 70% of patients as part of symptomatic control until death.

- NETTER-1 is representative of clinical practice in patients with carcinoid syndrome. In that the dose escalation of SSA is often up to twice the recommended dose, albeit clinical practice in the UK is to deliver this at standard maximum dose, but twice the recommended frequency.

- The key result is that *Data from non-randomised trials of 177Lu-dotatate have consistently shown high response rates and long durations of median progression free survival in heterogenous patients populations with gastroenteropancreatic neuroendocrine tumours. NETTER01 trial validates these early phase data in the context of a prospective randomised trial.*

- Patients with pNETs have a comparable response to 177Lu-dotatate as those in the NETTER-01 trial.

- Post-progression patients receive External Beam Radiotherapy to bone metastases and liver embolization to abate liver symptoms as therapies.

At the end of this letter, I would also like to draw on the results of the Phase III data was published in January in the New England Journal of Medicine with the following title and key results, which are in line with our real world clinical experience.

Phase III Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumours

Hazard ratio for disease progression or death with 177Lu-Dotatate vs control: 0.21 (95% CI, 0.13 to 0.33: P<0.001), which represents a 79% lower risk of disease progression or death in in the 177Lu-Dotatae arm.

Please do contact me if you have further questions.

Yours sincerely,

[redacted]

[redacted]

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08th February 2017

Re: Novartis response to the Peninsular Technology Assessment Group (PenTAG) Assessment Report for ID858 everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression

Dear Sir/Madam,

Novartis thank the Assessment Group (AG) for the opportunity to comment on the assessment report. The report acknowledges the available evidence supporting the safety and efficacy of everolimus in patients with well- or moderately-differentiated neuroendocrine tumours (NET) of the pancreas (pNET), gastrointestinal tract (GI NET) and lung whose disease has progressed. It also recognises that in the absence of any head-to-head clinical evidence with some of the relevant comparators in the scope, estimates of relative efficacy are associated with a degree of uncertainty.

Novartis would, however, like to highlight that some of the analyses included in the report include a number of fundamentally flawed assumptions that lack a clinical basis. These assumptions ultimately result in estimates of cost-effectiveness that are highly uncertain and yield misleading conclusions around the cost-effective use of NHS resources for patients with NET.

To ensure that any recommendations for the interventions in this appraisal are based on a fair and accurate representation of the available evidence, we have identified a number of clinical and economic issues that we kindly request the AG and committee consider. These issues are structured according to the different tumour types for which everolimus is indicated and we welcome the opportunity to provide ongoing support for this appraisal.

Yours sincerely,

Health Economics & Outcomes Research Manager

Novartis Pharmaceuticals UK Limited

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

Novartis response to the Peninsular Technology Assessment Group (PenTAG) report

File name	Version	Contains confidential information	Date
		Yes (Redacted)	

Contents

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1. Executive Summary

In this response document Novartis summarise our key comments on the Peninsular Technology Assessment Group (PenTAG) assessment of everolimus, lutetium-177 DOTATATE (lu-177 DOTATATE) and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression (ID858). As the manufacturer of everolimus, we highlight that everolimus is the only targeted therapy with licensed indications across multiple NET types, including pNET, GI NET and lung NET. Consequently, our response to the assessment report is structured according to the different tumour types for which everolimus is indicated, and describes the key clinical and economic points for consideration.

pNET

The AG's economic analysis predicts superior survival outcomes for sunitinib compared to everolimus and concludes that only sunitinib is likely to meet the end of life criteria in this tumour type; results that we consider counterintuitive. There is no robust evidence to suggest that sunitinib will confer better survival than everolimus. The estimates of efficacy upon which the economic case is based are derived from indirect treatment comparisons (ITCs) that variably favour either everolimus or sunitinib, depending on the outcome being assessed and the methodology employed. The results of the ITCs are associated with wide confidence intervals suggesting both a high level of uncertainty in the ITC results and little evidence of a difference in clinical efficacy. Furthermore clinical experts experienced in the treatment of the patient population in question support the view that the efficacy of sunitinib and everolimus is comparable. Finally, given that everolimus and sunitinib are being assessed for the same patient population, it is illogical that sunitinib but not everolimus was considered to meet the end of life criterion of short patient life expectancy.

Re-conducting the AG analyses based on more realistic assumptions of equal efficacy and treatment duration (specific considerations around treatment duration are provided in the response), sunitinib yields the same level of benefit as everolimus and is associated with a cost saving of only £146 at list price. For the comparisons with BSC, we find the ICERs for everolimus and sunitinib to be similar (£32,673/QALY vs. and £32,505/QALY, respectively), and note that everolimus is more cost effective at the discounted PAS price.

GI and lung NET

The AG estimated the ICER for everolimus vs. BSC in GI and lung NETs to be £44,557/QALY at list price. While there are differences between Novartis' approach and that employed by the AG, this result is consistent with the economic analysis presented in our original manufacturer's evidence submission (£43,642/QALY) and consequently we consider this analysis to be a fair appraisal of everolimus in this indication.

GI (midgut) NET

In the absence of head-to head trial evidence for everolimus and lu-177 DOTATATE, the AG conducted an ITC using comparative efficacy data from the RADIANT-4 and NETTER-1 trials. Because of differences in the populations of the two trials and the lack of robust data on OS, the results of the ITC are subject to a high level of uncertainty and potentially biased. We therefore share the AG's reservations around these analyses and strongly advise that the results be interpreted with caution.

Finally, we note that the analyses included in the AG report were conducted at the respective list prices rather than at the confidential PAS prices available to the NHS. Upon consideration of the

PAS for everolimus, we consider that everolimus represents a clinically and cost-effective treatment option to the NHS at the [redacted] for both pNETs and GI and lung NETs.

2. Key Clinical Considerations in pNETs

Novartis politely request the AG and committee consider six key points with regards to the available clinical evidence and the interpretation of such evidence in pNETs:

- The lack of relevance of lu-177 DOTATATE as a comparator in pNETs
- The lack of relevance of best supportive care (BSC) as a comparator for everolimus and sunitinib in well- or moderately-differentiated progressive pNETs
- The clinical and statistical uncertainty surrounding the estimates of OS derived from crossover adjustment methodology and the impact on cost-effectiveness analyses
- The uncertainty associated with the ITCs and the impact on the cost-effectiveness analyses
- The treatment duration of everolimus and sunitinib is not expected to differ in clinical practice
- The appropriateness of the methods uses to assess whether the interventions meet the end of life criteria

These key points are described in further detail in the relevant sections below.

2.1. Lu-177 DOTATATE is not an appropriate comparator in pNETS

Novartis wholly agree that a comparison of lu-177 DOTATATE with everolimus or sunitinib in pNET is inappropriate on the basis that the pivotal trial for lu-177 DOTATATE in GI NET (NETTER-1) did not include any patients with pNETs and that the ERASMUS study in progressive pNETs was non-randomised and included only a small subgroup of patients treated with lu-177 DOTATATE. Consequently, we believe that the results of the ITC and economic evaluation of lu-177 DOTATATE in pNETs lack any robustness and should not be used to inform decision making around the cost-effective use of NHS resources in NETs.

2.2. Best supportive care (BSC) is not a relevant comparator to everolimus in patients with metastatic, well- or moderately-differentiated pNETs whose disease has progressed, due to the evolution of the treatment pathway with the approval of targeted treatments

Novartis presented a clear clinical case (page 13 of our manufacturer's submission) describing why it is appropriate to consider sunitinib as the sole relevant comparator to everolimus in the patient population under review. This rationale was based on consideration of the available evidence base in addition to current clinical practice.

Although the pivotal trials for everolimus (RADIANT-3)[1] and sunitinib (A6181111)[2] were head-to-head trials with BSC, it should be noted that at the time that these studies were initiated (2007), limited treatment options were available and BSC was considered the standard of care. The regulatory approval of everolimus and sunitinib in 2011 signalled a step-change in the treatment paradigm for a disease with a high unmet clinical need. It is in this context that we considered sunitinib to be the sole relevant comparator to everolimus in this patient population. This is supported by current UK (UKINETS)[3] and European (ENETS)[4] clinical guidelines which recommend both everolimus and sunitinib as second-line treatment options for patients with advanced, progressive well- or moderately-differentiated pNETs. These therapies are now considered the standard of care in this patient population and this was confirmed with internationally recognised UK clinical NETs experts who validated our rationale on the relevant comparators for this tumour type.

Consequently, the statement that *"the company did not provide reasons for omitting BSC from the analysis, for which head-to-head trial data were available against each of the targeted treatments in RADIANT-3 and A6181111"* is not consistent with the rationale provided in our submission.

In addition, the report also states *"in the opinion of our clinical experts, BSC is a relevant initial treatment option for patients with advanced, progressive pNETs and small or asymptomatic tumours, in whom active treatment may be considered upon disease progression"* (page 190). Whilst BSC may still be considered a treatment option for patients with poorly differentiated pNETs, or for advanced patients who have failed several lines of existing therapy, this is not the case for patients with well- or moderately-differentiated pNETs, who are the focus of this assessment. For these patients, the treatment pathway has now changed; everolimus and sunitinib are now considered standard of care.

Therefore, we politely request that the relevance of BSC as a comparator to everolimus and sunitinib in pNETS is reconsidered, given that everolimus and sunitinib are considered the current standard of care.

Furthermore, NETs are a complex condition to treat and, within the UK, treatment tends to be centralised in European NET (ENETS) centres of excellence. We therefore suggest that it is important that as part of the ongoing consultation on this appraisal, NICE consult with oncologists actively prescribing these drugs in these centres in order to confirm the current treatment pathway.

2.3. Estimates of OS derived from the rank preserving structural failure time (RPSFT) crossover adjustment should be interpreted with caution

Novartis agree with the AG that the RPSFT model is the most appropriate approach for adjusting for treatment crossover in the RADIANT-3 and A6181111 trials. Nevertheless, Novartis believes that it is critically important to understand and acknowledge the following assumptions underlying this approach:

- the effect of treatment is the same regardless of the timing of such treatment; and
- the effect of treatment is to extend survival, as in an accelerated failure time model, rather than to reduce the hazard (as in a Cox proportional hazards model).

It should be noted that the first assumption is untestable and that the second was not evaluated in either of the trials.

Novartis also note that potential bias in the application of the RPSFT method can be avoided by the application of a re-censoring algorithm that reduces the effective follow-up for the placebo group in the analysis. Such re-censoring increases the statistical uncertainty around the point estimate of treatment effect, and limits the utility of the placebo data for projecting outcomes beyond the end of follow-up in the trial.

Accordingly, whilst the RPSFT approach is generally the most approach for assessing the overall survival (OS) benefit of treatment in clinical trials with a high degree of crossover, the estimates of OS derived from such analyses should be interpreted with caution and evaluated with reference to other supporting information from the trial, including the benefit of treatment on response rates and progression-free survival (PFS), as well as external data from appropriate historical controls.

2.4. The ITCs are associated with wide confidence intervals, suggesting uncertainty in the results and little difference between everolimus and sunitinib

Novartis and the AG both used the Bucher method to compare everolimus and sunitinib in a number of ITCs, including survival (PFS and OS (ITT and RPSFT)), adverse events (AEs) and the use of somatostatin analogues (SSAs). The AG also conducted an ITC of response rates. In all the ITCs (with the exception of OS in the ITT population), the assessment report concludes that the "*analyses were associated with wide 95% CIs, including the null hypothesis of no difference, suggesting little evidence of a difference between everolimus and sunitinib"*. These conclusions with regards to PFS and crossover adjusted OS are consistent with the findings from the ITC conducted by Novartis. In consideration of the potential biases associated with the RPSFT assumptions, priors based on similarity of PFS and response and the lack of reliable evidence for a difference in treatment effect, we believe that an assumption of no difference in efficacy is reasonable as discussed further below.

2.4.1. PFS

The results of the ITCs for PFS conducted by Novartis and the AG were similar, suggesting no evidence of a difference in effectiveness between everolimus and sunitinib. It is also important to note that whilst the ITC for PFS by local review (the primary endpoint in RADIANT-3 and A6181111) numerically favoured everolimus (HR 0.83, 95% CI 0.49, 1.42), the ITC of PFS by central radiological review numerically favoured sunitinib (HR 1.06, 95% CI 0.57, 1.97), although the 95%CI of the HRs for both comparisons spanned 1.0. In addition, the median PFS by local investigator assessment was similar for the everolimus arm in RADIANT-3 (11.0 months) and the sunitinib arm in A6181111 (11.4 months). Considering all of the above, Novartis considers it reasonable to assume no difference in PFS between the two treatments.

2.4.2. OS

We agree with the AG that the results from the ITC derived from HRs for OS from the ITT populations of the RADIANT-3 and A6181111 trials are unreliable, and that the ITC based on the OS adjusted for treatment crossover using the RPSFT method is more appropriate. We also acknowledge the difference in the RPSFT adjusted HR of sunitinib versus placebo estimated from our ITC (HR 1.40) and that estimated by the AG in their analysis (HR 1.76) as an oversight in our review of the latest available data. We also note, however, that this difference does not affect the direction of the comparison or qualitatively impact the width of the CI on the HR for the RPSFT adjusted OS of everolimus vs. sunitinib.

As highlighted above, one of the major criticisms from the AG on the Novartis ITC relates to the interpretation of the results; *"Novartis misrepresent the wide confidence intervals in the results of the ITC as evidence of no effect"* (pages 16 and 192). In response to this, Novartis would like to clarify the following:

- **The estimates of OS are based on the RPFST model; thus the potential biases and uncertainty associated with the RPFST estimates of OS may be further magnified in an ITC.** As discussed previously, the RPSFT method requires the assumption of a common treatment effect; therefore, if this assumption does not hold then the estimates of treatment effect derived from the method may be biased. Additionally, if the timing of crossover in the two trials varies, then the degree of bias can differ across trials, which would violate the similarity assumption required by the ITC. Information on the timing of crossover (with respect to randomisation and whether it occurred before or after progression) in both trials is not available, and it is therefore not possible to assess the extent of any such bias.

- **In an ITC of two treatments based on two trials with a single common comparator, the variance of the indirect estimate of treatment effect is equal to the sum of the variance of the two treatment effect estimates. This may also introduce further uncertainty into the analysis.** Given the high degree of uncertainty associated with the RPSFT estimates from A6181111 and RADIANT-3 independently, the degree of uncertainty in estimating the treatment effect of everolimus versus sunitinib on OS in an ITC based on the RPSFT estimates is considerable (the HR for OS for everolimus vs. sunitinib based on the RPSFT estimates is associated with wide confidence intervals ranging from 0.20 – 15.78).

- **The ITC of response rates and PFS provided little evidence of a difference between everolimus and sunitinib** (page 100), and therefore little evidence to support a clinically meaningful difference in survival. Given the established clinical link between tumour response, PFS and OS, it is not unreasonable to be critical of any suggestion of clinically meaningful differences in PFS and OS between everolimus and sunitinib when there is no suggestion of a difference in PFS or response rates.

When considering all of the above points in their entirety, the estimates of relative efficacy are subject to considerable uncertainty, and it is not unreasonable to assume no difference in efficacy between everolimus and sunitinib, as assumed in our economic analyses.

We also note that the results of a published matching-adjusted indirect comparison (MAIC) sponsored by Novartis[5] and a more recent analysis by Pfizer as part of their evidence submission, provide further evidence to support the assumption of no difference in efficacy between the two therapies. In the MAIC sponsored by Novartis, patients receiving everolimus in RADIANT-3 were matched to those receiving sunitinib in the A6181111 trial, and the results of the comparison suggested more favourable OS outcomes with everolimus than sunitinib. In contrast, the MAIC submitted by Pfizer was conducted using more mature data, with patients receiving sunitinib in the A618111 trial were matched to those receiving everolimus in RADIANT-3, and the results of this comparison suggested more favourable OS outcomes with sunitinib than everolimus. The inconsistency between the MAICs that are derived from attempts to match the same two trial populations in order to obtain an indirect estimate of relative efficacy highlight the high degree of uncertainty regarding the true relative treatment effects of everolimus and sunitinib.

2.5. Treatment duration is not expected to be different for everolimus and sunitinib in clinical practice

On page 183 of their report, the AG state that *"Novartis assumed that the cost of sunitinib drug acquisition and dispensing was incurred for the same number of mean treatment cycles as everolimus, on the basis that their indirect treatment comparison found no difference in PFS duration between the two treatments. This assumption seems untenable in the light of the available data on treatment duration from A6181111 and RADIANT-3. The company performed sensitivity analysis using an alternative figure of 9.66 months of sunitinib treatment duration, which the company attributes to the literature without providing reference. It also cites a submission by Pfizer to the AWMSG where the company is reported to have assumed "patients receive an average of 293 days of treatment per year. However, in their submission to NICE, Pfizer reported an average duration of sunitinib of 8.3 months in clinical practice (253 days; Pfizer submission to NICE, p. 17).*

*Further, the median treatment duration with sunitinib in A6181111 was 4.64 months (Raymond et al. 2011) as opposed to the ********** of everolimus use in RADIANT-3."*

Novartis would like to suggest that an assumption of similar treatment duration for everolimus and sunitinib is reasonable and appropriate.

In clinical practice, treatment with everolimus and sunitinib is to be continued until no clinical benefit is observed or until unacceptable toxicity occurs. Further to this, it is important to note that the median PFS by local assessment for everolimus (11.0 months) and sunitinib (11.4 months) in their respective trials were similar, further supporting an assumption of a similar treatment duration between the two treatments. Moreover, as stated and clearly referenced in our manufacturer's submission, the manufacturer of sunitinib reported an average treatment duration of 293 days in their submission to the AWMSG.[6] Since 293 days is approximately 9.66 months, Novartis strongly disagrees with the statement from the AG that no reference was provided for this assumption.

Finally, we note that a treatment duration of 293 days or 253 days, as reported by Pfizer in their submissions to the AWMSG and NICE, respectively, still provide supportive evidence that everolimus and sunitinib are likely to have a similar treatment duration and that the treatment duration of 4.64 months observed in A6181111 is much lower than would be expected in clinical practice.

2.6. Inappropriate approach to the assessment of end of life criteria

The AG report states that *"based on the data from the three sources of effectiveness data (RADIANT-3, A6181111, and RADIANT-4), only sunitinib plus BSC in the pNETs population of A6181111 may meet the end of life criteria"* (Page 20).

The end of life criteria stated in the NICE guide to the methods of technology appraisal[7] and accompanying addendum to the methods to support the proposed new Cancer Drugs Fund arrangements[8] are as follows:

- *the treatment is indicated for patients with a short life expectancy, normally less than 24 months*
- *there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment*

Since the first criterion refers to the life expectancy of the patient population, Novartis find it inappropriate for the AG to consider one treatment to meet this criterion and the other to not, given that both everolimus and sunitinib are being appraised for use in the same patient population in clinical practice.

The methodology the AG used to assess whether each treatment met this criterion is fundamentally flawed since it involves assessing whether the 95% confidence intervals for the mean OS of placebo in the RADIANT-3 and A618111 trials includes 24 months. Since this approach is dependent on the specific patient population within each of the different trials, rather than the expected patient population in clinical practice, the conclusion that only sunitinib meets the end of life criteria is inappropriate.

Moreover, with regards to the criterion of a 3-month extension of life, and as discussed in detail above, Novartis would like to highlight that the effectiveness data generated by the ITC is subject to considerable uncertainty; consequently, there is insufficient evidence to suggest a difference in efficacy between everolimus and sunitinib. This is supported by expert clinical opinion and as such

we re-iterate that the applicability of this criterion should be the same for both everolimus and sunitinib.

In conclusion, Novartis kindly request that the AG and the appraisal committee strongly reconsider their assessment on which treatments meet the end of life criteria and base any decisions on the applicability of these criteria on considerations of the patient population in clinical practice and the lack of evidence to support a significant difference in efficacy between everolimus and sunitinib.

3. Key Economic Considerations in pNETs

The key points Novartis would like to highlight with regards to the cost-effectiveness analysis for everolimus and sunitinib in pNETs are as follows:

- The underlying assumptions in the economic case do not reflect the available clinical evidence and are flawed.
- The results of the economic analyses are highly uncertain and unreliable
- Everolimus may potentially represent a cost-effective treatment to the NHS when the confidential Patient Access scheme is considered.

These points are discussed in further detail below.

3.1. The estimates informing the AG model are unreliable as key assumptions underpinning the model are flawed

Firstly, as described previously, the estimates of efficacy derived from the ITC of everolimus and sunitinib are associated with considerable uncertainty, with little evidence to suggest any difference in efficacy between the two treatments. An assumption of equal efficacy is therefore supported.

Secondly, base case extrapolations in the assessment report were selected according to goodness of fit, visual fit and clinical plausibility. For PFS, this ultimately resulted in the Weibull function being selected for everolimus and BSC, and the exponential function selected for sunitinib. For OS, the exponential was selected for all treatment arms. The sunitinib PFS and OS exponential parametric curves were then adjusted by the ratio of the area under the non-parametric Kaplan-Meier curves for placebo in A6181111 and RADIANT-3 in order to derive comparable estimates of survival for sunitinib and everolimus (page 231).

The differences in assumptions around efficacy and choice of parametric functions in our evidence submission and those described in the assessment report have ultimately translated to:

- What the AG describe as a *"superior PFS and OS for people treated with sunitinib compared to everolimus (OS of 6.39 years versus 4.62 years)"* (page 284)
- Greater QALYs for sunitinib (3.24) compared to that of everolimus (2.51) due to longer PFS and OS

These analyses lack face validity for several reasons:

- A similar PFS based on local assessment for everolimus (11.0 months) and sunitinib (11.4 months) was observed in their respective trials. Furthermore, there is no evidence or plausible explanation as to why this would translate into an OS difference of nearly 2 years
- The ITC for PFS suggested little evidence of a difference in the two treatments. Moreover, uncertainty in any difference in PFS was highlighted by the fact that the point estimate for locally assessed PFS favoured everolimus whereas the estimate for centrally assessed PFS favoured sunitinib
- The OS estimates were based on RPSFT analysis which further compounds the uncertainty in the survival estimates as a result of susceptibility of these analyses to bias
- Combining the estimates of PFS and OS in the model projects a gain of 1.37 post-progression life years for sunitinib vs. everolimus, a value that is more than 4 times greater than the gain in pre-progression life years (which is also highly uncertain and contingent on the choice of the PFS measure used in the analysis [central or local]). This result lacks

face validity since the analysis assumes that sunitinib is administered on average for only 7.5 months, and that mean pre-progression life years are 1.6 years (19 months). While it is reasonable to assume that targeted therapies may yield benefits on post-progression survival, the magnitude of the gain in post-progression survival given the short treatment duration relative to PFS lacks clinical face validity. Even if it is assumed that the treatment duration for sunitinib is equal to that for everolimus (as assumed in our evidence submission), there is no evidence to support an assumption of a continuing benefit in post-progression survival of this magnitude, suggesting that the projections of the OS benefits of sunitinib versus everolimus are likely flawed.

In addition, despite PFS by local review being the primary endpoint in both trials, the AG did not use this in their base case, but used the post-hoc analysis of PFS by central review, whilst exploring locally-assessed PFS in the scenario analyses (page 271). PFS by local review is more likely to be reflective of outcomes in typical clinical practice, whilst PFS by central review may be subject to bias due to informative censoring in cases of unconfirmed investigator-assessed progression.[9] Analyses of hazard ratios for PFS from controlled trials have found no evidence of bias with investigator assessed versus BIRC-assessed PFS.[10] Consequently, Novartis believe that PFS based on local review is a more appropriate endpoint for use in the economic evaluation since it is most likely reflective of routine clinical practice, was the primary endpoint in both trials and unlikely to be biased

Moreover, clinical expert opinion from oncologists who actively prescribe everolimus and sunitinib in the UK also suggests little clinical evidence to support an assumption of superior efficacy of one treatment over the other. These treatments are considered as interchangeable in clinical practice and the choice of treatment is very much dependent on the toxicity profile and physician/patient choice.

Consequently, after considering all the potential uncertainty in the survival analysis, there is no robust evidence, plausible rationale or clinical support for the assumption that sunitinib confers a survival benefit versus everolimus.

3.2. The results of the AG's economic analyses are highly uncertain and unreliable

The AG's base case ICER (at list price) was £45,493/QALY for everolimus vs. BSC, £20,717/QALY for sunitinib vs. BSC and £745/QALY for sunitinib vs. everolimus. The cost-effectiveness results for everolimus vs. BSC are twice that of sunitinib vs. BSC, driven by the assumption that sunitinib confers greater additional life years and QALYs compared to everolimus. This assumption is inconsistent with the available clinical evidence and expert clinical opinion, as discussed previously.

Given the concerns with the assumptions noted above, and to assess a more plausible cost-effectiveness estimate for everolimus and sunitinib vs. BSC, Novartis have updated the PenTAG economic model to include an assumption of equal treatment duration and efficacy for everolimus and sunitinib using parametric functions jointly fit to the two treatments arms of RADIANT-3 (Appendix 10.1; Figure 10. 1 and Figure 10. 2). Based on this curve fitting analysis, we found the restricted lognormal model to be the most appropriate model for PFS and the restricted Weibull model to be the most appropriate model for OS.

These revised assumptions result in list price ICERs of £32,673/QALY for everolimus vs. BSC and £32,505/QALY for sunitinib vs. BSC. (Appendix 10.1). A comparison of the AG's analyses and our revised analyses is presented in below, with the disaggregated results in Appendix 10.1; Table 10. 2.

Table 1. Comparison of the AG's base case ICERs with Novartis's revised analyses (assuming equal efficacy, list price)

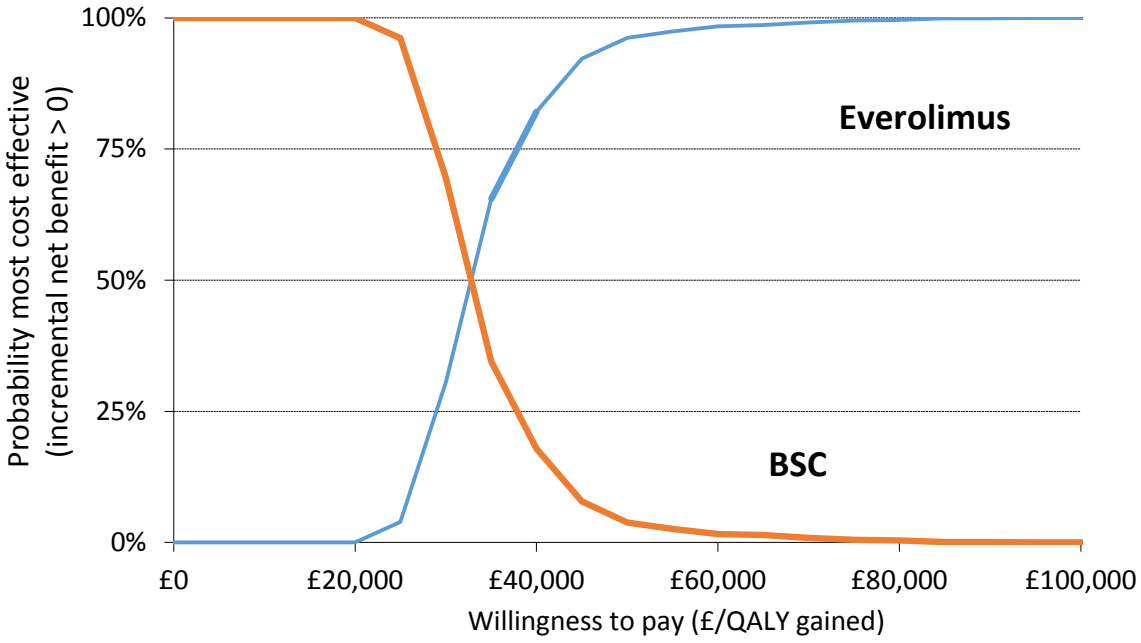
	Novartis Updated			PenTAG		
	EVE	BSC	Difference	EVE	BSC	Difference
LYs	4.39	2.70	1.69	4.69	3.46	1.23
QALYs	2.44	1.57	0.87	2.51	1.91	0.59
Cost	£42,381	£14,035	£28,346	£42,646	£15,761	£26,885
ICER (Cost / QALY)			£32,673			£45,493

BSC: best supportive care; EVE: everolimus; SUN: sunitinib; QALY: quality-adjusted life year

The results of the comparison of everolimus vs BSC above are more favourable than those reported by PenTAG, reflecting the substantially greater projected gain in LYs and hence QALYs with everolimus, and shorter projected LYs with BSC. While it is not possible to definitively state which of these two set are results is more accurate, we believe that the results for the updated Novartis analysis are more robust as the OS for the BSC arm in the assessment report is based solely on the RPSFT adjusted OS data, which are highly re-censored and therefore associated with substantial uncertainty. Conversely, the OS for BSC in the updated Novartis analysis was estimated jointly with the OS for everolimus, thus using the information on longer term OS from the everolimus arm to inform the estimation of OS for the BSC arm.

Our revised analyses show the probability of everolimus being cost-effective compared to BSC to be 33% at the £30,000/QALY threshold (Figure 1).

Figure 1. Cost-effectiveness acceptability curve for everolimus vs. BSC in pNETs



BSC: best supportive care; EVE: everolimus; pNETs; pancreatic neuroendocrine tumours; QALY: quality-adjusted life year

3.3. Everolimus represents a cost-effective treatment option when the confidential Patient Access scheme is considered

Novartis acknowledge that none of the analyses in the assessment report take into account the confidential Patient Access Schemes for everolimus, sunitinib and lu-177 DOTATATE (all

analyses presented in the assessment report are based on the list prices). However, we would like to highlight that when the current PAS for everolimus ([redacted] is applied to the AG's base case analysis, everolimus becomes more cost-effective, with the ICER vs. BSC decreasing to [redacted] and everolimus dominating sunitinib as a result of the lower drug acquisition costs. Consequently, the probability of everolimus being cost effective vs. BSC at the £30,000/QALY threshold is [redacted].

4. Key Clinical Considerations in GI and lung NETs

The clinical evidence for everolimus in advanced, progressive, non-functional GI and lung NETs is based on direct evidence from the RADIANT-4 trial and constitutes a comparison against BSC, the current standard of care in clinical practice. The RADIANT-4 trial showed that treatment with everolimus was associated with a significant improvement in PFS compared with BSC, in patients with progressive GI or lung NETs. Furthermore, we highlight that everolimus is the only targeted agent with demonstrable anti-tumour activity in NETs of GI and lung origin, with the potential to meet the unmet need for clinically effective treatments in this patient population.

5. Key Economic Considerations in GI and lung NETs

Whilst the Novartis economic evaluation of everolimus in GI and lung NETs is generally aligned with that of the AG (£43,642/QALY and £44,557/QALY respectively – Table 2), Novartis would like to highlight that when the confidential PAS for everolimus is considered, everolimus becomes a cost-effective treatment option in this patient population [redacted].

Table 2: Comparison of the AG's base case ICERs with Novartis's analyses

	Appraisal Group (page 269)		Novartis	
	EVE	**BSC**	**EVE**	**BSC**
Total Life years (undiscounted)	6.21	4.82	5.79	4.78
Total QALYs (discounted)	3.74	3.05	4.29	3.51
Total Costs (list price)	£47,334	£16,526	£59,720	£25,817
Total Costs (PAS price)	Not reported		[redacted]	
ICER (list price)	£44,557		£43,642	
ICER (PAS price)	Not reported		[redacted]	

BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; SUN: sunitinib.

6. Key Clinical Considerations in Midgut GI NETs

The key point Novartis would like to highlight with regards to the available clinical evidence for everolimus and lu-177 DOTATATE is that the assumptions underpinning the comparative analysis are fundamentally flawed and are not supported by the clinical evidence.

Although Novartis agree with the AG that lu-177 DOTATATE would represent a relevant comparator to everolimus in midgut GI NETs in clinical practice, we do not consider the AG's analysis to be sufficiently robust to form a clinically meaningful conclusion for the following reasons:

- **The evidence base for the analysis is severely limited, based on unpublished data from the NETTER-1 trial and a small subgroup of patients from the RADIANT-4 trial**

- **The patient populations in the NETTER-1 trial and the subgroup of GI patients that the AG considered from RADIANT-4 trial are not comparable.** The NETTER-1 trial included patients with functioning and non-functioning midgut NETs, whereas RADIANT-4 included patients with non-functioning NETs so it is unclear whether the midgut subgroup of RADIANT-4 represents a patient population with similar prognoses as to those in NETTER-1.

- **There is no clinical evidence to support the assumption that octreotide LAR 60 mg in NETTER-1 is equivalent to the placebo plus BSC in RADIANT-4.** As a naïve comparison, the PROMID study[11] compared Octreotide LAR 30 mg to placebo and demonstrated a statistically significant increase in PFS for Octreotide LAR 30 mg versus placebo; given this, the assumption that a higher dose of Octreotide LAR (60 mg) is of equal efficacy to placebo plus BSC is not considered to be appropriate.

- The analysis did not adjust for the extent of treatment crossover in RADIANT-4, limiting the interpretation of OS results

Given the high level of uncertainty in these analyses, we agree with the reservations in the assessment report and strongly recommend that the results of the ITC be interpreted with extreme caution.

7. Key Economic Considerations in Midgut GI NETs

Novartis would like to highlight that the economic evaluations for midgut NETs in the assessment report are based on assumptions derived from the limited clinical evidence described previously. Consequently, the results of such analyses are inappropriate, misleading, and lack robustness to inform any form of effective decision-making on the use of NHS resources.

- **The comparison of everolimus to BSC is subject to high levels of uncertainty as the estimates for everolimus OS were derived by assuming that OS is proportional to PFS.**

  In the absence of published OS data for the GI (midgut) population in RADIANT-4, estimates for OS were derived by assuming that OS for midgut GI NET is equivalent to OS in the overall RADIANT-4 population (GI and lung NET) adjusted by the proportional difference in mean PFS for GI (midgut) vs GI and Lung NET (page 244). This approach lacks internal validity since it yields estimates of an increase in life expectancy with everolimus vs. BSC (0.440) that are less than the gain in progression free life years (Table 148 in the assessment report). The high levels of uncertainty in this approach are further compounded when one considers that the midgut primary tumour location was not a stratification factor in the RADIANT-4 trial, and therefore there may be imbalances in baseline characteristics across treatment arm in the subgroup that could confound the comparison of everolimus and BSC. Also, GI midgut subgroup represented only 38% of the total study population and therefore estimates of treatment benefit from this group are associated with high degree of uncertainty. The AG's base case ICER of £199,233 for everolimus vs. BSC in midgut NETs is highly questionable.

- **The comparison of everolimus vs lu-177 DOTATE is subject to high levels of uncertainty since the comparative efficacy estimates are based on assumptions with no clinical basis and relevant costs may have been omitted**

  Inappropriate assumptions on survival (one of the key inputs in the model) and oversights in the costs of treatment, adverse events and resource use mean that the cost effectiveness estimates are subject to potential bias and are highly uncertain:

  - The ITC for everolimus and lu-177 DOTATATE is compromised by both the quality and quantity of data from the respective RADIANT-4 and NETTER-1 trials.
  - The AG model does not include the costs of octreotide LAR 30 mg that was part of the treatment protocol for patients in the study arm of the NETTER-1 trial. If the approved treatment regimen for lu-177 DOTATATE in the SmPC includes octreotide LAR 30 mg, then the cost of this therapy should be included in the economic evaluation.

  We agree with the AG's reservations on the analysis of lu-177 DOTATATE; however in order to address some of the limitations described above, we:

  - Conducted an analysis using the PenTAG model, incorporating assumption of equal efficacy for octreotide LAR (60mg) and placebo and fitting the different parametric functions to the PFS and OS in the GI subgroup of RADIANT-4 (Appendix 10.2). It is important to note that the whole GI population from RADIANT-4 (excluding carcinomas of unknown primary origin- CUP) was used in our analysis, whereas, the analysis reported in the assessment report is only based on the GI midgut population. We used the whole GI population rather than the midgut

population since the midgut population is a subset of the GI population and therefore constitutes a smaller population than GI and associated with greater uncertainty. The exponential model was found to be the most appropriate parametric distribution for both PFS and OS, which is the same distribution used in the assessment report.

- Estimated the cost of lu-177 DOTATATE by calibrating the PenTAG model to approximate the results presented in the assessment report.
- Included the cost of octreotide-LAR (30mg) as observed in NETTER-1.

These revised assumptions result in list price ICERs of £36,234/QALY for everolimus vs. BSC, £28,684/QALY for lu-177 DOTATATE vs. BSC and £23,965 for lu-177 DOTATATE vs. everolimus. A comparison of the AG's analyses and our revised analyses is presented in Table 3, with the disaggregated results in Appendix 10.2; Table 10. 6. The results of the PSA, including disaggregated results, PSA scatterplot and cost-effectiveness acceptability curves, are also presented in Appendix 10.2.

Table 3. Comparison of the AG's base case ICERs with Novartis's analyses in GI NETs

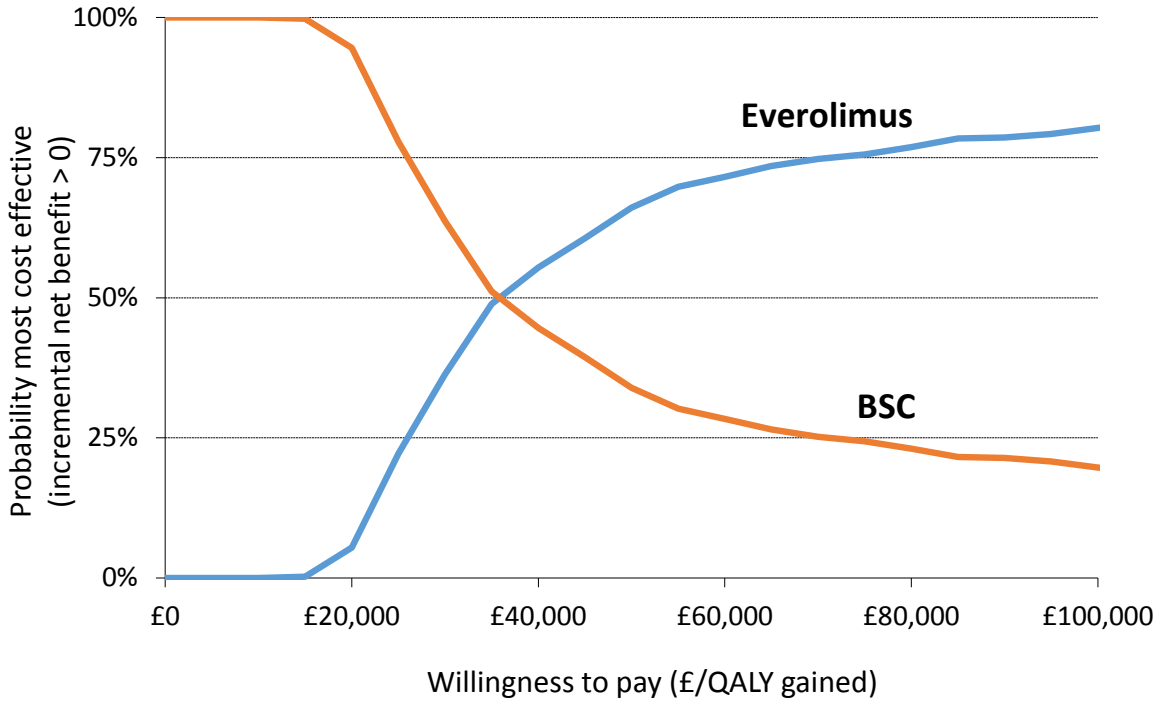
	Appraisal Group (Page 271)			Novartis analyses		
	EVE	**lu-177 DOTATATE**	**BSC**	**EVE**	**lu-177 DOTATATE**	**BSC**
Total Life years (undiscounted)	5.75	6.66	4.90	7.52	10.94	5.40
Total QALYs (discounted)	3.57	4.19	3.11	4.43	6.10	3.38
Total Costs	£52,018	£83,667	£16,628	£55,878	£96,044	£17,905
ICER EVE vs BSC	**£78,330**			**£36,234**		
ICER lu-177 DOTATATE vs EVE	**£50,499**			**£23,964**		
ICER lu-177 DOTATATE vs BSC	**£62,158**			**£28,684**		

BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

The results of the comparison of everolimus vs. BSC and 177-lu DOTATATE vs. BSC above are substantially more favourable than those reported by the AG, reflecting the greater projected gain in LYs and hence QALYs with everolimus and 177-lu DOTATATE in our updated analyses. For the 177-lu DOTATATE vs. BSC comparison, the greater projected costs for 177-lu DOTATATE reflect the inclusion of costs for octreotide LAR (30 mg) for all patients receiving 177-lu DOTATATE, and also reflects the different methods used to generate PFS and OS with 177-lu DOTATATE in our updated analysis vs. the analyses by PenTAG.

Our revised analyses show the probability of everolimus being cost-effective compared with BSC in GI tumours to be 36.3% at the £30,000/QALY threshold (Figure 2).

Figure 2. Cost-effectiveness acceptability curve for everolimus vs. BSC in midgut GI NETs



BSC: best supportive care; EVE: everolimus; GI NETs; gastrointestinal neuroendocrine tumours; QALY: quality-adjusted life year.

8. Minor Clarifications and Corrections

Novartis have identified a number of points for clarification in addition to factual inaccuracies within the AG report. These points are detailed below in Table 4 and Novartis kindly request that these points be acknowledged and amended in the final report.

Table 4: Minor clarifications and corrections

	AG Comment/ Description	Reference to the AG report	Clarification/correction
1	The justification for using the Bucher method of indirect comparison is not clear when a MAIC analysis would have been possible.	153	As described on page 49 of our manufacturer's evidence submission, given the limitations of the MAIC approach, the Bucher method was used to indirectly compare everolimus and sunitinib. The limitations of the MAIC are that it may address differences between studies where there are common factors to support the matching process; however, it is unclear if there were any unobserved differences in patient characteristics or other systematic differences between the two trials which may have affected the indirect comparison. In addition, the MAIC had been used in previous health technology appraisals for the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) and the SMC had regarded the methodology as "non-standard with uncertainty as to the robustness of this type of analysis". [12] Given the limitations of the MAIC approach, the Bucher method has instead been used to indirectly compare everolimus and sunitinib for this submission.
2	The median follow-up period in RADIANT-3 was 17 months, with median treatment durations of ********** for everolimus versus 3.74 months with placebo. However, in the economic analysis section, 6.5.2.2, the median treatment duration with everolimus is reported as 8.61 (Novartis submission, p. 101).	175	Novartis acknowledge the minor inconsistency between the treatment duration of everolimus reported in the primary publication (8.79 months)[1] and that used in the economic model (8.61 months). In our submission, patient-level data were used to derive the time on treatment Kaplan Meier curve, whereas the treatment duration in the primary publication was derived using the following formula: *Duration of exposure (days) = (date of last administration of study drug) – (date of first administration of study drug) + 1.* We consider the Kaplan Meier estimate to be a more accurate reflection of treatment duration. Ultimately, however, it should be noted that the difference between these values is minor and can be considered closely aligned (~ 9 months). The discrepancy is therefore not expected to have a material impact on the analyses.

	AG Comment/ Description	Reference to the AG report	Clarification/correction
	Use of everolimus in England	60	Novartis do not have data available from when everolimus was available via the CDF. However, recent data from the OBLIQUE study[13] (an observational study of everolimus in patients with progressive pNET in the UK) shows that 52 patients were recruited into the study within 18 months (August 2013–February 2015).

9. Conclusion

Everolimus is the only targeted therapy to show robust anti-tumour activity with acceptable tolerability across a broad range of NETs, and therefore has the potential to meet the significant unmet medical need for novel, clinically effective treatments in a disease area where there are limited treatment options (pNET) or no other effective alternatives (GI and lung NETs).

The clinical evidence for the comparisons of everolimus with sunitinib in pNETs and everolimus with lu-177 DOTATAE in GI (midgut) NET are derived from ITCs based on limited clinical evidence and are associated with high levels of uncertainty.

The suggestion that sunitinib is associated with superior outcomes compared to everolimus is not supported by the available evidence base or the views of clinical experts. In addition, as both everolimus and sunitinib are indicated for the same pNETs population, the assertion that sunitinib meets the end of life criteria but everolimus does not is unfounded and inconsistent. Additionally, the comparison of everolimus with lu-177 DOTATAE lacks robustness and should not be used to inform decision making around the cost-effective use of NHS resources in NETs.

In our revised analyses of the PenTAG model where we consider the same efficacy and treatment duration for everolimus and sunitinib in pNETs, we find the ICERs for everolimus vs. BSC to be lower than those included in the assessment report.

Our revised analysis of the PenTAG model in GI NETs that consider the whole GI population from the RADIANT-4 trial (excluding carcinomas of unknown primary origin) also result in lower cost-effectiveness estimates for everolimus vs. BSC than that included in the assessment report. Consequently, at list prices, we find the cost-effectiveness of everolimus in its different tumour types to be:

- £32,673/QALY for everolimus vs. BSC in pNETs. Additionally, in the comparison of everolimus vs sunitinib, sunitinib dominates everolimus as a result of lower drug costs and is associated with a cost saving of £146
- £43,642/QALY for everolimus vs. BSC in GI and lung NETs
- £36,234/QALY for everolimus vs. BSC in GI NETs

Moreover, when the PAS discount for everolimus is considered, everolimus represents a cost-effective treatment option for patients in a therapy area with a considerable unmet need for effective treatment options

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13. Ramage J, Punia P, Faluyi O, et al. UK Phase IV, Observational study to assess Quality of Life in patients (pts) with Pancreatic Neuroendocrine Tumours (pNETS) receiving treatment with Everolimus: The “Real-World” OBLIQUE Study. Endocrine Abstracts (2016) 46 P17 | DOI:10.1530/endoabs.46.P17.

10. Appendices

Revised analyses in response to assessment report

These appendices support the results of the revised analyses Novartis conducted in response to the PenTAG assessment report. The analyses we conducted are described in the economic sections of our response document and all results were generated from the PenTAG model (with the same assumptions, except the listed modifications (Table 10.1)) in order to ensure that results generated were consistent with those described in the assessment report.

10.1. Revised analyses for pNETs

Modifications to the pancreatic NETs model are shown in Table 10. 1. Visual fit of selected PFS and OS distributions are shown in Figure 10. 1, whilst PFS and OS distributions as used in the model are shown in Figure 10. 2.

Table 10. 1 Modifications to PenTAG pNET model

Modification	Justification
For everolimus and BSC, PFS and OS distributions were based on restricted lognormal (accelerated failure time [AFT]) and Weibull (proportional hazard [PH]) distributions, respectively, fitted to RADIANT-3 data. For the BSC arm, RPSFT-adjusted OS data was used. Background mortality was applied to OS for all comparators in order to assure the appropriateness of long-term projections.	PFS and OS distribution were selected based on evaluation of the consistency with the RADIANT-4 trial data as well as external SEER data.
PFS and OS for sunitinib were assumed to be equivalent to that of everolimus.	Any ITC of everolimus and sunitinib based on the RADIANT-3 and A6181111 trials is subject to a high degree of uncertainty due to the limitations, and potential biases of the RPSFT method, as well as the differences in patient populations between the two studies. This uncertainty is only partially captured by the wide confidence intervals associated with the HR for sunitinib vs. everolimus in the Bucher method ITC. Given the high degree of uncertainty in this comparison, any ITC performed is likely of little informational value and provides insufficient evidence to deviate from prior information suggesting similar efficacy for everolimus and sunitinib.

Figure 10. 1. PFS and OS distributions fitted to RADIANT-3 Kaplan Meier

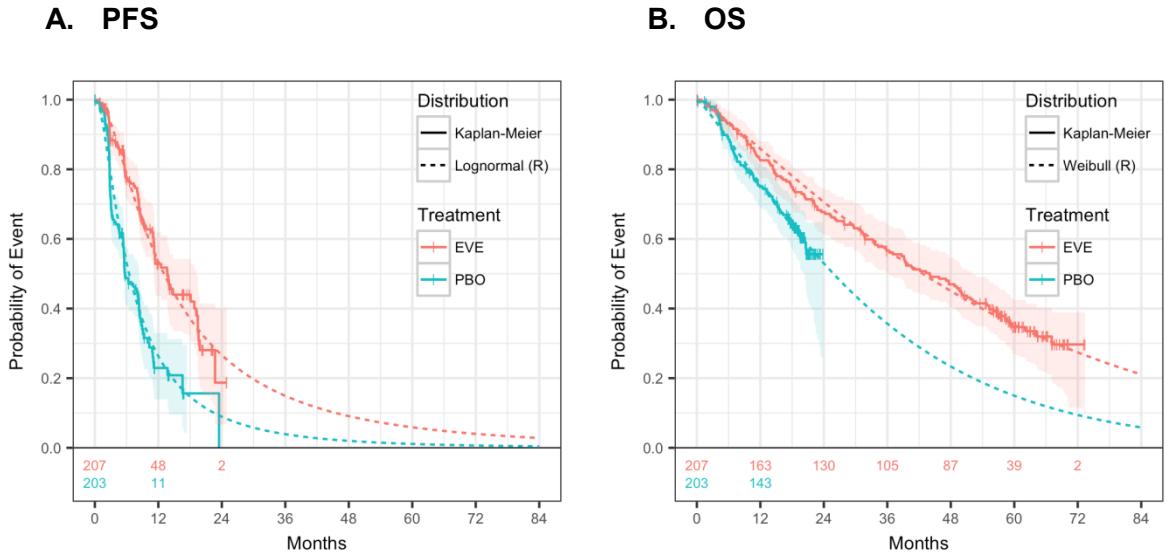
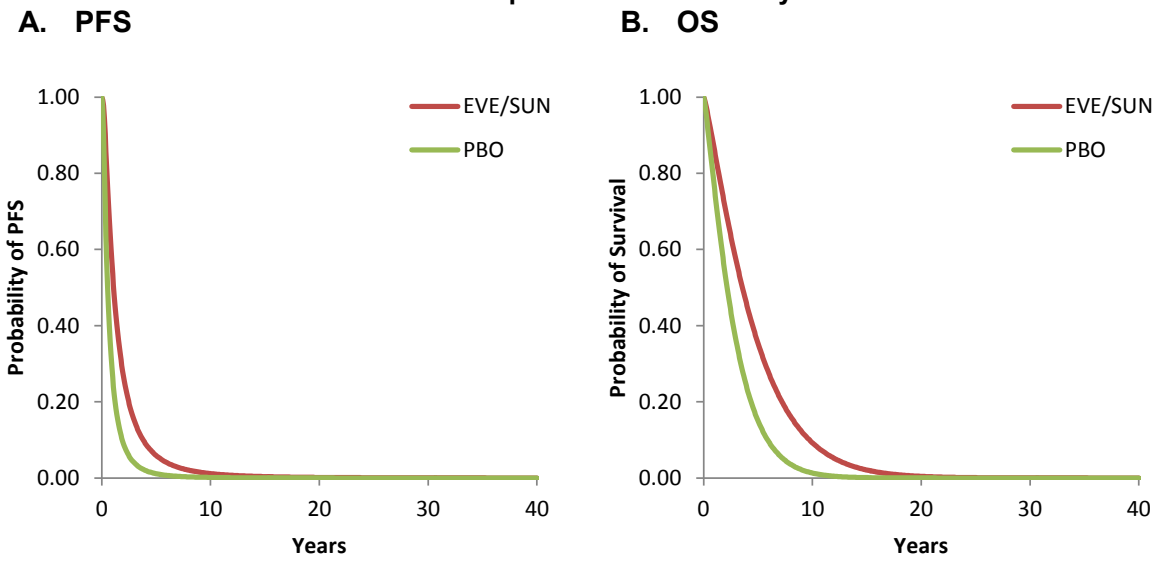


Figure 10. 2. PFS and OS used in model for pancreatic NETs analysis



The results of the economic evaluation of everolimus vs. BSC and everolimus vs. sunitinib based on list prices for everolimus and sunitinib described in Section 3.2 in the main response document are shown in Table 10. 2 (disaggregated results). The ICER for sunitinib vs. BSC is £32,505 per QALY and although everolimus is dominated by sunitinib, the difference in costs is only £146, which is immaterial relative to the costs of the medications. Results of the PSA are presented in Table 10. 3, and graphically in Figure 10. 3.

Table 10. 2. Results for updated Novartis analysis of pNETs analysis (disaggregated results)

	Sunitinib	EVE	BSC	EVE vs.		Sunitinib
				Sunitinib	BSC	BSC
Life years (undiscounted)						
Pre-progression	1.75	1.75	0.87	0.00	0.88	0.88
Post-progression	2.65	2.65	1.84	0.00	0.81	0.81
Overall survival	4.39	4.39	2.70	0.00	1.69	1.69
QALYs (discounted)						
Pre-progression	1.07	1.07	0.56	0.00	0.51	0.51
Post-progression	1.37	1.37	1.01	0.00	0.36	0.36
Total QALYs	2.44	2.44	1.57	0.00	0.87	0.87
Costs (discounted)						
Pre-progression						
Drug acquisition	£26,792	£26,864	£2,976	£72	£23,888	£23,816
Drug administration	£1,409	£1,440	£758	£31	£682	£651
Medical management	£1,021	£1,021	£273	£0	£748	£748
AE	£89	£132	£15	£43	£117	£74
Total costs pre-progression	£29,312	£29,458	£4,023	£146	£25,435	£25,289
Post-progression						
Drug acquisition	£4,935	£4,935	£3,070	£0	£1,865	£1,865
Drug administration	£1,185	£1,185	£729	£0	£456	£456
Medical management	£3,034	£3,034	£2,236	£0	£798	£798
End-of-life	£3,769	£3,769	£3,977	£0	-£208	-£208
Total costs post-progression	£12,923	£12,923	£10,012	£0	£2,911	£2,911
Total costs	£42,235	£42,381	£14,035	£146	£28,346	£28,200
ICER				Dominated	£32,673	£32,505

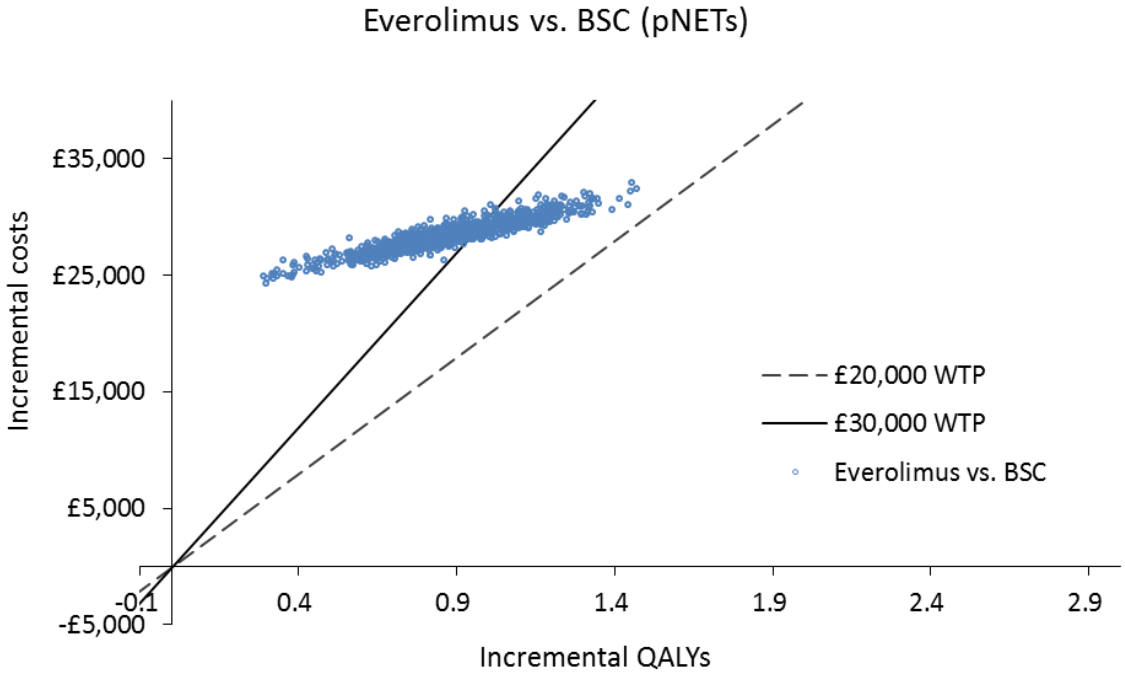
BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; pNETs; pancreatic neuroendocrine tumours; QALY: quality-adjusted life year

Table 10. 3. Results of probabilistic sensitivity analysis of updated Novartis analysis of pancreatic NETs

	Everolimus	Sunitinib	BSC	Everolimus vs. Sunitinib	Everolimus vs. BSC
Cost					
Mean	£42,447	£38,063	£14,061	£4,383	£28,385
SD	£1,289	£1,285	£970	£176	£1,354
95% Lower Bound	£40,063	£35,715	£12,292	£4,028	£25,724
95% Upper Bound	£45,087	£40,699	£16,177	£4,742	£31,017
Life years					
Mean	4.43	4.43	2.71	0.00	1.71
SD	0.34	0.34	0.28	0.00	0.42
95% Lower Bound	3.83	3.83	2.19	0.00	0.83
95% Upper Bound	5.12	5.12	3.36	0.00	2.53
QALYs					
Mean	2.45	2.45	1.57	0.00	0.88
SD	0.16	0.16	0.14	0.03	0.21
95% Lower Bound	2.16	2.16	1.31	-0.05	0.45
95% Upper Bound	2.77	2.78	1.89	0.06	1.28

BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; pNETs; pancreatic neuroendocrine tumours; QALY: quality-adjusted life year

Figure 10. 3. Results of probabilistic sensitivity analysis of updated Novartis analysis of pancreatic NETs: everolimus vs. BSC



BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; pNETs; pancreatic neuroendocrine tumours; QALY: quality-adjusted life year

If a shorter treatment duration is assumed for sunitinib (
Table 10. 4), the ICER for everolimus vs. BSC is £32,673 per QALY and the ICER for sunitinib vs. BSC is £27,627 per QALY. In the comparison of everolimus vs sunitinib, everolimus is dominated by sunitinib. However, it should be noted that the application of an assumption of shorter treatment duration with sunitinib in this analysis is based on a potentially biased estimate, as discussed in Section 2.5.

Table 10. 4. Scenario results for updated Novartis analysis of pancreatic NETs analysis (assuming shorter duration of treatment for sunitinib)

	Sunitinib	EVE	BSC	EVE vs.		Sunitinib
				Sunitinib	BSC	BSC
Life years (undiscounted)						
Pre-progression	1.75	1.75	0.87	0.00	0.88	0.88
Post-progression	2.65	2.65	1.84	0.00	0.81	0.81
Overall survival	4.39	4.39	2.70	0.00	1.69	1.69
QALYs (discounted)						
Pre-progression	1.07	1.07	0.56	0.00	0.51	0.51
Post-progression	1.37	1.37	1.01	0.00	0.36	0.36
Total QALYs	2.44	2.44	1.57	0.00	0.87	0.87
Costs (discounted)						
Pre-progression						
Drug acquisition	£22,569	£26,864	£2,976	£4,295	£23,888	£19,593
Drug administration	£1,400	£1,440	£758	£40	£682	£642
Medical management	£1,021	£1,021	£273	£0	£748	£748
AE	£89	£132	£15	£43	£117	£74
Total costs pre-progression	£25,080	£29,458	£4,023	£4,378	£25,435	£21,057

Post-progression						
Drug acquisition	£4,935	£4,935	£3,070	£0	£1,865	£1,865
Drug administration	£1,185	£1,185	£729	£0	£456	£456
Medical management	£3,034	£3,034	£2,236	£0	£798	£798
End-of-life	£3,769	£3,769	£3,977	£0	-£208	-£208
Total costs post-progression	£12,923	£12,923	£10,012	£0	£2,911	£2,911
Total costs	£38,003	£42,381	£14,035	£4,378	£28,346	£23,968
ICER				Dominated	£32,673	£27,627

BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; pNETs; pancreatic neuroendocrine tumours; QALY: quality-adjusted life year

10.2. Revised analyses for GI NETs

Modifications to the GI NETs model are shown in Table 10. 5. Visual fit of selected PFS and OS distributions are shown in Figure 10. 4. PFS and OS distributions as used in the model are shown in Figure 10. 5.

Table 10. 5. Modifications to PenTAG GI (midgut) NETs model

Modification	Justification
PFS and OS exponential distributions for everolimus and BSC were replaced by models fitted to RADIANT-4 GI subgroup. Background mortality was applied to OS in order to assure the appropriateness of long-term projections.	OS for PenTAG analyses were derived from PFS and are not valid. GI-subgroup data are more robust than data for the smaller GI (midgut) subgroup which was not a prespecified stratification factor. Exponential distributions were selected based on consistency with the PenTAG analysis, good statistical fit, and use of proportional hazards for comparison with lu-177 DOTATATE.
PFS and OS for lu-177 DOTATATE obtained by applying the hazard ratios for PFS (0.21) and OS (0.40) to the exponential distributions fitted to the BSC arm of RADIANT-4.	Necessary to facilitate indirect comparison w/ lu-177 DOTATATE. Consistent with the AG analysis, this assumes that the Octreotide LAR (60mg) arm of NETTER-1 is equivalent to the placebo arm of RADIANT-4.
Unit price of lu-177 DOTATATE solved for by matching the total drug acquisition cost reported in Table 163 of the PenTAG report.	Consistency with the PenTAG results.
The utilization rate of Octreotide LAR (30mg) was set to 100% for lu-177 DOTATATE in order to model the cost of Octreotide consistent with the NETTER-1 trial.	NETTER-1 trial compared lu-177 DOTATATE + Octreotide LAR (30mg) with Octreotide LAR (60mg). Since NETTER-1 was the primary source of PFS/OS for lu-177 DOTATATE, the cost of Octreotide LAR (30mg) was included for the sake of internal consistency. Note that the AG analysis assumes that the Octreotide LAR (60mg) arm of NETTER-1 is equivalent to the placebo arm of RADIANT-3. It does not make any assumptions regarding the impact (or lack thereof) of Octreotide LAR (60mg) added to lu-177 DOTATATE.

Figure 10. 4. PFS and OS distributions fitted to RADIANT-4 GI subgroup

A. PFS **B. OS**

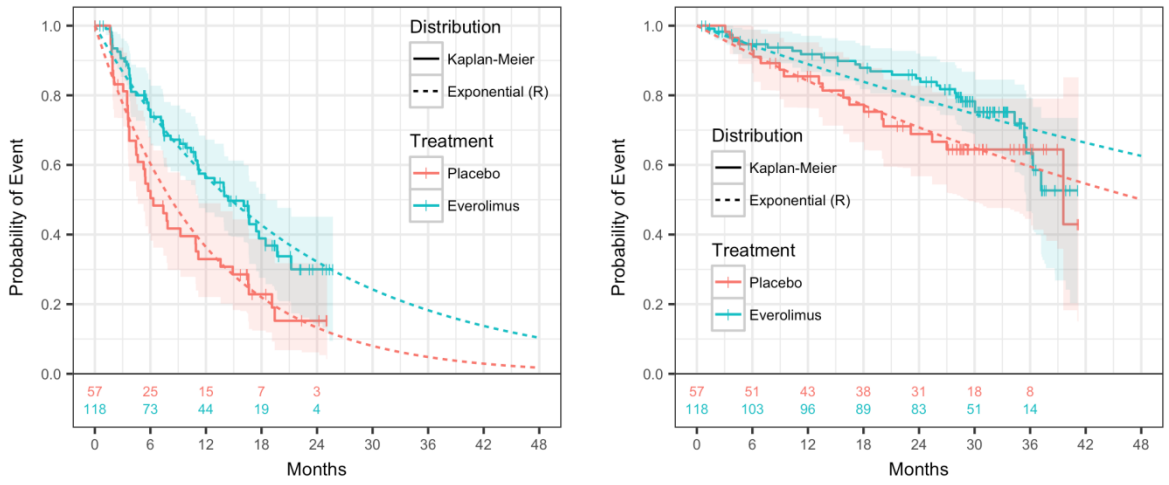
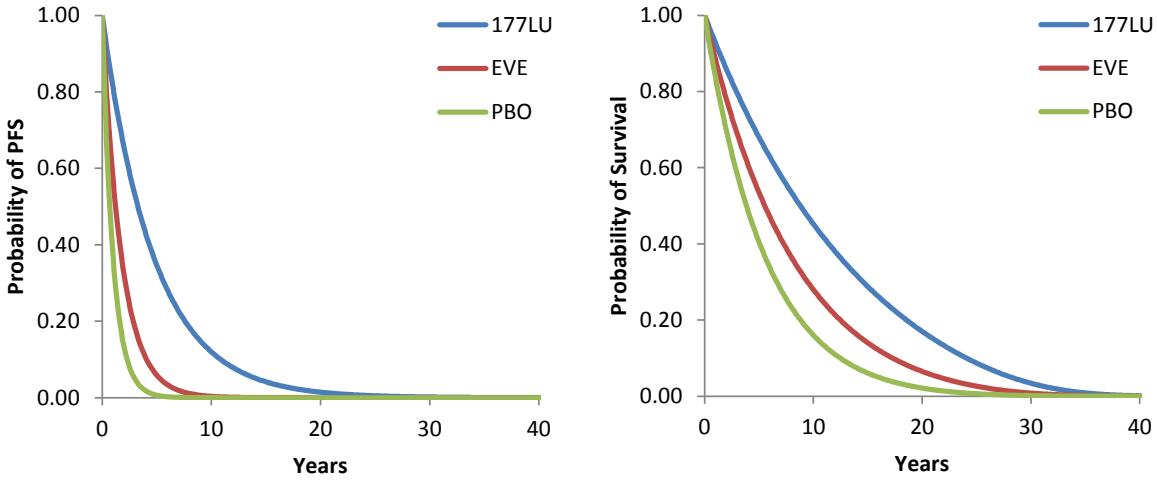


Figure 10. 5. PFS and OS used in model for gastrointestinal (midgut) NETs analysis

A. PFS **B. OS**



Results of the deterministic economic evaluation applying the modifications to the GI NET population are presented in Table 10. 6. Disaggregated results from the PSA for this evaluation are provided in Table 10. 7. The accompanying PSA scatterplot is provided in Figure 10. 6, with incremental cost-effectiveness acceptability curves provided in Figure 10. 7.

Table 10. 6. Disaggregated results for gastrointestinal NETs analysis

	EVE	lu-177 DOTATATE	BSC	EVE vs.	lu-177 DOTATATE vs.	
				BSC	BSC	EVE
Life years (undiscounted)						
Pre-progression	1.76	4.71	0.99	0.77	3.72	-2.95
Post-progression	5.76	6.23	4.42	1.34	1.82	-0.48
Overall survival	7.52	10.94	5.4047	2.11	5.54	-3.42

QALYs (discounted)						
Pre-progression	1.27	3.10	0.77	0.50	2.33	-1.83
Post-progression	3.15	3.00	2.61	0.55	0.40	0.15
Total QALYs	4.43	6.10	3.38	1.05	2.72	-1.68
Costs (discounted)						
Pre-progression						
Drug acquisition	£31,401	£62,070	£444	£30,957	£61,626	-£30,669
Drug administration	£177	£3,529	£3	£174	£3,526	-£3,352
Medical management	£5,084	£12,394	£2,409	£2,675	£9,985	-£7,310
AE	£287	£85	£105	£182	-£20	£202
Total Pre-Progression	£36,949	£78,078	£2,961	£33,988	£75,117	-£41,129
Post-progression						
Drug acquisition	£5,066	£4,860	£2,738	£2,328	£2,122	£207
Drug administration	£25	£24	£11	£14	£13	£1
Medical management	£10,395	£9,971	£8,530	£1,865	£1,442	£424
End-of-life	£3,443	£3,111	£3,666	-£222	-£554	£332
Total costs post-progression	£18,929	£17,966	£14,944	£3,985	£3,022	£964
Total costs	£55,878	£96,044	£17,905	£37,973	£78,139	-£40,165
ICER				**£36,241**	**£28,687**	**£23,965**

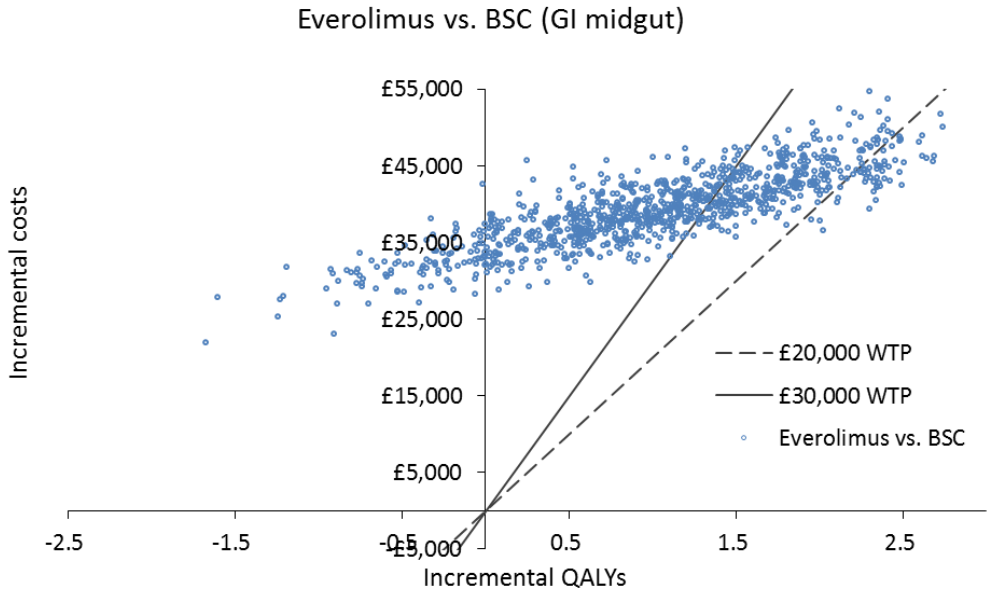
BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; NETs; neuroendocrine tumours; QALY: quality-adjusted life year

Table 10. 7. Results of probabilistic sensitivity analysis of updated Novartis analysis of GI NETs

	Everolimus	lu-177 DOTATATE	BSC	lu-177 DOTATATE vs. Everolimus	Everolimus vs. BSC
Cost					
Mean	£59,758	£101,394	£20,329	£41,636	£39,429
SD	£4,115	£8,141	£3,595	£7,803	£4,857
95% Lower Bound	£52,290	£86,595	£14,732	£26,393	£29,781
95% Upper Bound	£68,156	£118,821	£28,131	£56,870	£48,924
Life years					
Mean	7.58	10.97	5.47	3.39	2.11
SD	1.11	2.55	1.10	2.81	1.63
95% Lower Bound	5.43	6.33	3.59	-1.85	-1.32
95% Upper Bound	9.89	16.08	8.04	8.85	4.95
QALYs					
Mean	4.44	6.09	3.40	1.64	1.04
SD	0.53	1.13	0.57	1.26	0.81
95% Lower Bound	3.37	3.92	2.38	-0.78	-0.65
95% Upper Bound	5.53	8.22	4.68	4.00	2.44

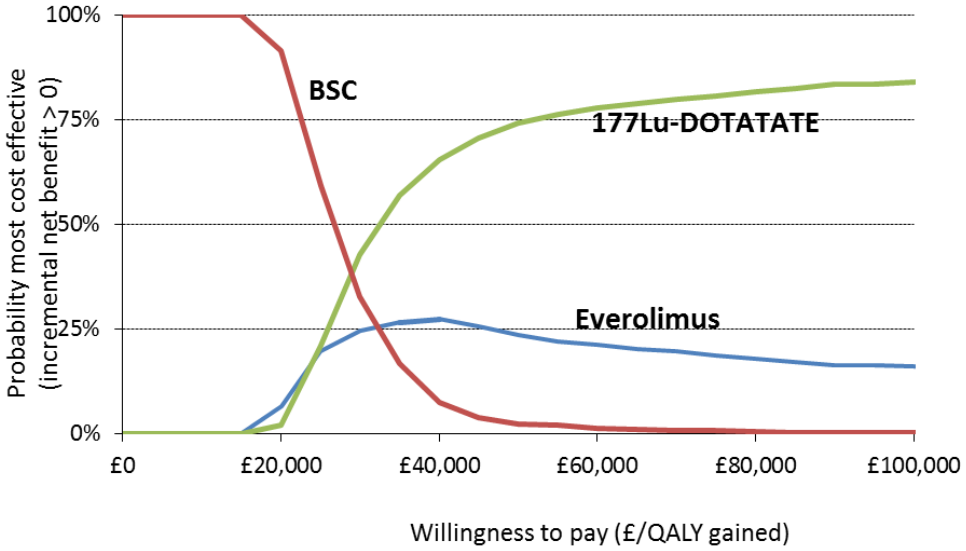
BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; NETs; neuroendocrine tumours; QALY: quality-adjusted life year

Figure 10. 6. Results of probabilistic sensitivity analysis of updated Novartis analysis of GI NETs: everolimus vs. BSC



BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; GI NETs; gastrointestinal neuroendocrine tumours; QALY: quality-adjusted life year

Figure 10. 7. Cost-effectiveness acceptability curves from Novartis analysis of GI NETs



BSC: best supportive care; EVE: everolimus; ICER: incremental cost-effectiveness ratio; pNETs; pancreatic neuroendocrine tumours; QALY: quality-adjusted life year

Pfizer Response to the Technology Assessment Report for: Everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression [ID858]

Pfizer would like to thank NICE for the opportunity to comment on the Technology Assessment Report (TAR) for the above appraisal. Overall, Pfizer believe that the TAR provides a balanced account of the randomised controlled trial data for sunitinib, along with an independent MAIC analyses [redacted]

Our main comment focuses on the fact that the Technology Assessment Group (TAG) expressed concern (first full paragraph on p. 159) about the potential generalisability of the OS findings from the MAIC because analyses matched on two additional variables were not included in the prior MAIC by Novartis. The concern is that matching on more variables focuses the analyses to a narrower subset of patients (those common in both trials), which may have further limited the generalisability. Pfizer believe this issue was addressed in sensitivity analyses carried out in our own MAIC and reported in our submission, where the [redacted]

The sensitivity of results to inclusion of these additional variables were assessed by repeating the analyses matching on the same set used by Signorovitch *et al*[1] as a sensitivity analyses. [redacted] These analyses and findings were reported in the discussion section of the MAIC analyses in the Pfizer submission. We would therefore suggest that the paragraph in the AG report should be adjusted to take account of the generalisability of the results, however we appreciate that the results of our MAIC analyses remain AIC presently.

References:

1. Signorovitch J, Swallow E, Kantor E, Wang X, Klimovsky J, Haas T, et al. Everolimus and sunitinib for advanced pancreatic neuroendocrine tumors: A matching-adjusted indirect comparison. Experimental Hematology and Oncology [Internet]. 2013; 2(1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/009/CN-00960009/frame.html.

NET Patient Foundation
Second Floor, Holly House
74 Upper Holly Walk
Leamington Spa
CV32 4JL

BY EMAIL

Kate Moore
Project Lead NICE

Dear Ms Moore,

Response to Multiple Technology Appraisal
Everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression
Assessment Report 21/12/16

Following review of the latest documentation, we provide the following response

Despite some adjustments to original scope and the apparent inclusion of a NET expert, we continue to have some concerns regarding the level of understanding of NETs – including subtypes,and the impact of diagnosis and disease on patients.
We also have some concerns regarding cost-analysis and number of assumptions made.

Concerns :

"NETs develop slowly and may remain undetected over a number of years, hence in many cases the cancer may have already metastasised"
Comment :
Not ALL NETs develop slowly. NET is an umbrella term that encompasses a range of cancers that originate in neuroendocrine cells. There is no uniform rate of development or growth, hence the grading system. The grade of a tumour refers to its biologic aggressiveness – determined by expert histological assessment of proliferation rate : Grade 1-3, with 3 being the most aggressive. Cell differentiation is also an important diagnostic and prognostic factor – Grade 1 and 2 are usually well-differentiated, whilst Grade 3 may be either well-differentiated (High grade neuroendocrine **tumours**) or poorly-differentiated (Neuroendocrine **carcinomas**) Grade 3 poorly-differentiated carrying the least favourable prognosis. Further evidence is emerging to further subdivide G3 tumours utilising proliferation index cut-offs.
(Sorbye et al 2013, Tang et al 2016, Basturk et al 2015, Heetfeld et al 2015)

"There are a vast array of treatment options for treating NETs. The initial treatments start with

surgery and symptom treatment. Treatments which follow surgery and symptom control include: liver transplant, interferon alpha, chemotherapy, ablation therapies, targeted radionuclide therapy (including 177Lu-DOTATATE), transhepatic artery embolisation/chemoembolization, external-beam radiotherapy and emerging therapies (including everolimus and sunitinib).

Comment :

Treatments are location, grade and differentiation, stage of tumour and secretory profile of the tumour dependent. Surgery may not be best treatment option following initial diagnosis.

Liver transplantation is currently not undertaken within the UK

Interferon-alpha is rarely used

Chemotherapy is primarily indicated in high grade NETs and NECs, and is a consideration in G1/2 NETs with a pancreatic primary.

Targetted radionucleide therapy (PRRT) is used in selected patients – MiBg primarily used in phaeochromocytomas/paragangliomas, and Yttrium was being replaced by Lutetium due to lower side effect profile and decreased requirement for hospitalistaion (reduced length of stay), until Lutetium was removed from the CDF pending this evaluation.

Ablation techniques : radio-frequency, microwave and irreversible electroporation : location and size dependent

Embolisation techniques – hepatic artery (+/- chemotherapy) and portal vein – are for targetting liver NETs (secondary deposits – primary liver NET being very rare) or to potentially increase operability where liver resction (hemi-hepatectomy) is being considered but limited by potential remnant liver volume

External beam radiation : primarily considered in Merkel Cell Carcinoma (a highly aggressive skin NET) but may be indicated in the treatment of symptomatic bone metastases

Emerging therapies : incl Everolimus - is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease., and more recently for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease

and Sunitinib : is indicated for the treatment of unresectable or metastatic, well-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease

Not included but possibly assumed in the term “symptom control” :

Somatostatin analogues including Octreotide (Sandostatin LAR) and Lanreotide (Somatuline Autogel) : used in managing most functional NETs – with an extended utilisation in non-functioning tumours due to anti-proliferative effect

Diazoxide may be used in insulinomas

High dose PPIs in gastrinomas

Symptom control management is also location, grade and differentiation, stage of tumour and secretory profile of the tumour dependent

Also included in guidelines management – and indeed clinical practice are :

clinical trial enrolment (pending appropriateness, risk/benefit analysis and inclusion/exclusion criteria) and supportive / palliative care

Interpretation of PHE data also raises concern about understanding terminology : Neuroendocrine carcinoma NOS : A neuroendocrine carcinoma (NEC) is a poorly differentiated, highgrade malignant neoplasm.“NOS” is printed in both the numerical lists and the alphabetic index to indicate to the coder and to the decoder that other modifiers of the term are listed elsewhere. It is also utilised where previous modifiers have become obsolete.

For further and more comprehensive information regarding NETs we would direct you to : http://www.ukinets.org/net-clinics-research/ for National and European Guidelines

http://www.netpatientfoundation.org/support-information/general-information-on-net/the-net-handbook-your-guide-to-life-with-a-neuroendocrine-tumour/ for patient directed, evidence and guideline based information resource.

Regarding patients views and quality of life / issues of import :
Many NET patients have had to become experts in their own diagnosis - treatments and processes – and have, in England, seen their options become increasingly restricted over the past two years. Particularly galling is to see that these restrictions and exclusions are geographically dictated (comparison with devolved nations – who incidentally travel to England to access these therapies).

NET patients were not consulted in pre2015 National Cancer Patient Experience surveys – leading the NET Patient Foundation to commission (Quality Health) to undertake its own national survey http://www.netpatientfoundation.org/wp-content/uploads/159-NPF-4pp-A5-PATIENT-SURVEY-LEAFLET-v2.pdf – Full report available from NPF.

NPF had previously been involved in – and encouraged UK NET patient participation in the first Global NET patient survey :
http://incalliance.org/the-first-global-net-patient-survey/

Clarification on definitions used.
For example "Disease progression".
In NETs reliance on imaging alone – especially utilising CT and RECIST criteria – can be misleading and is often late evidence that the disease is progressing. Clinical and biochemical indications should be incorporated – symptom deterioration and rising markers are more likely to represent early indication of disease change and / or refractory syndrome - triggering treatment plan review/change.
This would also apply to the term "Response".
Recommend : full involvement of a recognised NET expert .
Utilisation of current National and European Guidelines – to understand complexity of NET (disease and management).
Can be sourced from : http://www.ukinets.org/net-clinics-research/

"Best supportive care" - how will this be costed ? And will it include SSAs ? - this would be a more accurate reflection as a comparison to the listed treatments under review (though not all subgroups of NETs will have a clinical indication for SSA)
Recommend : full involvement of recognised NET experts and
Utilisation of current National and European Guidelines – to understand complexity of NET (disease and management).
Can be sourced from : http://www.ukinets.org/net-clinics-research/
Additional comment :
In practice and reported by patients is difficulty in accessing palliative care – current limitations in available resource, understanding of disease – and despite definition within NICE appraisal process regarding end-of-life care time-frame: postponement / refusal of referral/ review if prognosis >6 months

Licensing / Existing and anticipated marketing authorisations : has been updated.

Re publications : Lutetium paper (NETTER-1 now published : Strosberg et al (2017) NEJM

Policy / NSF section : we are somewhat bemused at the inclusion of guidance relating to unknown primary but no mention of the UK Rare Cancer Strategy or indeed the National Cancer Strategy – Achieving World Class Outcomes itself – though given that only 2 of the 96 recommendations refer

to rare cancers .
And that the Service Specification that includes NETs is still to implemented (though given time delay it would need revising)

Cost analysis : our concern here is the number of assumptions and inferred conclusions – particularly if utilising the scientific disease background information within this assessment as a basis – indeed if taking note of subgroups , especially in regard to location and functionality – it is hard to see how Lutetium can be assessed against Everolimus and Sunitinib (different patient cohorts)
Our results suggest that there is a high degree of uncertainty in the effectiveness and cost-effectiveness in advanced, progressive pancreatic NETs and GI and Lung NETs. This uncertainty has its origins in the lack of data that naturally accompanies a rare condition

Trial data : we accepted each trial assessed within the assessment has flaws – due to trial design, limitations in data collected, etc. . .but maybe reflects timing of trial and endpoints.
However we would query the assumption that RCTS utilising placebo as control are of superior quality - and indeed for this cohort of patients – particularly in small intestinal NETs with carcinoid syndrome – raise the issue of ethical clinical care.

If this were a situation where a patient had to decide on whether to sign a consent form or not – we would recommend deferring a yes or no decision until further explanation (data) ensuring INFORMED consent was made available

Our position regarding potential outcome is that given the uncertainty and limited information available – that rather than seek a definite yes (at risk of getting a no) consideration is made of the option of CDF access

- **Recommended for use within the CDF (new)**

  We consider that there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid long delays, but we need more information on its effectiveness before it can be considered for routine commissioning (when the guidance is reviewed).

This group and clinical environment lends itself to this option.

Yours sincerely
and on behalf of the NPF

[redacted]

[redacted]

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From [redacted]

8 February 2017

Dear Kate

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

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Our experts are practising clinical oncologists in the UK with considerable experience in dealing with neuroendocrine tumours so our comments will focus predominantly on the clinical aspects.

Our first observation is that there is no identified specialist neuroendocrine tumour clinician recognised as a key opinion leader in the UK who has been involved in the process. The current Chairman of UKINETs is credited but is neither a practising oncologist nor a nuclear medicine specialist. This lack of expert oncology input must be seen as a substantial deficiency in the document and we believe is responsible for frequent inaccuracies in the advisory document.

The document overlooks the fact that these are not necessarily rival treatments but may be used in different phases of the cancer journey for neuroendocrine patients. Other important factors used to select treatment and intervention will include the presence or absence of symptoms, and whether the tumour is somatostatin receptor imaging positive. The care of an individual patient will be jointly determined by the individual consultant looking after the patient together with the multidisciplinary team since the management of neuroendocrine tumours involves multiple disciplines both medical, surgical and radiotherapeutic. NET tumour management is genuinely one of the most truly multidisciplinary cancers in the whole field of oncology.

The paper has a number of flaws, errors and misunderstandings which our experts believe reflects the fact that there is neither a nuclear medicine specialist nor a recognised UK key opinion leader oncologist in the field of neuroendocrine tumours on the committee.

The document is excessively long and often highly repetitive. We believe it is difficult to digest for a practising clinician since it is couched heavily in complex economic terminology. Some of the economic arguments seem to rely upon soft, incomplete or incorrect data and have led to inappropriate conclusions.

The paper makes frequent and regular reference to the NETTER-01 study which was only published on 13 January 2017 and therefore a full manuscript and set of data was not available to the authors of the document. Reference is made to preliminary reports and conference proceedings only.

The costs of the drugs seem to take no account of patient access schemes which will clearly influence cost. Costs also assumes that the patient remains on the same dose throughout the period of administration but again a knowledgeable and experienced oncologist would advise that most patients finish up with dose reductions whether it be with sunitinib or everolimus and therefore the costs will significantly reduce. This will have significant impact on the full costs and the ICER calculations.

Our experts are concerned by the differences in ICER between sunitinib and everolimus when they are equally effective, used for similar lengths of time, and fairly similarly priced. The health economic case between the two is confusing and we cannot understand why there is such a substantial discrepancy.

The document suggested no patients meet the NICE end of life criteria but this is incorrect as the majority of patients who will be commenced on these drugs have progressive advanced disease and are likely to die within 2 years without intervention. Some subgroups of patients with advanced neuroendocrine tumours can have an excellent prognosis but these are probably the ones who do not need interventions such as this. Confirmation of this comes from the survival of the control arm in the NETTER01 where the majority show disease progression within 2 years. Our experts believe that this meets the end-of-life criteria.

There seems to be an assumption that sunitinib and everolimus are interchangeable in clinical practice. This is not the case as there are huge differences in the toxicities and in the United Kingdom the majority of clinicians will use everolimus as the first choice targeted agent in Pancreatic NETs (not yet approved although now licenced in bronchial and small intestinal NETs) and keep sunitinib in reserve for either toxicity, intolerance or lack of response. The response rates for both drugs are almost identical and given that both studies used progression free survival as the end point it is very difficult to interpret overall survival considering that many patients will have had crossover from placebo/BSC to active drug or will have had other interventions such as PRRT which started to become available during this time period.

We would therefore argue that there is no logic in accepting sunitinib but rejecting everolimus as clinicians will be forced to use a drug with far greater toxicity if this is the only choice. This decision must be seriously reconsidered and addressed. Further no allowance is made for patients unable to tolerate sunitinib due to toxicities. A choice must be made available. Regarding the ICERs, no account is taken of patient access schemes which we understand are confidential but clearly have a significant impact in reducing the cost and in turn reducing the ICER. Our experts note that experience has shown that both these drugs are capable of dramatically improving the quality of life of patients who can return to work or lead normal activities while on the drug apart from a monthly visit to collect the prescription and be monitored by the oncologist.

Much weight seems to be put on the differential toxicities of these drugs but an experienced oncologist treating NETs cancers will modify the dose or even give drug interruptions which allows patients to cope. The paper seems to assume that sunitinib is the preferred choice of drug in the UK but this is unlikely to reflect standard practice. There is no published data on this but it is more likely that clinical and medical oncologists in the United Kingdom who treat patients with neuroendocrine tumours preferentially use everolimus over sunitinib due to the more manageable side-effects therefore the recommendation only to approve sunitinib will deprive most patients access to what is generally proceed as the first choice of drug.

On page 7 interferon alfa is included as a choice of comparator. Comparator for pancreatic NETS would certainly include chemotherapy with streptozotocin based regimes whilst the comparator for small bowel and well-differentiated bronchial NETS would probably be either, best supportive care, clinical trials, or increasingly PRRT when it is available but not routinely chemotherapy for extra pancreatic NETs as these

drugs are generally of limited effectiveness and used very selectively. New studies are being developed to look at other agents such as temozolamide with or without capecitabine or for more aggressive tumours (G3) irinotecan based regimes which should fall out with the remit.

On page 7 it is suggested that the results of the NETTER 01 trial might be of interest to the committee but they did not have access to anything other than conference highlights and abstracts, our experts are unclear as to how this can be used since the data were only published on 13 January 2017 after the completion of this report. Given the detailed health economic assessment for the comparator target agents, it seems an unfair comparison.

On page 11, the first paragraph specifically comments that the evidence consistently suggested a treatment effect in favour of everolimus compared to placebo plus BSC and yet goes on to reject everolimus as a standard of care for these patients.

Page 10 refers the overall survival data but we believe it is extremely dangerous to use this since crossover to active drug will have occurred on progression in many patients and progression free survival was the primary endpoint, and there are too many other potential interfering factors that will influence this. Other treatment interventions will include clinical trials, other TKIs and PRRT. Since PFS was the primary end point this should be the key comparator.

On page 12 there is discussion of the Netter 1 study and we would dispute the fact that there is no control arm, the patients were given higher dose octreotide LAR (60 mg). Even in the abstracts and oral presentations there is clear rationale as to why this dose was chosen and there is even some evidence that higher non-licensed doses of octreotide may have some clinical benefit. Therefore to say that the study was poorly designed and has no control arm is highly inaccurate. There are several papers published which have shown that dose escalation of octreotide LAR beyond 30 mg is associated with a response and this is evidenced by the fact that there is some response seen in the control arm patients in the trial.

On page 14 the opening paragraph comments that studies had severe limitations due to the fact that they were based on phase 3 trials with no active treatment comparator reflects the fact that there are often no standard alternative treatments, which is why the study is needed to be done. Our experts find this contradictory and strongly disagree.

Other examples of errors include page 6 where it states that symptoms are more common with functioning pancreatic metastases when hormones are significantly elevated. There are many patients with high levels of gut hormones who are asymptomatic.

As non-health economists, we struggle to understand how the models can predict 20 year survival. If we were to look at the 20 year survival from 20 years ago we would never have predicted the remarkable developments in medicine that have occurred. 20 years ago patients with advanced neuroendocrine tumours would virtually all be dead within 5 years and now with modern treatments, even newly diagnosed very advanced cases can expect to live at least 5-10 years and patients with small volume metastatic disease can probably expect up to 20 year survival. Therefore any extrapolation must be flawed since it cannot take into account any future medical developments.

We were completely unaware that Amazon was a source of 5 fluorouracil. We trust no British patients are obtaining it this way.

The most important thing to stress is that these interventions commonly make patients feel better with manageable side effects and improve the quality of life allowing them to functioning more normally. The document as it stands would deprive a significant number of patients of an effective and well tolerated treatment on offer them an alternative admittedly equally effective but more toxic treatment. PRRT with lutetium offers an additional and not a rival approach as it will commonly be used in a different clinical setting and a different sequence.

Patients in the UK should be able to receive internationally accepted drugs as part of their standard of care. The proposed recommendations of this document would make UK citizens with NET tumours second class citizens deprived of effective life prolonging drugs. The committee should overturn this recommendation.

Yours sincerely

[redacted]

ASSESSMENT REPORT:

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

Comments provided to Healthcare Improvement Scotland by: [redacted]

I am writing this response as a practising clinical oncologist in the UK with considerable experience in dealing with neuroendocrine tumours and will focus my comments predominantly on the clinical aspects. I was a founding member and later Chairman of the UKINETS and I am a member of the advisory board of the European Neuroendocrine Tumour Society. My first observation is that there is **no identified specialist neuroendocrine tumour clinician recognised as a key opinion leader in the UK who has been involved in the process**. The current Chairman of UKINETs is credited but is neither a practising oncologist nor a nuclear medicine specialist. This lack of expert oncology input must be seen as a substantial deficiency in the document and I think is responsible for what I would consider to be an unhelpful, and frequently inaccurate advisory document.

The document seems to ignore the fact that these are not necessarily rival treatments but may be used in different phases of the cancer journey for neuroendocrine patients. Other important factors used to select treatment and intervention will include the presence or absence of symptoms, and whether the tumour is somatostatin receptor imaging positive. The care of an individual patient will be jointly determined by the individual consultant looking after the patient together with the multidisciplinary team since the management of neuroendocrine tumours involves multiple disciplines both medical, surgical and radiotherapeutic. NET tumour management is genuinely one of the most truly multidisciplinary cancers in the whole field of oncology.

The paper has a number of flaws, errors and misunderstandings which probably reflects the fact that there is neither a nuclear medicine specialist nor a recognised UK key opinion leader oncologist in the field of neuroendocrine tumours on the committee.

The document is excessively long, often highly repetitive and for a practising clinician difficult to digest since it is couched heavily in complex economic jargon. Some of the economic arguments seem to rely upon soft, incomplete or incorrect data and have led to inappropriate conclusions.

The paper makes frequent and regular reference to the NETTER-01 study which **was only published on 13 January 2017** and therefore a full manuscript and set of data was not available to the authors of the document. Reference is made to preliminary reports and conference proceedings only.

The costs of the drugs seem to take no account of patient access schemes which will clearly influence the cost of the drugs. Costs also assumes that the patient remains on the same dose throughout the period of administration but again a knowledgeable and experienced oncologist would advise that most patients finish up with dose reductions whether it be with sunitinib or everolimus and therefore the costs will significantly reduce.

This again will have significant impact on the full costs and the ICER calculations. I am left bamboozled by the differences in ICER between sunitinib and everolimus when they are equally effective, used for similar lengths of time and fairly similarly priced. The health economic case between the two is lost on me and I cannot understand why there is such a substantial discrepancy.

NICE end of life criteria. The document suggested no patients meet this but this is incorrect as the majority of patients who will be commenced on these drugs have progressive advanced disease and are likely to be dead within 2 years without intervention. Some subgroups of patients with advanced neuroendocrine tumours can have an excellent prognosis but these are probably the ones who do not need interventions such as this. I think confirmation of this comes from the survival of the control arm in the NETTER01 where the majority show disease progression within 2 years. This surely meets the end-of-life criteria.

There seems to be an **assumption that sunitinib and everolimus are interchangeable** in clinical practice. This is not the case as there are huge differences in the toxicities and in the United Kingdom the majority of clinicians will use everolimus as the first choice targeted agent in Pancreatic NETs (not yet approved although now licenced in bronchial and small intestinal NETs) and keep sunitinib in reserve for either toxicity, intolerance or lack of response. The response rates for both drugs are almost identical and given that both studies used progression free survival as the end point it is very difficult to interpret overall survival considering that many patients will have had crossover from placebo/BSC to active drug or will have had other interventions such as PRRT which started to become available during this time period.

I would therefore argue that there is no logic in accepting sunitinib but rejecting everolimus as clinicians will be forced to use a drug with far greater toxicity if this is the only choice. This decision must be seriously reconsidered and addressed. Further no allowance is made for patients unable to tolerate sunitinib due to toxicities. A choice must be made available. Regarding the ICERs, no account is taken of patient access schemes which I understand are confidential but clearly have a significant impact in reducing the cost and in turn reducing the ICER. Personal experience has shown that both these drugs are capable of dramatically improving the quality of life of patients who can return to work or lead normal activities while on the drug apart from a monthly visit to collect the prescription and be monitored by the oncologist.

Much weight seems to be put on the differential toxicities of these drugs but an experienced oncologist treating NETs cancers will modify the dose or even give drug interruptions which allows patients to cope. The paper seems to assume that **sunitinib is the preferred choice of dru**g in the UK but this is unlikely to reflect standard practice. There is no published data on this but it is more likely that clinical and medical oncologists in the United Kingdom who treat patients with neuroendocrine tumours preferentially use everolimus over sunitinib due to the more manageable side-effects therefore the recommendation only to approve sunitinib will deprive most patients access to what is generally proceed as the first choice of drug.

Choice of comparator which includes interferon alfa. Comparator for pancreatic NETS would certainly include chemotherapy with streptozotocin based regimes whilst the comparator for small bowel and well-differentiated bronchial NETS would probably be either best supportive care, clinical trials or increasingly PRRT when it is available but not routinely chemotherapy as these drugs are generally of limited

effectiveness and used very selectively. New studies are being developed to look at other agents such as temozolamide with or without capecitabine or for more aggressive tumours (G3) irinotecan based regimes.

On page 7 it is suggested that the results of the NETTER 01 trial might be of interest to the committee but they did not have access to anything other than conference highlights and abstracts, I do not see how this can be used since the data was only published on 13 January 2017 after the completion of this report.

On page 11, the first paragraph specifically comments that the evidence consistently suggested a treatment effect in favour of everolimus compared to placebo plus BSC and yet goes on to reject everolimus as a standard of care for these patients.

Page 10 refers the overall survival data but I think it is extremely dangerous to use this since crossover to active drug was allowed as these were progression free survival studies and there are too many potential interfering factors that will influence this. Other treatment interventions will include clinical trials, other TKIs and PR RT . Since PFS was the primary end point this should be the key comparator.

On page 12 there is discussion of the Netter 1 study and I would hotly dispute the fact that there is no control arm, the patients were given higher dose octreotide LAR (60 mg). Even in the abstracts and oral presentations there is clear rationale as to why this dose was chosen and ironically there is even some evidence that higher nonlicensed doses of octreotide may have some clinical benefit. Therefore to say that the study was poorly designed and has no control arm is rubbish. There are several papers published which have shown that dose escalation of octreotide LAR beyond 30 mg is associated with a response in and this is evidenced by the fact that there is some response seen in the control arm patients in the trial

On page 14 opening paragraph comments that studies had severe limitations due to the fact that they were based on phase 3 trials with no active treatment comparator reflects the fact that there are often no standard alternative treatments which is why the study is needed to be done. You cannot have UK can eat it!

Other Examples of errors include page 6 where it states that symptoms are more common with functioning pancreatic metastases when hormones are significantly elevated. There are many patients with high levels of gut hormones who are asymptomatic

As an non-health economist, I struggle to understand how the models can predict 20 year survival. If we were to look at the 20 year survival 20 years ago we would never have predicted the remarkable developments in medicine that have occurred. 20 years ago patients with advanced neuroendocrine tumours would virtually all be dead within 5 years and now with modern treatments, even newly diagnosed very advanced cases can expect to live at least 5-10 years and patients with small volume metastatic disease can probably expect up to 20 year survival. Therefore any extrapolation must be flawed since it cannot take into account any future medical developments.

I was completely unaware that Amazon was a source of 5 fluorouracil. I trust no British patients are obtaining it this way.

Probably the most important thing to stress is that these interventions commonly make patients feel better with manageable side effects and improve the quality of life allowing them to functioning more normally. The document as it stands would deprive

a significant number of patients of an effective and well tolerated treatment on offer them an alternative admittedly equally effective but more toxic treatment. PR RT with lutetium offers an additional and not a rival approach as it will commonly be used in a different clinical setting and a different sequence.

	Company's comment	AG responses
AAA	The NETTER-1 study is a well-designed clinical study that has been designed to meet regulatory requirements and has been peer-reviewed and published in the New England Journal of Medicine	At the time of writing NETTER-1 was an unpublished study. The AG appreciate that the design of the study was in line with the FDA and EMAs ethical requirements, however this does not negate the fact that there is no control arm for comparison of effectiveness. Are any differences seen because of lutetium or the increase in dose of Octreotide. The wording used on page 65 of the AG report is referenced and taken from the NICE scope.
	The Assessment Group's analysis has failed to take into consideration the anticipated marketing authorisation for 177Lu-DOTATATE	The AG have focused on all RCT data available, since this is within our guidance from NICE. This is NETTER-1 a study for which only mid-gut individuals were recruited. We have in-addition conducted a non RCT evidence review (including the Erasmus trial).
	Somatostatin analogues (SSAs - octreotide LAR) are an established part of the care pathway in UK clinical practice for progressive and advanced patients with unresectable or metastatic gastrointestinal neuroendocrine tumours (GI-NET). The AG fail to define BSC. They appear to have selected the control arm of RAD-4 to represent BSC, but the rationale for this selection is unclear given that the BSC arm of the RAD-4 study does not represent UK clinical practice.	No comment. In pNETs, BSC from RADIANT-3 was used as the comparator given the larger sample size available from this trial arm than the comparator arm in A6181111. For GI and lung, BSC was from RAD-4 since this was the only placebo plus BSC arm in a head-to-head trial that met the scope patient population and used a targeted treatment in the marketing authorisation (everolimus – please note that RADIANT-2 included patients for whom the drug was not being given marketing authorisation).
	There are serious flaws in the Assessment Group's analysis of the cost-effectiveness of 177Lu-DOTATATE i. The PFS drug acquisition costs for BSC in GI (midgut) NETs is too low, so the AG may overestimate the ICER of 177Lu-DOTATATE versus BSC	 i. There is a large disparity in the estimated use of SSAs between the AG and AAA models. AAA model 100% of patients as being treated with octreotide LAR 30mg in BSC, versus 1-2% in the AG economic model. AAA are guided by the design of the

	• There is no justification for use of Octreotide in only 1% of patients • There is no justification for use of supportive therapies lidocaine, dexamethasone, prednisone, prochlorperazine, biofermin, saccchromyces boulardii, and external beam radiation.	NETTER-1 trial, whereas we have used RCT-based data supplied by Novartis in their submission, which are detailed in the RAD-4 CSR (CRAD001T2302), as referenced. Page 96 Section 12.1.3 Concomitant medication of the CSR details the SSA usage: *Concomitant medication and significant non-drug therapies initiated after the start of treatment with everolimus or placebo… Further, concomitant use of SSA for the treatment of carcinoid symptoms was reported for 4 patients (2%) in the everolimus group and one patient (1%) in the placebo group.* The RADIANT-4 CSR does not detail the utilisation rates of lidocaine, dexamethasone, prednisone, prochlorperazine, biofermin, saccchromyces boulardii, and external beam radiation, these are supplied in the Novartis model, referenced data on file, but their derivation described as follows: *A KOL validation survey (…) and a KOL advisory board, both of which were conducted with UK experts indicated that the following therapy categories might typically be used as part of BSC in the UK: Analgesics, Anti-emetics, Anti-diarrhoeals, EBRT, SSAs. The rates for each of these BSC therapy categories used in the model were derived from RADIANT-4 data. Since some of these categories included multiple drugs, the most frequently used treatment in each category from RADIANT-4 was considered representative of that category and costed within the analysis.* In summary, we have utilised RCT-based evidence in patients free from progression in the placebo and BSC arm of RADIANT-4 trial to estimate the proportion of patients who receive SSAs as part of BSC. This source of evidence represented the only known pre-existing evidence of supportive therapy resource utilisation in this patient population and acts as a reasonable source for the base case analysis. However it may also be reasonable to assume that a higher proportion of patients with stable GI (midgut) NETs would receive concurrent SSAs as part of BSC in clinical practice, and in this scenario the cost of BSC would be higher than estimated in the AG base case. We have therefore included a new sensitivity analysis in which BSC includes the rate of SSA usage observed in patients with PNETS, as reported in RADIANT-3; and excluded the cost of all supportive therapies (see p. 13 below).

	ii. The PFS drug acquisition cost of 177-Lu DOTATATE should not include supportive therapies, and as such the AG may overestimate the ICER versus BSC. • There is no justification for the inclusion of supportive therapies lidocaine, dexamethasone, prednisone, prochlorperazine, biofermin, saccchromyces boulardii, and external beam radiation. iii. AG model included drug acquisition costs for patients who progressed (PPS) and therefore the AG overestimate the ICER versus BSC. • In the absence of no UK recommendations there is no justification for the inclusion of these treatments following progression • No evidence for re-treatment with 177-Lu DOTATATE following progression, and in any case the use of 177-Lu DOTATATE should not be higher in the 177-Lu DOTATATE strategy.	ii. We have used RCT-based evidence in patients free from progression in the active arm of the RADIANT-4 trial to proxy the type and rate of utilisation of supportive therapies. In the absence of superior evidence it was necessary to assume that these estimates of supportive care therapies are the same for 177-Lu DOTATATE as was observed in-trial for everolimus. However, it may also be reasonable to assume that the use of supportive treatments for patients with stale GI-midgut NETs who are receiving 177-Lu-DOTATATE would in clinical practice be moderately different in nature, rate and therefore cost. In a new sensitivity analysis we have excluded all costs arising from supportive therapies for patients with stable disease receiving 177-Lu DOTATATE (see p. 13 below). iii. • In the absence of superior evidence we have used RCT-based evidence collected from patients who progressed in the active arm of the RADIANT-4 trial to proxy the utilisation of *supportive* therapies in patients who had received 177-Lu DOTATATE. And equally the AG used data from the BSC arm of RADIANT-4 to inform supportive therapy usage in patients who progressed following BSC. The nature and rate of utilisation of included post-progression *supportive* therapies were based on data submitted to the AG by Novartis, based on data collected in patients who progressed in the RADIANT-4 RCT. The cost of *supportive* therapies were included in the first cycle post-progression and all subsequent cycles until death. In using patients progressing on everolimus as a proxy for progression on 177-Lu DOTATATE it was necessary to assume that the nature and utilisation rate of *supportive* therapies post-progression would be the same for 177-Lu DOTATATE as was observed in-trial for everolimus. However, the absolute cost and the difference in cost of supportive treatments between strategies is small, and the impact on the ICER also small. • The nature (treatment categories) of *active* treatments post progression (SSAs, PRRT, IFN-alpha, chemo-embolisation, and chemotherapy) were described by UK expert clinicians in NETS in surveys commissioned by Novartis. The calculation of

	• Use of 177-Lu DOTATATE post-progression is not recommended practice, inclusion in the AG model leads to an overestimation of the ICER versus BSC v : Comparing 177Lu-DOTATATE to a non-prespecified subgroup of the RADIANT-4 study.	rate resource utilisation for individual therapies was calculated using RADIANT-4 trial data for patients who progressed in the trial. However, the AG did not include these costs in the base case, since they were limited to the first cycle post-progression, for costs were applied only in a sensitivity analysis. The exception was octreotide LAR 30mg which continued at the same rate of utilisation as applied pre-progression (2% for the 177-Lu DOTATATE strategy, and 1% for the BSC strategy). Indeed it may be reasonable to assume that the proportion of patients treated with SSAs would increase post-progression. We have included a new sensitivity analysis which removes the cost of all supportive therapies post-progression in both strategies (see p. 13 below). • For patients with GI (midgut) NETS entering the model (pre-progression) we applied the cost of 177-Lu DOTATATE as per expected license as described by the manufacturer in its submission, that is 7.4GBq in 4 administrations cycles at intervals of 8 weeks. Regarding retreatment with 177-Lu DOTATATE post-progression, *active* treatments costs (SSAs, PRRT, IFN-alpha, chemo-embolisation, and chemotherapy) were not included in the base case, but applied only in a sensitivity analysis. However, in the calculation of PRRT retreatment for the purposes of the sensitivity analysis, the number of cycles of treatment was based on data collected from patients who progressed on active treatment in RADIANT-4, and does not reflect the expected licensed dosage of 177-Lu DOTATATE. No new sensitivity analysis is undertaken to further address this issue. v. As written on page 109, section 4.2.5.4. data was requested from Novartis for GI NETs. The AG was not provided with IPD, but the analysis results performed by Novartis. We agree, that for a multitude of reasons, as stated in our report, the ITC for GI NETs has considerable uncertainty. The fact that the GI midgut location was not a stratification variable for randomisation in RADIANT-4 means that the Bucher ITC may be subject to a high risk of bias.

	vi. Overestimation of the cost of 177-Lu DOTATATE administration leads to overestimation of ICER versus BSC The AG assumes analysis assumes that an overnight stay is required for the administration of 177Lu-DOTATATE in 90% of patients. However, 177Lu-DOTATATE can be administered as a day case in the majority of patients and an overnight stay is not required in most cases. In UK clinical practice approximately 65% of patients could receive 177Lu-DOTATATE as day case patients (see letter from Dr. Srirajaskanthan in Appendix 1)	vi. We consulted senior nuclear scientists at two tertiary care hospitals, one in London (The Royal Free London NHS Foundation Trust) other in the southwest (Plymouth Hospitals NHS Trust). Normal practice for the majority of patients at each is an overnight stay for the purposes of patient observation following treatment with 177-Lu DOTATATE. We were informed that one particular London centre (Kings College Hospital NHS Foundation Trust) does operate a day case service for the majority of their NETs patients, but that this practice was not currently the norm elsewhere in England. We therefore averaged the resource estimates from each of the two selected centres and adjusted to include 10% of all treated patients as day cases since Kings College Hospital NHS Foundation Trust is one of ten NHS NETS Centres of Excellence in England. We have included a new sensitivity analysis which assesses the impact on the ICER of every patient treated with 177-Lu DOTATATE being a day case (see p. 13 below).
	Response to criticisms of the systematic review submitted by AAA	i. RADIANT-2 was excluded as there is no marketing authorisation for functioning NETs for everolimus ii. The ITC analysis submitted by AAA for other outcomes did not use subgroup data iii. The AG agree with AAA that some of the studies not accounted for would have been excluded based on patient numbers less than 15 or because the outcome reported was only response rate. However, since RR is an outcome within the NICE scope, the AG query why AAA did not include RR as an outcome of interest for inclusion.
	iv. Choice of model for extrapolation of the NETTER-1 trial AG has focused exclusively on the fit of the data and not considered the clinical and biological plausibility of the inferred outcome. The AG has inappropriately chosen an exponential model as the best fit to the data. This is not clinically plausible for GI-NETs, who typically have 60-70%	iv. We did not choose our parametric functions for survival extrapolation based solely on goodness of fit; in addition to this criterion, we considered clinical plausibility based on expert opinion, and the requirement of consistency between extrapolations of PFS and OS curves (i.e. that the two did not cross; see details in 7.1.5.3.2). AAA are correct that the reason we did not consider sensitivity analyses on the survival extrapolation of NETTER-1 data was that 177Lu-DOTATATE was only evaluated as part

	5 year survival rate (Oberg et al., 2012). We believe the exponential model underestimates the amount of treatment benefit from 177Lu-DOTATATE Although the AG chose to fit both lognormal and exponential curves to all other groups (pNETs and GI/lung) in their analysis, they have only fitted the exponential model to the NETTER-1 data. The AG has not given any explanation for this differential treatment; the only logical explanation for this omission is the fact the 177Lu-DOTATATE has been relegated to a scenario analysis vii. There are other inconsistencies in the way the AG has modelled the cost-effectiveness of 177Lu-DOTATATE compared to other treatments - The AG exclude all-cause mortality in their base case analyses for everolimus and sunitinib, but include it in their analysis of 117Lu-DOTATATE	of a scenario analysis, given the strong caveats presented in our AR about the validity of including this assessment subject to the NICE scope. vii. Unlike other analyses, in the GI midgut analysis we applied adjustments for background mortality. The reason for this was that the survival data from NETTER-1 was much more immature, than those in RADIANT-3 and A6181111 (pNETs) and RADIANT-4 (GI/lung).
	viii. Utility values AAA have provided evidence on HRQL from a real world setting in the UK (Guys and St Thomas NHS hospital) for patients following treatment with 177Lu-DOTATATE. This has not been fully considered by the AG.	We adopted the pre-progression utility values of 0.77 as opposed to the 0.79 values from Guys and St Thomas, which are referred to by AAA as the best source of utility outcomes. Given the high uncertainty and strong caveats in the indirect treatment comparison with RADIANT-4 midgut patient population, we chose these values as they were very close to the pre-progression values for everolimus, of 0.767. It would be very difficult to claim any difference in utility between these two targeted treatments given the strong caveats affecting this analysis.

Novartis	Pancreatic NETs	
	2.1 Lu-177 DOTATATE is not an appropriate comparator in pNETS	No Comments. We did not include this comparator in our analyses.
	2.2 Best supportive care (BSC) is not a relevant comparator to everolimus in patients with metastatic, well- or moderately-differentiated pNETs whose disease has progressed, due to the evolution of the treatment pathway with the approval of targeted treatments	BSC is a comparator included by NICE – perhaps this is a point that should be raised with NICE and discussed at the AC meeting.
	2.3 Estimates of OS derived from the rank preserving structural failure time (RPSFT) crossover adjustment should be interpreted with caution	Agree. The RPSFT model assumption that the treatment effect is the same regardless of when the targeted treatment is started is the major shortcoming of this method in this particular application. As stated in the AR, given insufficient information provided by Pfizer we could not verify that the method was applied consistently by the two companies sponsoring the targeted treatments (Novartis to RADIANT-3 data and Pfizer to A6181111 data).
	2.4 The ITCs are associated with wide confidence intervals, suggesting uncertainty in the results and little difference between everolimus and sunitinib	No comment
	2.4.1: PFS The results of the ITCs for PFS conducted by Novartis and the AG were similar, suggesting no evidence of a difference in effectiveness between everolimus and sunitinib.	No comment other than refer to our response to 3.1-3.3, below.
	2.4.2: OS The estimates of OS are based on the RPFST model; thus the potential biases and uncertainty associated with the RPFST estimates of OS may be further magnified in an ITC. In an ITC of two treatments based on two trials with a single common comparator, the variance of the indirect estimate of treatment effect is equal to the sum of the variance of the two treatment effect estimates. This may also introduce further uncertainty into the analysis.	No comment other than refer to our response to 3.1-3.3, below.

	The ITC of response rates and PFS provided little evidence of a difference between everolimus and sunitinib	
	2.5.Treatment duration is not expected to be different for everolimus and sunitinib in clinical practice	No comment
	2.6: Inappropriate approach to the assessment of end of life criteria	We treated the evidence from RADIANT-3 and A6181111 separately, effectively allowing for the possibility that the two trials refer to two different populations. If one is reluctant to accept that the observed differences in baseline characteristics between the two trials reflect two different patient populations then the life expectancy test result of the End of Life criteria should be the same for everolimus and sunitinib. Nevertheless, we found that the life extension test result is different between the two treatments, the criterion being rejected statistically for everolimus, but not rejected for sunitinib.
	3.1-3.3. Key considerations in pNETs 3.1The estimates informing the AG model are unreliable as key assumptions underpinning the model are flawed "These analyses lack face validity for several reasons: 1. A similar PFS based on local assessment for everolimus (11.0 months) and sunitinib (11.4 months) was observed in their respective trials. Furthermore, there is no evidence or plausible explanation as to why this would translate into an OS difference of nearly 2 years 2. The ITC for PFS suggested little evidence of a difference in the two treatments. Moreover, uncertainty in any difference in PFS was highlighted by the fact that the point estimate for locally assessed	As a general response, our modelling approach was guided by the principle that 'lack of evidence effect did not mean evidence of no effect'. Instead of imposing the assumption of no difference in outcomes between sunitinib and everolimus, we adopted the point estimates of OS and PFS with information on their uncertainty in the Probabilistic Sensitivity Analysis (PSA). Therefore, the deterministic results should be interpreted alongside the probabilistic results (i.e. the probability of cost-effectiveness at the £20,000 and £30,000 threshold; see Claxton, Schulpher, Buxton and Briggs). More detailed responses: 1. These PFS and OS figures are not directly comparable. The PFS figures cited by Novartis refer to median PFS values whereas the OS difference cited from the AG's report are mean estimates. 2. Again, these refer to HR as opposed to mean estimates derived from areas under the K-M curves. Please also note that the sensitivity analysis by AG using Local Assessment produced no material difference to results and led to same conclusions (see section 7.2.3 in AR). 3. Our projected OS benefits of sunitinib vs. everolimus were derived from an ITC OS data from A6181111 and RADIANT-3 (p. 233 in AG report). Our base case

	PFS favoured everolimus whereas the estimate for centrally assessed PFS favoured sunitinib 3. Combining the estimates of PFS and OS in the model projects a gain of 1.37 post-progression life years for sunitinib vs. everolimus, a value that is more than 4 times greater than the gain in pre-progression life years (which is also highly uncertain and contingent on the choice of the PFS measure used in the analysis [central or local]). This result lacks face validity since the analysis assumes that sunitinib is administered on average for only 7.5 months, and that mean pre-progression life years are 1.6 years (19 months). While it is reasonable to assume that targeted therapies may yield benefits on post-progression survival, the magnitude of the gain in post-progression survival given the short treatment duration relative to PFS lacks clinical face validity. Even if it is assumed that the treatment duration for sunitinib is equal to that for everolimus (as assumed in our evidence submission), there is no evidence to support an assumption of a continuing benefit in post-progression survival of this magnitude, suggesting that the projections of the OS benefits of sunitinib versus everolimus are likely flawed.	estimates are affected by our choice of parametric functions for the OS data for sunitinib and everolimus, i.e. the exponential and Weibull respectively. Although this choice may underestimate mortality in sunitinib relative to that of everolimus, our sensitivity analysis addresses this potential issue by adopting a more optimistic, lognormal OS curve for everolimus (as well as a loglogistic PFS curve) and retaining the exponential curve for sunitinib: these results in a reduced projected gain of 0.48 post-progression life years, and an ICER for everolimus vs. BSC of 28,098 vs. sunitinib's £20,726. Notice that if there is any issue of face validity about treatment duration vs. pre-progression life years in the model, it affects both sunitinib and everolimus arms in the comparison in the same degree and direction, and thus does not affect the ICER calculations.
	3.2 The results of the AG's economic analyses are highly uncertain and unreliable Novartis presents an updated analysis using the AG model with their preferred assumptions, namely: 1. equal PFS, OS and treatment duration outcomes	The validity of the updated analysis presented by Novartis is questionable due to the limitations relating to point 1, as discussed in our response to 3.1. As for point 2, it is questionable whether the Novartis parametric model estimates are more robust than our separate curve fitting estimates, since any gain in precision in model parameter estimates for the BSC arm comes at the cost of arbitrarily restricting one of the two parameters in its distribution to be equal to the targeted trial arm's.

	2. joint estimation of parametric survival modes in both treatment arms (i.e. 'restricted model') of each trial as opposed to our separate curve fitting to each arm – this is claimed to provide more robust estimates for the BSC arm due the limited follow-up data left after recensoring for this arm.	
	3.3. Everolimus represents a cost-effective treatment option when the confidential Patient Access scheme is considered	Please note that there is a confidential Appendix produced by the AG where these results are provided.
	4. Key clinical considerations in GI and lung NETs	No comment, apart from noting that there is a confidential Appendix produced by the AG where results with PAS discounts are provided.
	5. Key economic Considerations in GI and lung NETs	No comment, apart from noting that there is a confidential Appendix produced by the AG where results with PAS discounts are provided.
	6. Key Clinical Considerations in Midgut GI NETs Although Novartis agree with the AG that lu-177 DOTATATE would represent a relevant comparator to everolimus in midgut GI NETs in clinical practice, we do not consider the AG's analysis to be sufficiently robust to form a clinically meaningful conclusion for the following reasons: • The evidence base for the analysis is severely limited, based on unpublished data from the NETTER-1 trial and a small subgroup of patients from the RADIANT-4 trial • The patient populations in the NETTER-1 trial and the subgroup of GI patients that the AG considered from RADIANT-4 trial are not comparable. The NETTER-1 trial included patients with functioning and non-functioning midgut NETs, whereas RADIANT-4 included patients with non-functioning NETs so it is	Whether the evidence is sufficiently robust to form a clinical opinion is a decision for the committee to make. The AG have made clear the limitations of the ITC. • We have made it clear that the NETTER-1 trial was unpublished at the time of writing. The everolimus arm in the small subgroup of patients from RADIANT-4 (n=142) is larger than lutetium (n=116) and octreotide (n=113) arms form NETTER-1. • Yes, we agree with this. It was not reported what proportion of patients were functioning/non-functioning from the NETTER-1 trial. • Yes, we agree with and highlighted this concern in our limitations of the report. The PROMID trial was conducted in treatment naïve individuals. Therefore it is very likely Octreotide would be superior to placebo. In addition some patients in the placebo arm of RADIANT-4 would have been receiving Octreotide • In RADIANT-4, treatment crossover was not allowed.

	unclear whether the midgut subgroup of RADIANT-4 represents a patient population with similar prognoses as to those in NETTER-1. • There is no clinical evidence to support the assumption that octreotide LAR 60 mg in NETTER-1 is equivalent to the placebo plus BSC in RADIANT-4. As a naïve comparison, the PROMID study[11] compared Octreotide LAR 30 mg to placebo and demonstrated a statistically significant increase in PFS for Octreotide LAR 30 mg versus placebo; given this, the assumption that a higher dose of Octreotide LAR (60 mg) is of equal efficacy to placebo plus BSC is not considered to be appropriate. • The analysis did not adjust for the extent of treatment crossover in RADIANT-4, limiting the interpretation of OS results	
	7. Key Economic Considerations in Midgut GI NETs	We acknowledge that our analysis in the GI midgut population is subject to the caveat that 1. this location was not a stratification factor in RADIANT-4 and as such a Bucher analysis such as that underpinning our results is subject to the risk of bias due to unbalanced baseline characteristics between that trial's arms. Nevertheless, this was the closest patient population that we could identify from the available evidence, especially since responses to our data requests to Novartis arrived with insufficient or incorrect data and too late in the assessment period to allow us to use the best potential source of evidence. In particular, this issue resulted in 2. our inability to request and use OS data in the GI midgut population (as opposed to our imputation of OS from PFS data).

		(Novartis also highlight a costing issue, involving octreotide use in the 177Lu-DOTATATE arm, which is addressed in scenario analyses presented in the table below) While Novartis has provided further analyses involving the GI only population (including midgut and non-midgut), claiming to be able to address the limitations raised against our analysis, it leaves the first issue unaddressed since the GI (midgut and non-midgut) population was not a stratifying variable in the randomised allocation used in RADIANT-4 and, more importantly the GI midgut and non-midgut population subgroup in RADIANT-4 differs in the location of tumours of the NETTER-1 patient population. We also note that the updated ITC analysis by Novartis suffers from the fact that it relied on HR to derive the OS and PFS outcomes for 177LU-DOTATATE, thus imposing the proportional hazard assumption without proper testing, as opposed to directly estimating the mean PFS and OS as the area under the Kaplan and Meier curve as we did. The latter is a more robust treatment effect estimator for estimating LYs and therefore QALYs.

Manufacturer/ Issue number/ tumour / ICER pair	Issue description	Sensitivity analysis description	Reference <worksheet> and cell for switch in AG model	AG base case ICER / Manufacturer ICER / Revised AG ICER (£ per QUALY gained) [Deterministic]
AAA1/GI midgut/ 177-Lu DOTATATE versus BSC	The PFS drug acquisition costs for BSC in GI (midgut) NETs is too low, so the AG may overestimate the ICER of 177Lu-DOTATATE versus BSC. All patients should receive Octreotide60mg, and opioid supportive therapy.	a. Proportion on SSAs in BSC in SD is 40% (equated to that observed in PNETS), and dose doubled to Octreotide 60mg. Plus all patients receive a corticosteroid and an anti-diarrheal. b. Proportion on SSAs in BSC in SD is 100%, and dose doubled to Octreotide 60mg. Plus all patients receive a corticosteroid and an anti-diarrheal. Otherwise all other supportive therapies in the base case are excluded.	a. <Cycle costs>, AB35 = 0.8; AB45, AB46, AB48 and AB49 = 0.5 b. <Cycle costs>, AB35 = 1.0; AB45, AB46, AB48 and AB49 = 0.5	62,158 (AG b/c: 177 v BSC) 37,991 (AAA: 177 v Oct30) **a. 49,709 (-20.0%)** **b. 38,748 (-37.7%)**
AAA2/GI midgut/ 177-Lu DOTATATE versus BSC	The PFS drug acquisition cost of 177-Lu DOTATATE should not include supportive therapies, and as such the AG may overestimate the ICER versus BSC	Supportive therapy costs are excluded for patients in the 177-Lu DOTATATE strategy whilst disease is stable (but retained for BSC arm)	<Cycle costs> Z44:Z50 = 0	62,158 (AG b/c: 177 v BSC) 37,991 (AAA: 177 v Oct30) **61,827 (AG SA: 177 v BSC)** **+0.5%**
AAA3/GI midgut/ 177-Lu DOTATATE versus BSC	AG model excluded uptake of SSAs, external beam RT and liver embolisation for all patients who progress and therefore the AG overestimate the ICER versus BSC	All those who progress on 177-Lu DOTATATE or BSC receive octreotide 60mg, plus external beam radiotherapy and hepatic embolisation. All other active and supportive therapies excluded.	<Cycle costs> AF44:50 and AJ44:50 = 0 AF35 and AJ35 = 2 <Control panel> 1st cycle costs switch 'on'. AD29:AD49, AD52:AD55 = 0; AH29:AH49, AH52:AH55 = 0; AD50:AD51 = 1; AH50:AH51 = 1	62,158 (AG b/c: 177 v BSC) 37,991 (AAA: 177 v Oct30) **24,306 (AG SA: 177 v BSC)** **-60.9%**
AAA5/GI midgut/ 177-Lu DOTATATE versus BSC	Overestimation of the cost of 177-Lu DOTATATE administration leads to overestimation of ICER versus BSC	All patients receive 177-LU DOTATATE as day case treatment	<Cycle costs> G65 = 720.78	62,158 (AG b/c: 177 v BSC) 37,991 (AAA: 177 v Oct30) **61,119 (AG SA: 177 v BSC)** **-1.7%**
AAA1-6/GI midgut/ 177-Lu DOTATATE versus BSC [All together]	All of above	All of above	All of above	43,348 (AG b/c: 177 v BSC) 30,115 (AG up to DP) 37,991 (AAA: 177 v Oct30) **10,488 (AG SA: 177 v BSC)** **-83.1%** **27,935 (AG up to DP)**

Minor Clarifications and Corrections

Novartis state that they "have identified a number of points for clarification in addition to factual inaccuracies within the AG report. These points are detailed below in **Error! Reference source not found.** and Novartis kindly request that these points be acknowledged and amended in the final report". However, the three points raised relate to a clarification in response to our critique for their omission of MAIC data in their economic analyses, an acknowledgement of minor discrepancy in the treatment duration reported in the trial and that used in their economic analysis, and a clarification on patient numbers using everolimus in England.

The justification give for not using MAIC (i.e. mainly, that in the previous submission to the SMC on this topic the appraisal committee dismissed this evidence as 'non-standard and of uncertain robustness') at least as a sensitivity analysis is not satisfactory, because the relative costs and benefits implicit in the choice between using a method such as Bucher (unadjusted for known observed confounders) as opposed to a MAIC (adjusted for known confounders but that may miss unobserved confounders or introduce bias by adjusting for confounders) is an empirical question that was never considered by the Novartis submission.

Responses to comments from Pfizer

Issue 1 Progression-free patients die at the general mortality rate in PNET

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The TAR states that background mortality is only taken into account for 177Lu-DOTATATE (7.1.5.2 in TAR). Nevertheless, it is included in the model engine for Sutent in PNET. This raises two issues: 1) It is unclear why progression-free patients are dying at the rate of general mortality? 2) Pfizer identified different calculations, whereby some start from cycle 22 for EVE, cycle 19 for SUN and cycle 18 for BSC?	1. Keep all the cells consistent in column E in <Everolimus pancreatic> sheet, <Sunitinib pancreatic> sheet, and <BSC pancreatic> sheet. Suggest amending the formulas so they don't include general mortality. 2. Recommend that general mortality should be used as a cap for the OS curve, to ensure that the hazard rate of the OS curve will not go above the hazard rate of the general mortality.	No impact on the base case ICER. Impacts the scenario analysis ICER when background mortality is switched on.	1) In the sensitivity analysis (section 7.2.3.6, p.276), background mortality was applied only to extrapolated parts of OS and PFS curves. 2) As stated above, background mortality was applied only to extrapolated parts of the survival curves. Since the length of observational period differed among the trials used in our analysis, background mortality was applied to the survival curves starting from different model cycles (depending on the length of observational period in the relevant trials).

Issue 2 Calculation of probability of on treatment

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
It appears that the calculation of probability on drug is not consistent with the approach described in the report. The report mentions the use of the median treatment duration, however mean (5.0 dummy value for EVE vs. 7.51 for SUN) was used in the model's base case and the median (12.42 for EVE vs. 10.85 for SUN) in the scenario analysis.	Column C in <Everolimus pancreatic> sheet, <Sunitinib pancreatic> sheet, and <BSC pancreatic> sheet. E.g. Cell C7=IF(Control!$C$52=1,EXP(-A7/(Treatment_duration_evero_pancreas/12)),EXP(-A7/('Treatment Duration & DI'!$B$19/12)) The red highlights the two components to amend (below in gree suggested amendment): Cell C7=IF(Control!$C$52=1,EXP(-A7/('Treatment Duration & DI'!$B$19/12)), EXP(-A7/(Treatment_duration_evero_pancreas/12)))	Base case ICER of EVE vs. BSC = £61,951/QALY Base case ICER of SUN vs. BSC = £20,744/QALY If the base case is amended to use the median (as mentioned in the report), the ICER for EVE vs. BSC significantly increases and the ICER for SUN vs. BSC slightly decreases.	This is a misunderstand of what is written in the AR. We did indeed use mean treatment durations, as intended and dictated by best practice. What we meant to say is that in the absence of Kaplan-Meier time on treatment data we derived mean treatment duration from reported median durations in RCTs, using exponential extrapolations. This approach was used to address the high rate of administrative censoring in the trial data. The sensitivity analysis simply used the values Novartis assumed in their model, which we could not justify given the available evidence.

Issue 3 Calculation of ICER

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The ICER calculation does not show if the treatment is more or less effective, or whether it is more or less costly. In this case (e.g. cell F36), EVE should be less costly and less effective than SUN, however the result shows a positive ICER for EVE vs. SUN, which may be misleading in decision making.	Range F36:H36 in <DisaggregatedResults> sheet for pNET relevant sections. E.g. Cell F36 =$F$34/$F$13 We recommend this is amended to: Cell F36 = IF(AND($F$13>0,$F$34>0),$F$34/$F$13,IF(AND($F$13>0,$F$34<0), "More effective and less costly", IF(AND(($F$13<0,$F$34<0), "Less effective and less costly", "Less effective and more costly")))	There is no impact to the other model results except for EVE vs. SUN EVE is less effective and less costly when comparing with SUN.	We do state in our report that sunitinib is more cost-effective than everolimus for treating pNETs.

Issue 4 Calculation of PSA ICER

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The PSA ICER appears to be calculated incorrectly and is thus underestimating the PSA ICER. The PSA average cost and average LY/QALYs are being underestimated due to the identified error. However, Pfizer also notes that the average, resulting ICER may remain unaffected as a consequence of the relevant magnitude of the numbers being divided.	The calculation in the range P6:U6 is not correct. E.g. Cell P6 =AVERAGE(P10:P2008) The red highlighted cell should respond dynamically to the number of PSA iterations. When calculating the average, it currently includes all cells from P10 to P2008, including cells with 0 values, which are underestimating the result. When the calculation is corrected, the cell P6 should result in a reading of 0.73, instead of 0.37. Pfizer suggest that the red, highlighted cell formula above be amended to: Cell P6= =SUM(P10:P2008)/(COUNT(P10:P2008)-COUNTIF(P10:P2008,0))	There is significant impact on the PSA average costs and average QALYs if the PSA runs above 1000 iterations. However, Pfizer note that this may not substantially affect the PSA ICER due to the relevant magnitude of the costs and QALYs within the calculation.	The code has been corrected, and updated results for PSA were sent to NICE in January, 2017.

Issue 5 Calculation of PSA CEAC

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
There appears to be a reference error in the calculation of the CEAC	Column AN, AO, AP in <PSA> sheet (all formulas) E.g. Cell AN10 =AVERAGE(IF((PSA_C_q*$AR10)-PSA_C_c>(PSA_P_q*$AR10)-PSA_P_c, IF((1)-0>0, IF((PSA_C_q*$AR10)-PSA_C_c>(PSA_CI_q*$AR10)-PSA_CI_c, 1, 0), 0), 0)) Pfizer suggest that the red, highlighted section should refer to cell $AM10.	No impact to the model results as long as the willingness to pay threshold list is the same among pNET, GI/Lung, and GI (midgut).	Since the values in AR and AM columns are identical, we do not regard it as an error.

Issue 6 Figure label of PSA CEAC

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The figure entitled "pNETs CEAC" are incorrectly labelled. The BSC and sunitinib curves appear to be the wrong way around, i.e. the sunitinib curve should be above BSC curve.	“pNETs CEAC” figure in the <PSA> sheet. Pfizer recommend that the labels for SUN and BSC should be amended (exchanged).	No impact to the model results.	We believe that the labelling for SUN and BSC on pNETs CEAC” figure is correct.

Issue 7 AE frequency calibration

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The source of AE frequency used in the model was not specified, so it is therefore difficult to check. However, the observed frequency (sum=0.37 for EVE and sum=0.25 for SUN) was calibrated to EVE=0.35 and SUN=0.43	Pfizer tested this scenario without calibration by changing cell K115 to 0.37 and cell K116 to 0.25.	ICER of EVE vs. BSC = 31,467/QALY; a slight increase from the base case model. ICER of SUN vs. BSC = 21,936/QALY; a slight decrease from the base case model.	The source of these values is given in the AR, section 7.1.5.3.3,and in Appendix 9. The rationale of this issue is also discussed in section 6.1.1.2. As stated in Summary and Discussion of the AG report these values led to negligible differences in utility.

Issue 8 Calculation of 1st cycle PPS (post-progression survival) cost

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The method used to calculate PPS 1st line and PPS subsequent lines may result in double counting (columns O, P and R).	Column O, P and R in <Everolimus pancreatic> sheet, <Sunitinib pancreatic> sheet, and <BSC pancreatic> sheet. E.g. Cell O8=IF(Control!$C$46,(IF((F8-F7)>0,(F8-F7)*'Cycle costs'!$F$8,0)+AVERAGE(F8:F9)*'Cycle costs'!$G$8),AVERAGE(F8:F9)*'Cycle costs'!$G$8) We would recommend calculating patients on PPS 1st line and PPS subsequent lines explicitly to verify the results.	No impact on the base case model. Impact to scenario analysis when the 1st cycle cost is included for the PPS cost calculation.	The values used were such that the 1st cycle costs were only excess costs in addition to average cycle costs of post progression.

Issue 9 Sutent drug costs

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
It is unclear how cost per cycle for sunitinib has been calculated based on the unit costs presented in the model.	The cost for sunitinib should be calculated as 12.5mg + 25mg = 37.5 mg dose per day and equate to £2354.10 (instead of £2353.7 that is presented in the model). £784.7 £1569.4 £2354.10	Minimal impact on ICER (+2 GBP)	We acknowledge this error but given its minimal impact on teh ICER no re-analysis is undertaken to further address this issue.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal: ID858: everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression

Executive summary for lutetium-177 DOTATATE

Advanced Accelerator Applications SA

8 September 2016

File name	Version	Contains confidential information	Date
ID858_177Lu-DOTATATE _MTA Executive summary_[ACIC]	1	Yes	08 September 2016

1 Executive summary

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are rare neoplasms arising in the diffuse neuroendocrine system, many of which are located throughout the length of the gastroenteropancreatic (GEP) and bronchial tract. Well-differentiated carcinoid tumours express somatostatin receptors, specifically subtype 2 (SSTR2), in high abundance (over 80%).

Gastrointestinal neuroendocrine tumours (GI-NET) are classified according to their point of origin, into tumours of the foregut (stomach, gall bladder, and proximal duodenum), mid-gut (distal duodenum, jejunum, ileum, caecum and appendix, ascending, and right two thirds of transverse colon) and hindgut (left one third of transverse colon, and rectum). Pancreatic neuroendocrine tumours (P-NET) develop from pancreatic islet cells. The relative incidence of GEP-NETs is highly variable depending on the geographic area. Based on its embryological classification midgut is the most frequent (ranging from 20−67% of all NETs); foregut occurs in around 40% (of which pancreatic is a subgroup ranging from 7−34%) and hindgut in around 40% in the western world (Europe-US).

GEP-NETs have profound impact on lives of patients. Symptoms include non-specific pain (which may be intermittent and present for many years), nausea and vomiting, and, in some cases, anaemia due to intestinal blood loss; as a result there is often a delay in diagnosis and treatment (Ramage et al., 2012). At diagnosis, near 50% of patients present with distant metastases (liver and lymph nodes are the most common spread site while other sites dissemination include, bone, lung, brain and peritoneum) and curative treatments are no longer possible (Pavel et al., 2016).

While the impact on health-related quality of life (HRQoL) may vary by the type of GEP-NET, patients have reported that NETs have a large impact on their daily lives, including emotional health, interactions with friends and family, and ability to perform household tasks or travel (Leyden et al., 2015). Up to 72% reported a large to moderate negative impact of NETs on their quality of life, with only 5% reporting no effect at all. The disease has impact on work productivity as well. More patients with GI-NETs (84%) or P-NETs (83%) reported having to stop working because of these NETs than patients with lung NETs (69%) (Ruszniewski et al. 2015).

GEP-NETs are classified as orphan diseases by the European Medicines Agency (EMA) but its incidence is increasing globally. The estimated prevalence of GI-NETs and P-NETs is 6.49 and 0.79 per 100,000, respectively. The incidence of GI-NETs and P-NETs is 1.33 and 0.43 per 100,000 respectively. For England and Wales, there will be 3,287 patients with GI-NETs and P-NETs in 2017.

The primary treatment for GEP-NETs is surgery with curative intent in patients. However, only a minority of GEP-NET patients can be cured by surgery (Oberg, 2012a) as most patients present with advanced, inoperable disease. Treatment options with significant efficacy for these patients are limited.

177Lu-DOTATATE is a novel compound that will be the first to market of an emerging class of treatments known as Peptide Receptor Radionuclide Therapy (PRRT), which target neuroendocrine tumours with radiolabelled somatostatin analogue (SSA) peptides. PRRT involves the systemic administration of a specific radiopharmaceutical to deliver cytotoxic radiation to a tumour. 177Lu-DOTATATE is composed of a lutetium radionuclide chelated to a peptide which is designed to target somatostatin receptors with a high binding affinity. Lutetium emits high energy electrons (therapy) and gamma rays (imaging). The affinity for SSTRs and the specificity of binding enables a high level of specificity in the delivery of radiation to the tumour as 80% of NETs overexpress somatostatin receptors (particularly SSTR2).

Clinical efficacy and safety of 177Lu-DOTATATE

The phase III ‘NETTER-1’ RCT (Advanced Accelerator Applications. 2016b) and single-arm phase I/II ‘Erasmus’ study (Advanced Accelerator Applications. 2016a) provide the main evidence to support the 177Lu-DOTATATE clinical and economic case for this appraisal. It is also in line with the evidence supporting the marketing authorisation for 177Lu-DOTATATE.

[redacted]

Erasmus study (Advanced Accelerator Applications. 2016a)

In a single centre non-controlled phase I/II open-label study, conducted in 810 Dutch patients with different somatostatin receptor positive tumour types, the objective

response rate (ORR) (including complete response [CR] and partial response [PR] according to RECIST [response evaluation criteria in solid tumours] criteria) for the full analysis set (FAS) population with GEP-NETs and bronchial NETs (360 patients) was 44% (95% confidence interval [CI] 38% - 49%). ORR in the different tumour subtypes were: midgut NET 34% (95% CI 28% - 41%), bronchial NET 37% (95% CI 15% - 59%), hindgut NET 46% (95% CI 19% - 73%), foregut NET 50% (95% CI 22% - 78%) and P-NET 56% (95% CI 48% - 65%).

The overall median PFS across all tumour subtypes was 29.8 months (95% CI 25.4 - 33.0 months). Patients with pancreatic NET tumours had the longest median PFS, 30.5 months, across all tumour subtypes, with hindgut NET and midgut NET with nearly similar values (median PFS of 29.3 and 29.6 months, respectively). The overall median OS across all tumour subtypes was 64.4 months (95% CI 57.0 - 75.3). The longest median OS estimate was found for the pancreatic NET (70.8 months) followed by midgut NET (55.4 months) and bronchial NET (50.5 months). In patients that were progressive at baseline median PFS was highest in P-NET patients (n=62) [35.6 months (95% CI 25.0 - 43.8)] while in progressive midgut NET (n=98) median PFS was similar to progressive GEP-NET (n=184) [28.4months (95% CI 22.8 - 33.9 and 29.8 months (95% CI 25.3 - 33.4) respectively].

The overall median time to progression (TTP) in GEP-NET patients was 34.6 months (95% CI 30.9 - 39.4). In progressive GEP-NET patients, median TTP was 34.9 months (95% CI 30.5 - 40.1), progressive P-NET, median TTP was 35.6 months (95% CI 25.0 - 45.1) and in progressive midgut NET was slightly higher (40.0 months 95%CI 32.3 - 46.1).

The median overall survival (OS) across GEP-NET patients was 64.4 months (95% CI 57.0 - 75.3). The longest median OS estimate was found for P-NETs followed by midgut NETs and bronchial NET: 70.8 months (95% CI 63.2 - ND), 55.4 months (95% CI 49.8- 70.1) and 50.5 months (95% CI 31.2 - ND), respectively. Median OS was not reached for foregut and hindgut. The median OS of patients with P-NET that were progressive at baseline was 80.7 months (95% CI 57.0 - ND). In progressive GEP-NET patients, median OS was 60.2 months (95%CI 53.5 - 73.6) and 49.0 months (95%CI 36.4 - 60.2) in progressive midgut NET.

Duration of response (DoR) was 15.9 months in the FAS Dutch population with GEP-NETs and bronchial NETs, and was ranging from 13.1 months (midgut NETs), 16.2 months (P-NET), and up to 23.8 months (bronchial NETs).

The incidence of serious adverse events (SAEs), laboratory abnormalities, and other physical examination findings did not indicate a worsening of the safety variables relative to the baseline, nor did they indicate any issues with tolerability. The most severe adverse events were related to haematological toxicity, as expected according to the mechanism of action of this therapy.

The Erasmus study affirmed that there is strong evidence that treatment with 177Lu-DOTATATE has an anti-tumour effect. Substantial efficacy improvement in PFS, TTP, and OS was achieved for GEP-NET patients receiving treatment with 177Lu-DOTATATE compared to responses reported for GEP-NET patients treated with the current best standard(s) of care. This was found to be the case in the selected tumour classes examined which included; progressive GEP-NETs, progressive P-NET, metastatic midgut NET.

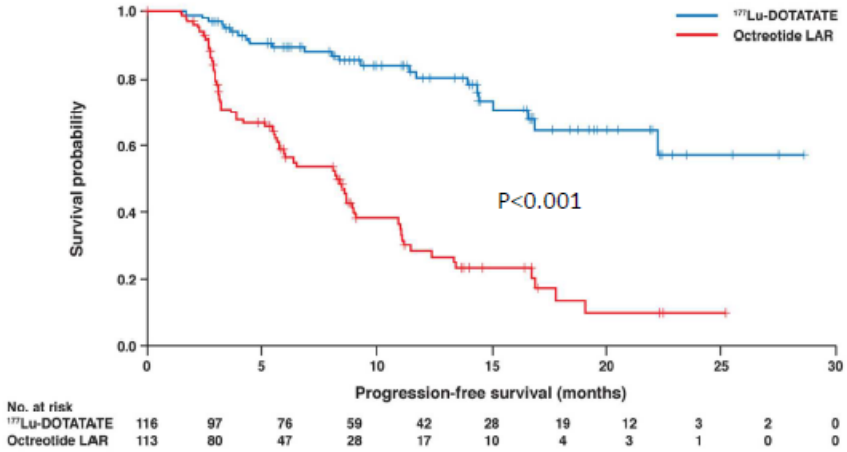
NETTER-1 study (Advanced Accelerator Applications. 2016b)

In the randomised phase III study (NETTER-1), 177Lu-DOTATATE, 7.4 GBq every 8 weeks (4 administrations, intravenously), plus best supportive care,: octreotide long-acting release (LAR, 30 mg), [N=116] was compared to octreotide LAR 60 mg intramuscularly every 4 weeks [N=113] in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumours. The primary endpoint was PFS and secondary endpoints included; ORR, OS, and safety endpoints.

At the cut-off date for statistical analysis, the number of centrally confirmed disease progressions or deaths was 23 events in the 177Lu-DOTATATE arm and 68 events in the octreotide LAR arm. PFS differed significantly ($p<0.0001$) between the treatment groups. The median PFS for 177Lu-DOTATATE was not reached at the time of analysis whereas the one of octreotide LAR was 8.4 months. The hazard ratio (HR) for 177Lu-DOTATATE was 0.21 with 95% CI of 0.13 to 0.33, indicating a 79% reduction in the risk for a patient to progress or die under 177Lu-DOTATATE compared to octreotide LAR.

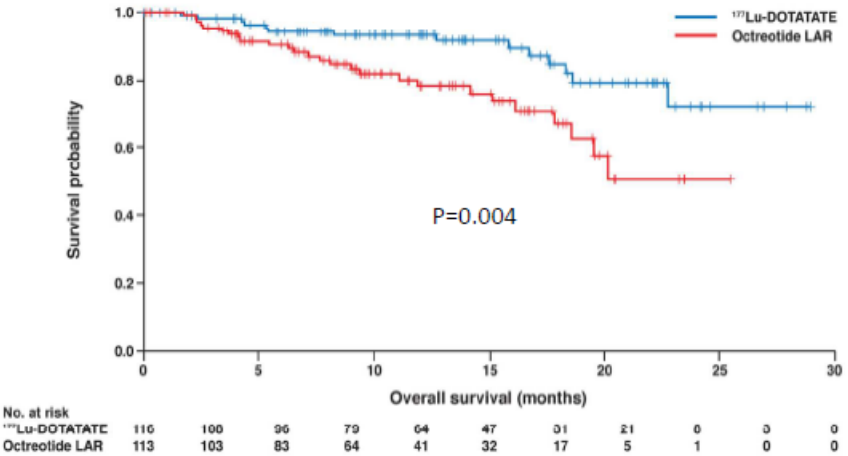
The Kaplan-Meier (KM) PFS curves of patients with progressive midgut carcinoid tumour - (Phase III NETTER-1 study; FAS, N=229), are shown in Figure 1.

Figure 1. PFS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - (Phase III NETTER-1 study; FAS, N=229)



With respect to OS, at the time of interim analysis, there were 14 deaths in the 177Lu-DOTATATE arm and 26 in octreotide LAR 60 mg arm (p=0.0043, HR 0.398 [95% CI: 0.207 – 0.766]), indicating a trend for increased life expectancy for patients treated with 177Lu-DOTATATE. The statistical significance for OS had not been reached due to a very conservative multiplicity-adjusted statistical significance level defined for the interim analysis (alpha = 0.0085%). The OS KM curves are presented in Figure 2.

Figure 2. OS Kaplan Meier curves of patients with progressive midgut carcinoid tumour - (Phase III NETTER-1 study; FAS, N=229)



Few treatments are available for patients with advanced GEP-NETs progressing under SSAs, and the NETTER-1 study (Advanced Accelerator Applications. 2016b has shown that 177Lu-DOTATATE provides a major therapeutic benefit for this patient population showing 79% reduction in the risk of disease progression/death; significant difference in overall response rate and survival benefit based on interim analysis are shown.

177Lu-DOTATATE 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, this included toxicity 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 using peptides binding to receptors expressed by the tumour, minimising the effect on healthy cells.

PRRTs are already in guidelines for the treatment of NETs (orphan disease): ENETs (2016), ESMO (2010), and NANETs (2011). They are in a position in the treatment pathway that aligns with the proposed positioning of 177Lu-DOTATATE in this submission i.e. second-line treatment option in patients with advanced, unresectable GI-NET and P-NET.

As of July 2016, 3,577 doses of 177Lu-DOTATATE had been provided to 1,293 patients treated under AAA-named patient and compassionate use programs in 63 centres and 10 European countries. In the UK, although unlicensed, 177Lu-DOTATATE has significant clinical support and it has been used to treat a number of patients in England through the Cancer Drugs Fund (CDF) [redacted]

Statement of decision problem

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with progressed unresectable or metastatic neuroendocrine tumours • according to the specific locations covered by the existing and anticipated marketing authorisations of the interventions	The company submission presents clinical and cost-effectiveness evidence on adult patients with GEP-NETs, including mid-gut and P-NET. [redacted]	
Intervention	• Lutetium-177 DOTATATE (neuroendocrine tumours of gastrointestinal or pancreatic origin)	Lutetium-177 DOTATATE (neuroendocrine tumours of gastrointestinal or pancreatic origin)	
Comparator (s)	• Everolimus (NETs of gastrointestinal, pancreatic or lung origin) • sunitinib (P-NETs) • interferon alpha • chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • best supportive care	Clinical and cost-effectiveness comparison to: • Everolimus (NETs of gastrointestinal, pancreatic or lung origin) • sunitinib (P-NETs) Due to changes in the scope for this appraisal, octreotide and lanreotide were included in network metal-analysis but are not relevant comparators in the decision problem. Further details are provided in section 4.10. For completeness, cost-effectiveness versus octreotide LAR (long-acting release formulation) based on pivotal	No data are available for comparison to interferon alpha or best supportive care.

		study, NETTER-1, are provided in an appendix.	
Outcomes	• overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life	The outcomes listed in the final scope are reported in this submission with respect to evidence on 177Lu-DOTATATE.	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The economic case presented is in line with the requirements for the final scope.	
Subgroups to be considered	• location of tumour • grade/degree of differentiation • stage of tumour • secretory profile • number of previous treatment(s)	The efficacy of 177Lu-DOTATATE has been studies across different tumour locations and tumour classes. For this submission, we based the clinical and cost-effectiveness case on progressive GI- NET and progressive P-NET populations. No other subgroup analyses are presented	This approach is based on availability of evidence as well as the scope of this appraisal.

1.2 Description of the technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	Approved name: 177Lu-DOTATATE (^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate) Brand name: Lutathera®
Marketing authorisation/CE mark status	177Lu-DOTATATE has not yet received marketing authorisation. 177Lu-DOTATATE has been granted Orphan Drug designation in Europe (EMA) and in the USA (US Food and Drug Administration [FDA]). [redacted] 177Lu-DOTATATE has been approved for treatment of NETs on a compassionate use and named patient basis since March 2012 in 10 European countries including the UK. 177Lu-DOTATATE is also available in the United States under similar access program.
Indications and any restriction(s) as described in the summary of product characteristics	[redacted]
Method of administration and dosage	177Lu-DOTATATE is administered by intravenous infusion at a total dose of 29.6 GBq (800 mCi), divided into four administrations of 7.4 GBq (200 mCi) at intervals of 8 ± 1 weeks. A course of treatment consists of 4 infusions.

1.3 Summary of the clinical effectiveness analysis

A full systematic literature review (SLR) was undertaken to identify all studies that provide information on the clinical efficacy and safety of 177Lu-DOTATATE and relevant comparators in the treatment of patients with inoperable GEP-NETs. The SLR was conducted in line with Cochrane methodology and following PRISMA (preferred reporting items for systematic reviews and meta-analyses) recommendations. Searches were performed on 26/11/15 and updated on the 20/01/16.

Five randomised controlled trials (RCTs) investigating relevant interventions had a progressive patient population that could be considered of interest to the decision problem. For GI-NET comparison, 177Lu-DOTATATE, everolimus, and octreotide LAR/placebo were included in a network. 177Lu-DOTATATE and everolimus are the main treatments of interest and were linked to each other through octreotide LAR/placebo based on 2 comparator studies and the NETTER-1 study. In order to

connect these treatments in a network it was assumed that octreotide LAR was the same as placebo/placebo plus best supportive care.

For P-NET comparison, 177Lu-DOTATATE, everolimus, sunitinib, and octreotide LAR/placebo were included in a network based on 2 comparator studies and the NETTER-1 study. 177Lu-DOTATATE, everolimus, and sunitinib are the main treatments of interest and were linked to each other through octreotide LAR/placebo. In order to connect these treatments in a network it was assumed that octreotide LAR was the same as placebo/placebo plus best supportive care. No relevant data were found on interferon alpha and chemotherapy to enable a comparison to 177Lu-DOTATATE.

To correctly incorporate data from every trial, a Bayesian mixed treatment comparison (MTC) model was used to combine the (log) hazard ratios for two outcomes measure of interest, PFS and OS. The results of this analysis are shown in Table 3 below.

Table 3. Bayesian MTA model results

Population	Comparator vs 177Lu-DOTATATE	Outcome	Hazard ratio	Credible interval
GI-NET	Everolimus	PFS	2.30	0.24, 18.38
GI-NET	Octreotide LAR/placebo	PFS	4.76	0.83, 27.50
GI-NET	Everolimus	OS	2.33	0.47, 10.75
GI-NET	Octreotide LAR/placebo	OS	2.52	0.68, 9..29
P-NET	Everolimus	PFS	1.66	0.10, 27.44
P-NET	Sunitinib	PFS	2.00	0.12, 34.12
P-NET	Octreotide LAR/placebo	PFS	4.77	0.65, 35.61
P-NET	Everolimus	OS	2.63	0.44, 15.26
P-NET	Sunitinib	OS	1.02	0.15, 6.68
P-NET	Octreotide LAR/placebo	OS	2.51	0.66, 9.16

GI-NET gastro-intestinal neuroendocrine tumour, P-NET pancreatic neuroendocrine tumour, PFS progression-free survival, OS overall survival

The results of the MTC scenarios indicate no significant difference in PFS or OS between any of the interventions. However, there was considerable variation observed in the baseline characteristics between studies overall, particularly in the type of NET patients recruited to each trial and wide ranging assumptions had to be made to enable a comparison.

1.4 Summary of the cost-effectiveness analysis

A decision analytic model was developed structured as a three health state Markov model (with health states defined as progression free survival, post-progression and death) with a 4 week cycle length over a 20 year time horizon. EORTC-QLQ-C30 data collected directly from patients in UK clinical practice mapped to EQ-5D was used in the base case for the relevant health states and utility decrements were applied to grade 3-5 adverse events. Drug acquisition costs, drug administration costs, monitoring costs, and the costs of managing adverse events were considered in the model.

[redacted]

The GEP-NET population in the model is separated into GI-NET (these patients are the same as those considered in the NETTER-1 clinical study) and P-NET (these patients are the same as those considered in the Erasmus clinical study). As GI-NET and P-NET have different clinical profile and management, separating the analysis on the basis of these sub-population within GEP-NET is appropriate.

Long-term outcomes were modelled via the direct extrapolation of OS data from the NETTER-1 and the Erasmus studies using a simple three state partitioned survival model. 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 GI-NET patient population, the model compares 177Lu-DOTATATE to everolimus in the base case and in the P-NET patient population to everolimus and sunitinib. The base case does not include comparison to octreotide LAR as it is not expected to be displaced in clinical practise with the adoption of 177Lu-DOTATATE and is not regarded as a relevant comparator in this appraisal. As it was the comparator in the NETTER-1 study, results are presented for completeness only in an appendix.

Given that there are multiple comparators in our analysis which have been examined in separate RCTs, we have had to rely on summary statistics (HRs) generated through a mixed treatment comparison. This lends itself to a proportional hazards modelling approach using HRs. Under this approach a HR has been applied to a base survival

curve to compare the experimental treatments to octreotide LAR (in the case of GI-NETs) and 177Lu-DOTATATE (in the case of P-NETs) so that all treatments can be compared to a common comparator. The assumption was made that treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape.

- GI-NET versus everolimus: 177Lu-DOTATATE is associated with an incremental costs of £28,099 and incremental QALYs of 1.42 resulting in an ICER of £19,816.
- P-NET versus everolimus: 177Lu-DOTATATE is associated with an incremental costs of £21,498 and incremental QALYs of 2.18 resulting in an ICER of £9,847.
- P-NET versus sunitinib: 177Lu-DOTATATE is associated with a costs saving of £6,646 and incremental QALYs of 0.10. This produces a dominant ICER in favour of 177Lu-DOTATATE , 177Lu-DOTATATE is cheaper and more effective than sunitinib
- The PSA found that at a willingness to pay threshold of £30,000 per QALY gained, the probability of 177Lu-DOTATATE being cost effective vs everolimus in GI-NET is approximately 68%, and 78% in P-NET. The probability of being cost effective vs. sunitinib is 60%.

The main limitations of this analysis are the requirements to extrapolate beyond the follow-up for NETTER-1 and Erasmus and the uncertainty in the everolimus and sunitinib comparison based on a mixed treatment comparison.

Table 4. Base case incremental cost-effectiveness analysis results- 177Lu-DOTATATE vs everolimus GI-NET patients

Technologies	Total			Incremental			ICER (£) (QALYs) vs Everolimus
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
177Lu-DOTATATE	[redacted]	[redacted]	[redacted]				£19,816
Everolimus	[redacted]	[redacted]	[redacted]	£28,099	1.77	1.42	

Table 5. Base case incremental cost-effectiveness analysis results- 177Lu-DOTATATE vs everolimus, P-NET patients

Technologies	Total			Incremental			ICER (£) (QALYs) vs Everolimus
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
177Lu-DOTATATE	[redacted]	[redacted]	[redacted]				£9,847
Everolimus	[redacted]	[redacted]	[redacted]	£21,489	2.75	2.18	

Table 6. Base case incremental cost-effectiveness analysis results- 177Lu-DOTATATE vs sunitinib, P-NET patients

Technologies	Total			Incremental			ICER (£) (QALYs) vs. sunitinib
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
177Lu-DOTATATE	[redacted]	[redacted]	[redacted]				Dominant
Sunitinib	[redacted]	[redacted]	[redacted]	-£6,648	0.07	0.10	

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal ID858

Unresectable or metastatic neuroendocrine tumours with disease progression

Company evidence submission:

Novartis Pharmaceuticals UK Ltd for everolimus

September 2016

File name	Version	Contains confidential information	Date
		Yes [redacted]	

Contents

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1 Executive summary

1.1 Statement of the decision problem

This submission presents the evidence supporting the clinical and cost-effectiveness of everolimus within its licensed indications for the treatment of:

- advanced, progressive, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin (pNETs), and
- advanced, progressive, well-differentiated, non-functional NETs of gastrointestinal (GI) and lung origin.[1]

NETs are a heterogeneous group of rare tumours arising from the hormone-producing cells of the body. The tumours can be distinguished by their primary site of origin and can be classified as either functioning (presenting with a clinical syndrome due to the hypersecretion of hormones) or non-functioning (presenting with no hormone-specific clinical features).[2]

The only curative treatment option for NETs is surgery; however, due to the non-specific and mild-to-moderate nature of symptoms during the early stages of disease, NETs are often diagnosed late. Delays of up to 7 years from symptom onset to diagnosis are reported for patients with functioning NETs[2] and for patients with non-functioning NETs, many cases may only be picked up incidentally as part of investigations for other health issues, with patients typically presenting with non-specific symptoms of advanced tumour growth such as abdominal pain, bowel/pulmonary obstructions, anorexia, and nausea.[2-4] As such, a considerable proportion of patients with NETs present with metastatic disease when surgery is no longer an option.[5, 6]

For patients with advanced (metastatic and unresectable) disease, the goals of treatment are to improve symptoms, delay/prevent tumour growth, prolong survival and maintain an optimal health-related quality of life (HRQoL). The prognosis of NETs is dependent on multiple factors including the primary tumour location, the presence of metastatic disease, the tumour grade and the stage of disease at diagnosis. UK-specific survival data for patients with NETs is limited, and although the European Neuroendocrine Tumour Society (ENETS) has set up a multinational registry to investigate the epidemiology of NETs, there are no published data from this registry to date. Data from the US population-based Surveillance, Epidemiology, and End Results (SEER) registry report the 5-year survival rate for patients with well- or moderately-differentiated NETs with distant metastases to be 35%.[2]

The HRQoL of patients with NETs can be substantially impaired as a result of non-specific symptoms such as abdominal pain, nausea and vomiting, fatigue and insomnia, occurring in both non-functioning and functioning tumours.[7, 8] In addition, symptoms of hypoglycaemia, diabetes, ulceration, acidosis and gallstones are associated with hormone secretion in functioning NETs, depending on the type of hormone that is overproduced.[9] In addition to the detriment in physical HRQoL, NETs have also been associated with increased levels of anxiety and depression, irrespective of physical symptom severity.[10,11]

Somatostatin analogues (SSAs) are generally recommended as first-line therapies for patients with NETs.[5] For patients with advanced disease who progress on SSAs, treatment options are limited and lack robust clinical evidence. As such, there is a significant unmet need for new evidence-based, well-tolerated treatment options that can delay or prevent disease progression and maintain patient HRQoL. This unmet need is particularly great in patients with lung NETs, for whom there is a severe lack of evidence-based treatment options. Everolimus is the first targeted agent to show robust anti-tumour activity with acceptable tolerability across a broad range of NETs, including those originating from the pancreas, GI system and lung. The decision problem addressed in this submission for everolimus is presented in Table 1.1 on the next page.

Table 1.1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Patients with progressed unresectable or metastatic neuroendocrine tumours • according to the specific locations covered by the existing and anticipated marketing authorisations of the interventions	Patients with: • Unresectable or metastatic, well- or moderately-differentiated pNETs with progressive disease • Unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional GI or lung NETs	Novartis Pharmaceuticals is the marketing authorisation holder for everolimus, thus the patient populations considered in this submission are consistent with marketing authorisations of everolimus in pNETs and GI or lung NETs
Intervention	• Everolimus (pNETs, GI or lung NETs) • Lutetium-177 DOTATATE (pNETs or GI NETs) • Sunitinib (pNETs)	• Everolimus (Afinitor®)	N/A
Comparator(s)	The technologies listed above will be compared with each other *where appropriate* and*:* • IFN-α • Chemotherapy regimens (including but not restricted to combinations of streptozocin, 5-FU, doxorubicin, temozolomide, capecitabine) • Best supportive care (BSC)	• Sunitinib (pNETs) • BSC (GI or lung NETs)	**pNETs (Section** Error! Reference source not found.**)** Sunitinib is considered to be the sole relevant comparator to everolimus for unresectable or metastatic, well- or moderately-differentiated pNETs in adults with progressive disease. This is based on consideration of the available evidence base in addition to current clinical practice: • The evidence base for everolimus and sunitinib shows that the populations included in the respective pivotal trials (RADIANT-3[12] and A6181111[13]) and the marketing authorisations are broadly comparable • Current clinical guidelines (UKINETS,[2] ENETS[5]) recommend everolimus and sunitinib as second-line treatment options for patients with metastatic well/moderately differentiated pNETs whose disease has progressed, and these therapies are considered the standard of care in this patient population.

			• There is a limited evidence base for PRRT in pNETs and no prospective trial, as noted in ENETs guidelines.[5] • There is a limited evidence base for chemotherapy in pNETs, the population for which everolimus is licensed, with no placebo-controlled trials having been performed.[5] In addition, chemotherapy is often limited to poorly differentiated (grade 3) NETs.[2, 5] • For IFN-α in pNETs, there is a limited evidence base and moreover, IFN-α is typically reserved for grade 3 NETs **GI or lung NETs (Section** Error! Reference source not found.**)** Current ENETS guidelines recommend the use of everolimus as a second-line therapy after failure of a SSA or as third-line therapy after failure of PRRT for patients with GI NETs.[5] In this submission BSC (as described by clinical experts as symptomatic and palliative relief such as analgesics, anti-emetics and anti-diarrhoeals) is considered to be the sole comparator for unresectable or metastatic, well-differentiated (non-functional NETs of GI or lung origin in adults with progressive disease. This is supported by UK clinician opinion and reflects the fact that: • There are no other licensed antineoplastic therapies for the population for which everolimus is licensed (unresectable metastatic progressive GI or lung NETs) • The evidence base for IFN-α, PRRT and chemotherapy in this patient population is too limited to perform a meaningful comparison with everolimus. In summary, this submission compares everolimus to sunitinib in pNETs and everolimus to BSC in non-functioning GI or lung NETs.
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Response rates	• OS • PFS • Response rates • Adverse effects of treatment	Symptom control outcomes are not included in this submission since all of the interventions in the scope are licensed for tumour control. Moreover, symptom control is usually managed in parallel with BSC, and was not assessed as an outcome in either of the RADIANT-3 (pNETs) or RADIANT-4 trials (GI and lung NETs) of everolimus.

	• Symptom control • Adverse effects of treatment • HRQoL	• HRQoL	
Economic analysis	In accordance with the NICE reference case which stipulates: • The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. • The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective.	The company submission is presented in accordance with the NICE reference case.	N/A
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Location of tumour • Grade/degree of differentiation • Stage of tumour • Secretory profile • Number of previous treatment(s) Guidance will only be issued in	None	The subgroup analyses by stage of tumour and secretory profile are not considered in this submission, since the RADIANT-3 and RADIANT-4 trials did not pre-specify these subgroups. Pre-specified subgroup analyses by number of previous treatment(s) were also unavailable. Subgroup analysis by prior chemotherapy status (yes/no) and prior SSA receipt (yes/no) demonstrated a consistent treatment benefit across these groups. For these reasons, no subgroup analysis by number of previous treatments was considered in the economic analysis. Pre-specified subgroup analysis of the grade/degree of differentiation was not considered in the economic analysis for either pNETs or GI and

	accordance with the marketing authorisation.		lung NETs since in the RADIANT-3 and RADIANT-4 studies, respectively, a consistent treatment benefit was observed across these subgroups (see Section **Error! Reference source not found.** and Section **Error! Reference source not found.**). With regards to tumour location, the RADIANT-3 and RADIANT-4 studies present separate evidence bases for the use of everolimus in NETs of pancreatic origin (RADIANT-3) and GI or lung origin (RADIANT-4) and hence separate economic analyses in these two populations are presented. The RADIANT-4 study demonstrated a consistent treatment benefit across GI and lung subgroups (Section **Error! Reference source not found.**) subgroup analysis for these two tumour locations separately were not considered in the economic analysis.
Special considerations including issues related to equity or equality	None	None	N/A

BSC: best supportive care, ENETS: European Neuroendocrine Tumour Society, FU: fluorouracil, GI: gastrointestinal, HRQoL: health-related quality of life, IFN: interferon, NETs: neuroendocrine tumours, N/A: not applicable, NICE: National Institute for Health and Care Excellence, NHS: National Health Service, OS: overall survival, PFS: progression-free survival, pNETs: pancreatic neuroendocrine tumours, PRRT: peptide receptor radionuclide therapy, QALY: quality-adjusted life year, SSA: somatostatin analogue, UKINETS: UK and Ireland Neuroendocrine Tumour Society.

1.2 Description of the technology being appraised

Everolimus is an orally-available, selective inhibitor of mammalian target of rapamycin (mTOR), a key serine-threonine kinase that plays a role in protein synthesis, angiogenesis and glucose metabolism.[1] As such, inhibition of mTOR interferes with tumour angiogenic processes and prevents the growth and proliferation of tumour cells.[1]

Everolimus received its marketing authorisation from the European Medicines Agency (EMA) for unresectable or metastatic, well- or moderately-differentiated NETs of pancreatic origin in adults with progressive disease in July 2011. More recently in May 2016, everolimus received its marketing authorisation for unresectable or metastatic, well-differentiated, non-functional NETs of GI or lung origin in adults with progressive disease. The dose for both indications is 10 mg orally once daily, with treatment continued as long as clinical benefit is observed or until unacceptable toxicity occurs.[1]

1.3 Description of the relevant comparators to everolimus

The comparators to everolimus presented in this submission for the two separate indications of pNETs and GI/lung NETs are those therapies for which treatment guidelines and clinical opinion support their use in practice and for which there is a sufficient evidence base to allow a robust comparison.

For pNETs, sunitinib is considered to be the sole relevant comparator for everolimus. Sunitinib is indicated for the same pNETs patient population for which everolimus is licensed[14] and current clinical guidelines recommend everolimus and sunitinib as alternative options for progressive grade 1 or grade 2 pNETs.[5] However, the choice of treatment between everolimus and sunitinib is dependent on the individual patient need, since the two treatments belong to different therapeutic classes and have very different safety/tolerability profiles. Further consideration of sunitinib and the other therapies that are considered in the NICE scope for this appraisal but that are not presented as comparators in this submission is provided in Section **Error! Reference source not found.**.

For GI NETs, the comparator to everolimus presented in this submission is best supportive care (BSC). Current European clinical guidelines recommend everolimus or peptide receptor radionuclide therapy (PRRT) such as lutetium-177 DOTATATE (^{177}Lu-DOTATATE) as second or third-line therapies for advanced disease.[5] However, ^{177}Lu-DOTATATE is an unlicensed therapy with limited availability in the UK and the clinical evidence base for ^{177}Lu-DOTATATE in GI NETs is in a different population to that for which everolimus is licensed. The limitations in the evidence base make any clinically meaningful comparisons between everolimus and ^{177}Lu-DOTATATE difficult; consequently, BSC is considered to be the sole comparator for everolimus in GI NETs in this submission since there are no other licenced therapies for progressive advanced GI NETs.

For lung NETs, everolimus is the first and only licensed medical therapy indicated for the treatment of patients with advanced, progressive lung NETs. Therefore, as for GI NETs, BSC is considered to be the appropriate comparator for everolimus in this submission for patients with lung NETs.

1.4 Summary of the clinical effectiveness analysis

Systematic literature reviews (SLRs) were conducted to identify clinical evidence of the efficacy and safety of everolimus and the relevant comparators in this submission in pancreatic, and GI and lung NETs, respectively.

For pNETs, the SLR identified a total of 4 randomised controlled trials (RCTs) evaluating the efficacy and safety of everolimus monotherapy,[12, 15-17] and 1 RCT evaluating the efficacy and safety of sunitinib.[13] For GI and lung NETs, the SLRs identified a single RCT evaluating everolimus monotherapy in both GI and lung NETs (RADIANT-4).[18] No RCTs were identified evaluating the efficacy and safety of

^{177}Lu-DOTATATE as a monotherapy in the relevant pNETs or GI NETs populations and, as described in Section 1.3 above, ^{177}Lu-DOTATATE is not considered a relevant comparator to everolimus for either pNETs or GI NETs in this submission. Further details of the methodology and results of the clinical SLRs for pNETs and GI and lung NETs can be found in **Error! Reference source not found.** and **Error! Reference source not found.**, respectively.

Of the RCTs for everolimus identified in the SLRs, 2 RCTs were considered directly relevant to the decision problem of this submission: RADIANT-3 in pNETs and RADIANT-4 in GI and lung NETs (see Sections **Error! Reference source not found.** and **Error! Reference source not found.** for further details). In addition, the SLR identified the A6181111 trial for sunitinib in pNETs and this trial is therefore also considered relevant to this submission given that sunitinib represents a clinical comparator to everolimus in this indication. Full details of this trial are not presented in this submission as Novartis are not the marketing authorisation holders of sunitinib; however, clinical efficacy data from this trial have been used to inform an indirect treatment comparison (ITC) between everolimus and sunitinib in pNETs (see Section **Error! Reference source not found.**).

1.4.1 Clinical effectiveness of everolimus in pNETs

The pivotal RCT informing the clinical evidence base for everolimus in pNETs is RADIANT-3, a double-blind, randomised, placebo-controlled phase III trial that compared the efficacy and safety of everolimus 10 mg once daily plus BSC (n=207) with placebo plus BSC (n=203) in patients with advanced, progressive, well- or moderately-differentiated pNETs.[12] Full details of RADIANT-3 are presented in Section 0 of this submission.

RADIANT-3 demonstrated that everolimus plus BSC more than doubled median progression-free survival (PFS) compared to placebo plus BSC. At the primary analysis (28th February 2010), median PFS assessed by local review was 11.0 months for everolimus plus BSC compared with 4.6 months for placebo plus BSC, representing a statistically significant 65% reduction in the risk of disease progression or death with everolimus (hazard ratio [HR] 0.35 [95% confidence interval (CI): 0.27–0.45], p<0.001).[12] In addition, disease control rate (DCR), defined as best overall result of complete response (CR), partial response (PR) or stable disease (SD), was 77.8% for patients treated with everolimus plus BSC compared with 52.7% for those treated with placebo plus BSC.[19] At the final analysis of overall survival (OS) (5th March 2014), everolimus showed a favourable but non-significant effect on median OS compared to placebo (44.02 months versus 37.68 months).[20]RADIANT-3 demonstrated that everolimus plus BSC more than doubled median progression-free survival (PFS) compared to placebo plus BSC. At the primary analysis (28th February 2010), median PFS assessed by local review was 11.0 months for everolimus plus BSC compared with 4.6 months for placebo plus BSC, representing a statistically significant 65% reduction in the risk of disease progression or death with everolimus (hazard ratio [HR] 0.35 [95% confidence interval (CI): 0.27–0.45], p<0.001).[12]In addition, disease control rate (DCR), defined as best overall result of complete response (CR), partial response (PR) or stable disease (SD), was 77.8% for patients treated with everolimus plus BSC compared with 52.7% for those treated with placebo plus BSC.[19] At the final analysis of overall survival (OS) (5th March 2014), everolimus showed a favourable but non-significant effect on median OS compared to placebo (44.02 months versus 37.68 months).[20]

Patient-reported outcomes were not collected in RADIANT-3, but the impact of everolimus on patient HRQoL has been demonstrated in a single-arm observational study (OBLIQUE). In the OBLIQUE study, the HRQoL of patients undergoing treatment with everolimus as part of routine clinical practice in the UK was maintained at 6 months from treatment initiation, measured by the European Organisation for Research and Treatment of Cancer quality-of-life core questionnaire (EORTC QLQ-C30), the disease-specific EORTC QLQ-GINET21 questionnaire, and the EuroQoL questionnaire (EQ-5D).[21]

The safety and tolerability of everolimus in RADIANT-3 was consistent with the well-known safety profile demonstrated in a large number of trials in multiple indications, including metastatic renal cell carcinoma,[22] and hormone receptor-positive advanced, progressive breast cancer.[23] The most common grade 3 or 4 adverse events (AEs) reported with everolimus plus BSC during the double-blind phase of RADIANT-3 were both predictable and manageable, namely anaemia (9%), hyperglycaemia (9%), diarrhoea (5%) and stomatitis (5%).

1.4.1.1 Indirect treatment comparison

There is no direct RCT evidence comparing everolimus and sunitinib in pNETs. A matching-adjusted indirect comparison (MAIC)[24] using data from RADIANT-3 and A6181111 found no significant difference in PFS between the two treatments and additional indirect treatment comparisons (ITCs) using the Bucher[25] methodology also found no significant differences in PFS, OS, and somatostatin analogue use. An ITC of treatment related grade 3 or 4 AEs also using the Bucher methodology, showed sunitinib to be associated with a higher frequency of AEs with differing tolerability profiles between the two treatments. Full details of the results of ITC are presented in Section **Error! Reference source not found.**.

1.4.2 Clinical effectiveness of everolimus in GI and lung NETs

The pivotal RCT informing the clinical evidence base for everolimus in GI and lung NETs is RADIANT-4, a double-blind, randomised, placebo-controlled phase III trial that compared everolimus 10 mg once daily plus BSC (n=205) with placebo plus BSC (n=97) in patients with advanced, progressive, well-differentiated, non-functioning GI or lung NETs.[18] Full details of RADIANT-4 are presented in Section **Error! Reference source not found.**.

Everolimus plus BSC more than doubled PFS compared to placebo plus BSC in patients with GI or lung NETs in RADIANT-4, a result consistent with everolimus in pNETs and the RADIANT-3 trial. At the primary analysis (28th November 2014), median PFS assessed by central review was 11.0 months for everolimus plus BSC compared with 3.9 months for placebo plus BSC, representing a statistically significant 52% reduction in the estimated risk of disease progression or death (HR 0.48 [95% CI: 0.35–0.67], p<0.00001).[18] Additionally, DCR was 82.4% for patients treated with everolimus plus BSC compared with 64.9% for those treated with placebo plus BSC. Although OS data were immature at the primary analysis, everolimus plus BSC was associated with a 36% reduction in the estimated risk of death relative to placebo plus BSC (HR 0.64 [95% CI 0.40–1.05], p=0.037) indicating a tendency to improved survival. Results from the second interim OS analysis (30th November 2015) continued to favour everolimus, demonstrating an estimated 27% reduction in the risk of death compared with placebo (HR 0.73 [95% CI: 0.48–1.11]).[18]

Everolimus plus BSC was associated with a slightly longer median time to definitive deterioration in HRQoL as measured using the Functional Assessment of Cancer Therapy – General questionnaire (FACT-G) (11.27 months) compared with placebo plus BSC (9.23 months), however this was not statistically significant (HR 0.81 [95% CI: 0.55–1.21]).

The safety and tolerability of everolimus in GI and lung NETs in RADIANT-4 was consistent with the known safety profile of everolimus and the profile observed in the pNETs indication. The majority of AEs were grade 1 or 2; grade 3 or 4 AEs were infrequent and included stomatitis (9%), diarrhoea (7%), infections (7%), anaemia (4%) and fatigue (3%).[18]

1.5 Summary of the cost-effectiveness analysis

Two SLRs were conducted to identify studies reporting economic evaluations, cost and resource use, or health state utility values relevant to the decision problem of this submission.

Two health technology assessment (HTA) economic evaluations of everolimus and sunitinib in pNETs were identified; no previous economic evaluations of everolimus in GI or lung NETs were identified. Two *de novo* economic models were subsequently developed in line with these previous HTA economic evaluations, using the partitioned survival approach to determine the proportion of patients occupying each of the three health states included in the model: stable disease, progressive disease and death. The patient populations considered in the pNETs and GI/lung NETs models reflected the patient populations in RADIANT-3 and RADIANT-4, respectively, and were consistent with the marketing authorisations for everolimus in these indications. Clinical parameters used in the model were based on survival function extrapolations fit to time-to-event data for PFS and death from RADIANT-3 and RADIANT-4. Both economic evaluations were conducted from the perspective of the National Health Service (NHS) and Personal Social Services, and incorporated a discount rate of 3.5%.

The cost-effectiveness analyses in this submission are based on both the list price and a potential discounted price of everolimus by way of a Patient Access Scheme (PAS). This potential PAS is in the form of a simple discount of [redacted] off the list price of everolimus.

1.5.1 Cost-effectiveness analysis of everolimus in pNETs

The base case economic evaluation of everolimus in advanced, progressive, well- or moderately-differentiated pNETs compared the costs and quality-adjusted life years (QALYs) associated with treatment with everolimus versus sunitinib over a 20-year time horizon.

The results of the base case deterministic analysis for everolimus in pNETs are presented in Table 1.2. At list price, everolimus dominates sunitinib and is associated with a 0.021 QALY gain and a cost saving of -£1,635.86. Despite the conservative base case assumption of equivalent PFS and OS, this marginal QALY gain is primarily due to the differences in the AE profiles of the two treatments. When considering the potential PAS price offered to the NHS, further cost savings can be achieved with everolimus, due to the reduction in drug acquisition costs.

Probabilistic sensitivity analyses (PSA) demonstrated a 76.0% probability of everolimus being a cost-effective use of resources at the £30,000/QALY threshold.

Table 1.2. Base case deterministic cost-effectiveness results for everolimus versus sunitinib in pNETs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
List price							
Sunitinib	38,568.97	4.177	2.711	-	-	-	-
Everolimus	36,933.11	4.177	2.733	-1,635.86	0	0.021	DOMINANT
PAS price							
Sunitinib (first cycle free)	36,246.57	4.177	2.711	-	-	-	-
Everolimus [redacted]	[redacted]	4.177	2.733	[redacted]	0	0.021	[redacted]

ICER: incremental cost-effectiveness ratio, LYG: life years gained, QALY: quality-adjusted life year, PAS: patient access scheme, pNET: pancreatic neuroendocrine tumour

1.5.2 Cost-effectiveness analysis of everolimus in GI and lung NETs

The base case economic evaluation of everolimus in advanced, progressive, well-differentiated GI or lung NETs compared the costs and QALYs associated with treatment with everolimus plus BSC versus BSC alone over a 30-year time horizon.

The results of the base case deterministic analysis for everolimus in GI and lung NETs are presented in Table 1.3. Under the potential PAS, everolimus plus BSC was associated with 0.777 additional QALYs and an additional cost of [redacted] compared with BSC alone, corresponding to an ICER of [redacted]. PSA demonstrated that the probability that everolimus (at the potential PAS price) represents a cost-effective use of resources at a £30,000/QALY threshold is [redacted]. Full details of the economic evaluation of everolimus plus BSC versus BSC alone in advanced, progressive, well-differentiated, non-functioning GI or lung NETs are presented in Section **Error! Reference source not found.**.

Table 1.3: Base case deterministic cost-effectiveness results for everolimus plus BSC versus BSC alone in GI and lung NETs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
List price							
BSC alone	25,817.42	4.775	3.508	-	-	-	-
Everolimus plus BSC	59,720.14	5.793	4.285	33,902.72	1.018	0.777	43,642.24
PAS price							
BSC alone	[redacted]	4.775	3.508				
Everolimus plus BSC [redacted]	[redacted]	5.793	4.285	[redacted]	1.018	0.777	[redacted]

BSC: best supportive care, ICER: incremental cost-effectiveness ratio, LYG: life-years gained, PAS: patient access scheme, QALY: quality-adjusted life year.

1.6 Conclusions

The RADIANT-3 and RADIANT-4 trials constitute the largest RCTs to date in pNETs and NETs of non-pancreatic origin, respectively. These studies provide robust evidence for the efficacy and safety of everolimus in adults with advanced, progressive, well- or moderately-differentiated pNETs and advanced, progressive, well-differentiated non-functional GI or lung NETs. The patient populations considered are relevant to the licensed indications of everolimus and its anticipated use in clinical practice and the BSC comparators included in the respective trials were reflective of the treatment options available at the time the trials were initiated.

Health economic analyses found everolimus to represent a cost-effective treatment option compared to sunitinib for patients with pNETs, with the ICERs consistently below the £30,000/QALY threshold. At the potential PAS price, the ICER for everolimus compared to BSC in patients with GI and lung NETs, is [redacted]. The cost-effectiveness analyses should be considered within the context of the unmet medical need of clinically effective treatment options for patients with this disease. In addition, given the relatively low numbers of patients with each tumour type in England (pNETs [179], GI NETs [505] and lung NETs [252]) and the relatively high level of potential discount, the budget impact of everolimus in these indications is expected to be low.

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1 Executive summary

Disease background and current treatments

Neuroendocrine tumours (NET) are classified according to the primary site of origin of the cancer. Pancreatic neuroendocrine tumours (PNETs) are a rare and distinct subgroup of NET, which have a different prognosis from other subgroups and are subject to separate treatment recommendations.[1] It is therefore important to note from the outset that treatments for PNETs should be assessed separately from those for other NETs (i.e. carcinoid, gastrointestinal and lung) within this appraisal.

Treatment options for patients with unresectable or metastatic, well-differentiated PNETs (WHO grades 1 and 2) with disease progression are limited. Sunitinib,[2] everolimus[3] and lanreotide[4] are each licensed to treat these PNETs, although there are subtle differences in the marketing authorisations relating to the patient populations of each pivotal trial, and there are no head-to-head trials comparing efficacy and quality of life outcomes of the two targeted agents.

WHO grade 3 PNETs (Ki67 >20%, Ki67 being a prognostic marker of aggressiveness of the tumour) are viewed by clinical experts as a separate tumour entity[5] with an entirely different treatment guideline;[6] neither targeted agent (everolimus nor sunitinib) is licensed for the treatment of these.

Cytotoxic chemotherapy regimens and various locoregional therapies are sometimes used off-label, but robust data on their efficacy in this patient population are lacking. For these reasons, we believe everolimus to be the only comparator for sunitinib in this appraisal.

Treatment selection for patients with PNET needs to account for tumour histology, symptoms, the potential impact of the side-effect profile of the available agents, as well as patients' performance status, comorbidities and individual treatment objectives; as such, treatment is highly personalised. Patients typically undergo multiple lines of therapy during the course of their disease, and there is a paucity of data (both from prospective clinical trials and real world) on treatment sequences. Of note, use of targeted agents can delay the need for chemotherapy (see **Error! Reference source not found.**), thus avoiding the toxicity and quality of life impact that may be associated with chemotherapy regimens. There is no evidence on whether the prescription of concurrent somatostatin analogues like lanreotide with targeted agents is of clinical benefit or not; data have been inconclusive thus far[1,7-9].

Sunitinib in PNETs

In 2010, sunitinib was the first targeted agent to gain marketing authorisation for its licensed indication to treat "unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (PNET) with disease progression in adults."

Robust evidence that sunitinib is an effective treatment for well-differentiated advanced PNET after disease progression was provided by the pivotal phase 3,

double-blind, multinational randomised controlled trial comparing sunitinib plus best supportive care to placebo plus best supportive care (study A6181111[7]). The trial was terminated early due to the early and significant progression-free survival (PFS) gain seen with sunitinib.

The cross-over design allowed patients randomised to placebo to receive sunitinib at disease progression or study termination. In total, 69% of placebo patients crossed over to sunitinib, with the majority of cross-over occurring early in the trial (30% within the first 3 months, up to 50% by 6 months.[10] This cross-over is likely to have confounded the results, limiting the extent to which conclusions can be drawn from any unadjusted (ITT) estimates of overall survival (OS).

- Patients randomised to sunitinib had a statistically significant and clinically meaningful improvement in PFS versus those randomised to placebo: median PFS was 11.4 months for the sunitinib arm vs 5.5 months for the placebo arm (HR = 0.418 [95% CI 0.26-0.66], p = 0.0001). [7]

- Sunitinib was associated with a clinically significant improvement in OS. After 5 years' follow-up:[11]

    - In the ITT population (i.e. analysing patients in their original randomisation groups regardless of crossover), median OS was 38.6 months in the sunitinib arm and 29.1 months with placebo, an improvement of 9.5 months (HR = 0.73 [95% CI 0.50, 1.06], P = 0.094)

    - After adjusting for crossover using the Rank Preserving Structural Failure Time (RPSFT) method, median OS in the placebo group (if the 69% of patients who crossed over had not gone on to receive sunitinib) was estimated at 13.2 months (HR = 0.34 [95% CI 0.15, 1.28], P = 0.094), suggesting a much greater OS benefit when patients were treated with sunitinib vs. placebo.

    - Subgroup analysis showed that survival benefit with sunitinib in patients who had received prior chemotherapy and in patients who had not received prior systemic therapy was similar, irrespective of whether either subgroup had received concurrent somatostatin analogues.

- Importantly, the survival benefits versus placebo seen with sunitinib were achieved without detriment to overall health-related quality of life data, which were collected prospectively; there were no statistically or clinically significant differences between the sunitinib and placebo arms in global quality of life scores.[7]

As stated above, there are no head-to-head comparisons between PNET treatments, and everolimus is the only agent that can meaningfully be compared with sunitinib. A matching-adjusted indirect comparison (MAIC) was conducted by Pfizer using the most recent published survival estimates from the pivotal trials (study A6181111 [sunitinib vs placebo][11] and the RADIANT-3 trial [everolimus vs placebo][12]). MAIC uses propensity weightings, based on patient characteristics in each trial, to

overcome the confounding effect of differences in patient populations when comparing interventions.[13] [redacted] Indeed, the 2016 ENETS guideline[1] recommend both agents for treatment of advanced, progressed PNET with equal weighting with regard to their placement within the guideline.

Sunitinib offers a much-needed treatment option to patients with a rare cancer for whom few proven alternatives exist, without detriment to their quality of life. Sunitinib meets the NICE 'end of life' criteria on the basis of the substantial extension to life achieved with sunitinib (median OS was extended by 9.5 months in the sunitinib group even without adjustment for crossover, and analyses that adjust for crossover indicate that the extension is considerably longer), and the short life expectancy in advanced, progressed PNET patients at the time in their cancer pathway where it would be deemed that a targeted agent should be prescribed. In the placebo arm of the pivotal trial after adjustment for crossover[11,14], the median survival was 13.2 months. That the expected survival in the absence of a targeted agent is below 25 months is confirmed by clinical expert opinion and by the SEER database, which represents the largest PNET patient database to date. From the SEER data it can be seen that median overall survival of PNET patients (at a time before targeted agents) was 17 months for functional and 16 months for non-functional PNETs.[15] Owing to the patient access scheme agreed as part of TA169 and TA179, the first cycle of sunitinib is offered free of charge to the NHS.

Sunitinib in the NHS

Clinicians have considerable experience optimising the use of sunitinib and managing its side-effects in their patients. Sunitinib has maintained its availability status through the Cancer Drugs Fund (CDF) from the time of sunitinib's launch and as such is widely used in the NHS in England for the treatment of patients with PNET (52 requests were made in the 12 months ending March 2015). In 2011 it was also approved by the Scottish Medicines Consortium and the All Wales Medicines Strategy Group (AWMSG), cementing its well-established position as part of the treatment landscape for advanced PNET in all parts of the UK. It is currently the only targeted agent available in this indication in England and Wales through their respective NHS commissioning systems.

The 2016 ENETS guideline[1] emphasises the role of targeted agents in the treatment of PNETs and recommends both sunitinib and everolimus for PNET patients with well-differentiated unresectable or metastatic tumours and disease progression. The NET Centre of Excellence protocols in the NHS are dictated by these guidelines and are audited against them for maintenance of their Centre of Excellence status, so it is essential these guidelines are upheld.

Sunitinib is administered orally and offers a practical and convenient treatment option with proven survival benefit, and an acceptable tolerability profile. Familiarity with the drug-related side effects, e.g. diarrhoea and hand-foot syndrome, and confidence in managing them, has increased over time. These toxicities are

generally manageable on an outpatient basis, and in the pivotal trial they did not have an impact on patients' global HRQoL compared with placebo.[7]

It is important that all licensed treatments for PNET are available on the NHS so that clinicians are able to select the most appropriate treatment for the individual patient, taking a personalised medicine approach for these rare tumours and planning a sequence of medicines that endeavours to optimise each line of therapy and align with the goal of overall survival benefit without detriment to global health-related quality of life.

It is therefore important that sunitinib continues to be available to PNET patients in England, allowing clinicians and their patients to choose the most appropriate agent from the full range of licensed treatments for this rare and heterogeneous condition.

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BY EMAIL

Kate Moore
Project Lead NICE

Dear Ms Moore,

Response to Multiple Technology Appraisal
Everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression
Final scope August 2016

Following review of the latest documentation, we provide the following response

Whilst we applaud a process to standardise and rationalise care inherent in the NICE process, we do have a number of concerns related to the accuracy and relevancy of the information in the MTA documentation. This calls into question the assurance of informed decision making.

Concerns :

Background information including incidence and prevalence data : historic and with generalisations made.
Lack of recognised NET expert in the process.
Recommend : full involvement of a recognised NET expert – not just to answer one or two questions – as was mentioned at the July meeting, but to inform the whole appraisal.
Utilisation of current National and European Guidelines – to understand complexity of NET (disease and management) and size of patient population.
Can be sourced from : http://www.ukinets.org/net-clinics-research/
There is also work in progress at PHE regarding NET patient population figures – with abstract submission to the National Cancer Registration Conference. Contact sean.mcphail@phe.gov.uk

Clarification on definitions used.
For example “Disease progression”.
In NETs reliance on imaging alone – especially utilising CT and RECIST criteria – can be misleading and is often late evidence that the disease is progressing. Clinical and biochemical indications should be incorporated – symptom deterioration and rising markers are more likely to

represent early indication of disease change and / or refractory syndrome - triggering treatment plan review/change.
This would also apply to the term “Response”.
Recommend : full involvement of a recognised NET expert .
Utilisation of current National and European Guidelines – to understand complexity of NET (disease and management).
Can be sourced from : http://www.ukinets.org/net-clinics-research/

“Best supportive care” - how will this be costed ? And will it include SSAs ? - this would be a more accurate reflection as a comparison to the listed treatments under review (though not all subgroups of NETs will have a clinical indication for SSA – but then not all groups will require all of the treatments on the list)
Recommend : full involvement of a recognised NET expert .
Utilisation of current National and European Guidelines – to understand complexity of NET (disease and management).
Can be sourced from : http://www.ukinets.org/net-clinics-research/

Licensing / Existing and anticipated marketing authorisations : to be updated.
Source : companies involved.

The only change that can be seen, despite July meeting consultation and recommendations, is that Lanreotide has been removed from the MTA. We support this.

Finally, and as important, if not more so, than NET expert involvement and Guidelines incorporation – are the people who will be directly affected by the outcome.
Many NET patients have had to become experts in their own diagnosis - treatments and processes – and have, in England, seen their options become increasingly restricted over the past two years.
Particularly galling is to see that these restrictions and exclusions are geographically dictated (comparison with devolved nations – who incidentally travel to England to access these therapies).
To think that such an important decision regarding life and treatments could be made on such limited and, in places, poor information – especially where more accurate, expert information is available (but not incorporated) – would be completely unacceptable.

Yours sincerely
and on behalf of the NPF

[redacted]

[redacted]

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Institute of Radiology
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
Nil

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Neuroendocrine tumours are a heterogeneous group of tumours ranging from well-differentiated to poorly differentiated and can be functioning and non-functioning. The majority of well differentiated NETS express somatostatin receptors on their surface which can be targeted by somatostatic receptor based radionuclide therapy

Lu-177 DOTATATE is an effective treatment for metastatic somatostatin receptor expressing neuroendocrine tumours. This treatment was previously available as an NHS treatment through the cancer drugs fund. Several guidelines (ENETS 2009, joint EANM/ SNM/ IAEA 2013) have advocated this treatment as a second line treatment when patients progress through first line treatments (SSA or chemotherapy in foregut tumours). The clinical guidelines are based on data from non-randomised phase 2/3 trials, which consistently showed progression free survival of >30 months.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Advantages: In patients who are progressing, this allows patients to stabilise disease and prolong survival. Data from the Rotterdam group have shown improved quality of life following Lu-177 DOTATATE (J Nucl Med 2011; 52:1361–1368; J Clin Oncol. 2004;22:2724–2729). Similarly our local currently unpublished data (using GI-NET 21 questionnaire) at the Royal Free in 39 consecutive patients have demonstrated significantly improved quality of life after Lu-177 DOTATATE treatment.

There has been a recently published multi-centre randomised controlled phase 3 study (NETTER-1 study) that has shown PFS +- 40 months vs. 8.4 months for high dose Octreotide LAR.

Side effects are uncommon. The main long-term side effect is permanent renal toxicity which occurs in approximately 0.5% of patients. Myelodysplastic syndrome can also occur in approximately 1% of patients.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

We have performed QOL of life analysis in 39 consecutive patients at the Royal Free London NHS Foundation Trust which is currently unpublished. This was performed using the EORTC GINET-21 questionnaire that was given to patients prior to consecutive cycles of Lu-177 DOTATATE. The module comprises of 21 Qs assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality. Categories include endocrine symptoms (ED; 3 items), GI symptoms (GI; 5 items), treatment related symptoms (TR; 3 items), social functioning (SF21; 3 items), disease related worries (DRW; 3 items). (Responses to the questionnaire were linearly transformed to a 0-100 scale using EORTC guidelines.

The individual categories were analysed, looking at the mean change in score. In addition the global score (S) was evaluated according to guidelines with a mean change in score between 0 and 5 was regarded as not clinically important; a change between 5 and 10 was regarded as little subjective change, whereas a change between 10-20 was regarded as moderate change and more than 20 was regarded as an important change.

The scores are summarise below

Score at baseline

ED	GI	TR	DRW	SF21	S
29.34	25.04	0.00	48.72	43.30	31.85

Score from after 1st therapy

ED	GI	TR	DRW	SF21	S
25.44	21.93	16.67	41.81	38.45	28.33

Score from after 2nd therapy

ED	GI	TR	DRW	SF21	S
24.22	18.12	17.95	38.60	36.47	26.45

Score from after 3rd therapy

ED	GI	TR	DRW	SF21	S
23.08	21.20	14.10	42.31	36.75	27.30

The mean scores within all categories (except treatment related effects) were reduced after 1 treatment and remained reduced prior to the 4th cycle of treatment (see table 1). The biggest changes were seen in disease related worries followed by SF21 and ED.

After 1 treatment the global quality of life score (S) showed changes as follows: 51% showed an improvement, 28% had no change/improvement, 20% worsening of QOL. Prior to the 4th cycle, 39% of patients had improvement of QOL.

In conclusion this study demonstrated a significant improvement in QOL in patients treated with Lu-177 DOTATATE in neuroendocrine tumours.

Implementation issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There are already established centres performing this treatment, so no further resources would be needed to continue at these centres.

Equality

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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation submission template

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To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Nuclear Medicine Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:
None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Neuroendocrine tumours are a heterogeneous group of tumours ranging from well-differentiated to poorly differentiated and can be functioning and non-functioning. The majority of well differentiated NETS express somatostatin receptors on their surface which can be targeted by somatostatin receptor based radionuclide therapy

Lu-177 DOTATATE is an effective treatment for metastatic somatostatin receptor expressing neuroendocrine tumours and its use and place in treatment algorithms is recommended by several international guidelines compiled by leading experts in the management of patients with neuroendocrine tumours, most notably the recently updated ENETS Consensus Guidelines (2016) and also the joint guidelines published by the EANM/ SNM/ IAEA (2013). The guidelines promote use of Lu-177 Dotatate as second-line therapy for disease progression through first line therapy (namely ‘cold’ somatostatin analogues, and in the case of foregut NETs, chemotherapy). The guidelines also recommend its use as third-line therapy after Everolimus in non-midgut NETs
The guidelines were initially developed using evidence predominantly from non-randomised phase 2/3 trials, which have demonstrated PFS of 30+ months, but more recently from the randomised phase III clinical trial of Lu-177 Dotatate vs high dose Sandostatin LAR (NETTER-1), which reported in 2015.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Advantages:
- In patients with progressive disease Lu-177 Dotatate stabilises disease and prolongs survival. The recently published multi-centre randomised controlled phase III study (NETTER-1 study) demonstrated PFS of 40 months vs. 8.4 months for high dose Sandostatin LAR.
- Patients also have improved quality of life (Published data from the Rotterdam group J Nucl Med 2011; 52:1361–1368; J Clin Oncol. 2004;22:2724–2729).

At the Royal Free Hospital, London our local data (currently unpublished) using a validated questionnaire (EORTC GI-NET 21) in 39 consecutive patients have demonstrated significantly improved quality of life after Lu-177 DOTATATE treatment (see next section).

- Side effects are uncommon: the major side effects are myelodysplatic syndrome (approximately 1% patients) and permanent renal toxicity (approximately 0.5% patients)

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

1. QUALITY of LIFE DATA

We have performed QOL of life analysis in 39 consecutive patients at the Royal Free London NHS Foundation Trust (currently unpublished) utilising a validated questionnaire (EORTC GI NET-21) that assesses disease symptoms, side effects of treatment, treatment related symptoms, body image, disease related worries, social functioning, communication and sexuality. Responses to the questionnaire were linearly transformed to a 0-100 scale using EORTC guidelines.
The questionnaire was given to patients prior to consecutive cycles of Lu-177 DOTATATE.
Categories include: endocrine symptoms (ED), GI symptoms (GI), treatment related symptoms (TR), social functioning (SF21), disease related worries (DRW).

The individual categories were analysed, looking at the mean change in score. In addition the global score (S) was evaluated according to guidelines with a mean change in score between 0 and 5 was regarded as not clinically important; a change between 5 and 10 was regarded as little subjective change, whereas a change between 10-20 was regarded as moderate change and more than 20 was regarded as an important change.
The scores are summarised below:

Score at baseline

ED	GI	TR	DRW	SF21	S
29.34	25.04	0.00	48.72	43.30	31.85

Score from after 1st therapy

ED	GI	TR	DRW	SF21	S
25.44	21.93	16.67	41.81	38.45	28.33

Score from after 2nd therapy

ED	GI	TR	DRW	SF21	S
24.22	18.12	17.95	38.60	36.47	26.45

Score from after 3rd therapy

ED	GI	TR	DRW	SF21	S
23.08	21.20	14.10	42.31	36.75	27.30

Mean scores within all categories (except treatment related effects) were reduced after 1 treatment and remained reduced prior to the 4th cycle of treatment (see table 1). The biggest changes were seen in disease related worries followed by SF21 and ED.

After 1st treatment 51% showed an improvement in global quality of life score, 28% had no change/improvement, 20% worsening of QOL. Prior to the 4th cycle, 39% of patients had improvement of QOL.

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Conclusion:
This study demonstrated a significant improvement in QOL in patients treated with Lu-177 DOTATATE in neuroendocrine tumours.

2. EARLY EFFICACY AND TOXICITY FOR THE INITIAL COHORT OF PATIENTS WITH METASTATIC NET TREATED AT A UK TERTIARY REFERRAL CENTRE
We presented a retrospective review of the first 79 patients treated with Lu-177Dotatate at the Royal Free Hospital, London, at the UKI NETS conference in December 2015. The data has also been recently submitted for publication

All patients had histologically confirmed well differentiated G1 or G2 disease. End of treatment outcome, time to progression and toxicity data of the 79 patients were analysed. All patients had radiologically confirmed progressive disease or uncontrolled symptoms despite maximum dose somatostatin analogues at the start of treatment.
Results:
Response - at the end of treatment 15% of patients demonstrated a partial response, 76% had stable disease and 9% had progressive disease.
Overall PFS (estimated from K-M curve with 95% confidence interval) was 28 months.
Toxicity – one patient experienced grade 1 nephrotoxicity. No patient experienced significant haematological toxicity.
Conclusion
Lu-177 Dotatate is a safe and efficacious treatment for patients with metastatic neuroendocrine tumours

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

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Currently there are a number of centres in the UK who are already providing Lu177 Dotatate. Some of theses centres are also ENETS Centres of Excellence. No further resources would be required for provision of Lu177 Dotatate

Equality

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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], submitting on behalf of:

Name of your organisation: NCRI-ACP-RCP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The management of neuroendocrine tumours (NETs) span a number of specialties including surgery, oncology, gastroenterology and endocrinology. Due to the complexity of this pathology, patients are managed through NET multi-disciplinary teams (MDTs). Most specialists are members of the UK and Ireland NET Society (UKINETS), a body responsible for development of UK guidelines. Moreover, the European NET Society (ENETS) has accredited 9 centres in the UK as ENETS Centres of Excellence (the largest number of such centres in any country) representing the centralised expertise.

The breadth of NET management is very wide; in brief, patients presenting with early disease amenable to curative resection undergo surgery. This MTA is limited to patients with advanced (inoperable or metastatic) disease. In addition, it is important to note that the scope of this MTA is limited to patients with well-differentiated (grade 1 or 2) NET (i.e. excludes grade 3 neuroendocrine carcinomas); this is appropriate.

The technologies are described in the final scope. In general, patients with non-progressive disease may be treated with a 'watch-and-wait' policy or with a somatostatin analogue until there is evidence of disease progression. On disease progression (the remit of this MTA) the treatment choice depends on the primary site of the tumour.

For patients with pancreatic NETs, systemic options include everolimus, sunitinib or chemotherapy. There is no recognised optimal sequence of these therapies; clinical trial evidence has demonstrated that the targeted therapies (everolimus or sunitinib) have the same level of activity regardless of prior chemotherapy use. When deciding about initial treatment, chemotherapy is preferred in patients with bulky disease, rapid disease progression and with a higher proliferation index (Ki-67). A targeted therapy is preferred in patients with lower volume disease, and a slower rate of disease progression. On progression, patients are then considered for targeted therapy after chemotherapy, or vice versa. In patients with well-differentiated NETs of gastrointestinal or lung origin with disease progression, everolimus would be considered.

^{177}Lutetium DOTATATE is considered for patients with midgut NETs on disease progression, this is aligned to the patient population in the pivotal NETTER-1

study. This decision-making process is in keeping with the updated ENETS guidelines.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

No specific factors have been identified which allow preferential patient selection except for the case of ^{177}Lutetium. In order for patient to be considered for lutetium, there needs to be evidence of uptake of the tumour at least as good as the background liver (as defined in the pivotal protocol, NETTER-1).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The decision for treatment should be made by a specialist team familiar with treatment of patients with NETs. Treatment with sunitinib or everolimus is overseen by the specialist NET clinical team (both treatments are taken orally at home by patients). ^{177}Lutetium is a radionuclide therapy administered in specialist oncology centres with ARSAC certification in place. Monitoring of adverse events and efficacy for all of the treatments is undertaken by the specialist NET team.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Both everolimus and sunitinib were initially available under the Cancer Drugs Fund for patients with pancreatic NETs; everolimus was later de-listed and accessed on a named-patient basis from Novartis. Sunitinib remains available under CDF arrangements.

^{177}Lutetium was also previously available under the CDF, although funding has again been withdrawn. Patients who are already receiving treatment at the cut-off date for funding are able to complete their planned course of therapy (4 cycles).

The results of the RADIANT-4 study (which included NHS patients) showing efficacy of everolimus in non-pancreatic NETs of the gastrointestinal tract and lung have recently led to European Medicines Agency approval for patients with unresectable or metastatic well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease. To date, everolimus has only been used in this

indication as part of clinical trials; however, there would be an expectation from the NET community to extend the use of everolimus to include these patients in keeping with the RADIANT-4 study population and licensed indication.

Everolimus is currently being reviewed by the Scottish Medicines Consortium (SMC) for bronchial and small bowel neuroendocrine carcinomas and a decision is expected towards the end of the year. SMC has already approved both everolimus and sunitinib for pancreatic neuroendocrine tumours.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The most recently-updated guidelines are 'ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site'.[1] These have been produced in light of the available evidence base.
The UK guidelines, provided by UKINETS[2] are currently being updated through the newly-established Clinical Practice Committee of UKINETS and do not include the results from recent pivotal studies (RADIANT-4 and NETTER-1). Therefore the ENETS guidelines should be referred to.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

In patients with pancreatic NETs the emergence of everolimus and sunitinib has provided patients with additional lines of therapy, where previously only chemotherapy was available. Both everolimus and sunitinib have been shown to improve progression-free survival (the primary endpoint of each of these studies) and therefore provides a clinically-meaningful additional treatment option.

In patients with intestinal NETs, treatment options beyond a somatostatin analogue are limited. Interferon has been used by some centres on disease progression, although this has issues of toxicity and patient acceptability.

[1] Pavel *et al* Neuroendocrinology 2016;103:172–185
[2] Ramage *et al* Gut 2012 Jan;61(1):6-32

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The emergence of ^{177}Lutetium allows the use of targeted radiotherapy using a baseline scintigraphy scan to exclude patients who would not benefit. The marked reduction in PFS is paradigm-changing in the treatment of patients with NETs. Whilst the NETTER-1 study was limited to patients with midgut NETs, the mechanism of action means that it is likely to be effective in all NETs demonstrating somatostatin receptor activity on the baseline scintigraphy scan.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Everolimus and sunitinib are indicated for patients with progressive disease, usually determined by cross-sectional imaging (CT scan or MR scan). Once treatment has been initiated, it continues until documented disease progression, also assessed by cross-sectional imaging. Interruptions may be required for the management of toxicity although permanent discontinuations for adverse events are uncommon.

In addition, for ^{177}Lutetium, a receptor scintigraphy scan (either octreotide scan or gallium PET scan) is required to ensure that there is adequate receptor uptake prior to therapy. The course of treatment consists of four cycles; there are no specific stopping rules as assessment of response is only undertaken upon completion of therapy.

There is no additional testing required to identify patient subgroups who may, or may not, benefit from treatment.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Everolimus and sunitinib are given in the out-patient clinic setting, under the supervision of NET specialist teams; this is standard UK practice. The primary endpoint of the studies was improvement in progression-free survival. Patients with disease progression have increased tumour-related symptoms leading to an impaired quality of life.[3] Thus, the improvement in PFS and delay of disease-related symptoms is clinically relevant to this patient population.

[3] Pearman *et al* Support Care Cancer. 2016 Sep;24(9):3695-703

^{177}Lutetium is targeted radiotherapy delivered in nuclear medicine units aligned to the NET centres treating these patients. This is established UK practice, as for other radiopharmaceuticals.

UK patients were included in the sunitinib (A6181111) study, the RADIANT-4 study and the NETTER-1 study; thus the evidence base is reflective of the UK patient population.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Everolimus and sunitinib have been in clinical use for some years and clinicians are familiar with the identification and management of emergent toxicities. The toxicity profile seen in the clinic is as described in each of the pivotal publications with no adverse events coming to light that are unexpected. Adverse events are manageable with the use of supportive measures and, if necessary, dose modification or brief treatment interruptions.

The use of ^{177}Lutetium has been somewhat limited and the results of the NETTER-1 study very recent so it is more difficult to comment. However, treatment is undertaken in centres familiar with targeted radiotherapy providing the appropriate governance infrastructure for patient follow-up and management of adverse events.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The evidence base was reviewed at the consultation meetings and it was agreed that the relevant evidence had been identified.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology

appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NICE guidance allowing the use of everolimus, sunitinib and 177Lutetium, within their licensed indications would allow these treatments to be implemented immediately. Clinicians at NET centres are familiar with the use of everolimus and sunitinib. The number of centres with the radiopharmacy capacity to able to deliver ^{177}Lutetium is limited across the UK. It is likely that referral pathways would be agreed with treating centres by those with no in-house access to ^{177}Lutetium.

A NICE positive guidance would allow the UK to remain as one of the leading countries in NET patient-centred care (evidenced by the high number of ENETS Centres of Excellence). As stated previously, UK patients were included in the sunitinib (A6181111) study, the RADIANT-4 study and the NETTER-1 study. A positive NICE guidance would not only allow UK patients to receive therapies that they have been instrumental in developing, but will also allow future UK patients to participate in clinical trials which build on these therapies and often require prior therapy with these technologies in order to be eligible.

Equality

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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **No equality issues are identified.**

NHS England submission to NICE re MTA of sunitinib, everolimus and lutetium-177 dotatate in the treatment of gastroenteropancreatic, midgut and lung well differentiated neuroendocrine tumours

1. Gastroenteropancreatic (GEP), midgut and lung neuroendocrine tumours (NETs) which are well differentiated are usually slowly growing tumours in which surveillance is an important part of the management of such patients. Systemic treatment for NETs is delayed until patients demonstrate evidence of disease progression and significant symptomatology. Lung NETs are more variable in their behaviour and thus chemotherapy plays a greater part in the management of lung NETs.
2. Sunitinib and everolimus have similar efficacies in GEP NETs although they have different portfolios of side-effects. Cross over in both the sunitinib and everolimus GEP NET trials has blurred the potential impact of these drugs on overall survival (OS). Everolimus has a wider licence in terms of including use in lung NETs. NHS England notes that no cross over was allowed in the everolimus vs placebo trial (RADIANT-4) in gastrointestinal and lung NETs and with a median duration of follow-up of 33 months, there is no difference in OS.
3. NHS England notes the results of the NETTER-1 study in which midgut NETs were randomised to lutetium-177 dotatate vs high dose long acting octreotide (the control arm recommended by the FDA and EMA). Although a big difference in progression free survival has been observed in NETTER-1, a pre-specified interim analysis for OS did not meet the p value set for statistical significance ($p<0.000085$). Long term safety and efficacy data have not yet been reported. Reports of late renal toxicity and myelodysplasia from other studies following treatment with lutetium-177 dotatate are noted but rare.
4. [redacted].
5. The analysis for this MTA by the ERG has not included the current Patient Access Schemes for sunitinib and everolimus. Sunitinib for its 2 other indications in baseline commissioning has a complex PAS operating in which the first cycle is free. Pfizer has agreed to honour this scheme if NICE recommends sunitinib in this NET indication. Everolimus is subject to a simple PAS.
6. [redacted].

[redacted]

[redacted] NHS England Chemotherapy Clinical Reference Group and [redacted] for the Cancer Drugs Fund

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Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Martin Eatock

Name of your organisation Belfast Health and Social care Trust

Are you (tick all that apply):

- ✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Neuroendocrine tumours (NET) are rare tumours arising from the diffuse endocrine system and most commonly arise in the small bowel, lung, pancreas, and upper GI tract. They are classified pathologically by their degree of differentiation and by their mitotic index (or Ki67 labelling index). Grade 3 tumours have a rapid clinical course and are highly aggressive malignancies and are not treated with the technologies currently being appraised.

NETs are functional (hormone producing) in around 40% of cases and in these cases symptoms caused by the hormone secretion can have a very significant impact on quality of life and can be difficult to control. The assessment of tumour grade is important in understanding the natural history of NET and tumour grade is determined by both the degree of tumour differentiation and tumour mitotic index. This information is used in determining treatment options to offer patients and these decisions are usually made in the context of mulit-disciplinary team meetings. There are a number of treatment options for these patients, however there are no trials examining the optimal timing and sequencing of treatment for these patients. These treatment options include somatostatin analogue therapy (octreotide or lanreotide), interferon (mid-gut NETs only), hepatic artery embolisation for the management of liver metastases, chemotherapy, PRRT with lutetium-177 DOTATATE, SIRT, sunitinib and everolimus. The choice of treatment will depend on previous treatments the patient has received (and response to these), extent of the disease, the symptoms the patient is experiencing and the rate of disease progression. It should be noted that the use of interferon is controversial. Whilst there is clear evidence of activity in controlling hormone secretion and also disease, it is considered toxic and there are no data to demonstrate convincing evidence of survival benefit.

It is helpful to distinguish between pancreatic NET (PNET) and other neuroendocrine tumours as these have a different spectrum of clinical behaviour and a worse prognosis. Pancreatic NET are rare tumours with an incidence of approximately 0.3 - 0.4/100000population/year. The median survival of patients with metastatic pancreatic NET is approximately 24 months and 77 months for those with locally advanced unresectable disease compared to 56 months and 105 months respectively for small bowel NETs (Yao et al. J Clin Oncol 2008;26:3063-3072).

Currently, everolimus is licensed for the treatment of unresectable or metatatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease. In addition, a recent randomised controlled clinical trial has demonstrated a progression free survival benefit in patients with well differentiated

neuroendocrine tumours of lung or GI tract origin and a decision on licensing of everolimus for this indication is awaited.

Sunitinib is licensed for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours, with disease progression in adults.

Lutetium-177 DOTATATE does not currently have a marketing license, however evidence from a previous large case series (Kwekkeboom et al: J Clin Oncol (2008); 26; 2124-2133) and one RCT in patients with advanced grade 1 or 2 midgut NET (the NETTER-1 trial - which has been presented but has not yet been published in a peer reviewed journal) demonstrate evidence of the activity of this treatment and improved progression free survival. This treatment is only considered in patients where there is evidence that their tumours express somatostatin receptors either with somatostatin receptor scintigraphy or PET scanning using ^{68}Ga labelled somatostatin analogues.

Sunitinib and everolimus in advanced pancreatic NETs:

Chemotherapy is an alternative treatment to sunitinib for patients with metastatic or locally advanced pancreatic NET. There are no RCT data comparing chemotherapy to sunitinib. In the registration trials for these agents, 50-66% of patients had previously been treated with chemotherapy and therefore the clinical evidence regarding the efficacy of sunitinib aand everolimus is based on a heavily pre-treated group of patients. For patients with liver metastases locoregional treatments such as embolisation or SIRT are considered, particularly where the tumours are functional, however the use of this treatment in these patients prior to trial entry was low (~10-20%).

There is evidence that both everolimus and sunitinib treatment may result in improvement of clinical syndromes related to hormone secretion by PNETS also. The improvement in progression free survival for patients with PNETS is valued by them and, anecdotally, this is associated with maintenance of quality of life for these patients whilst they remain progression free, despite the potential toxicity of treatment.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients with pancreatic NETs, whose tumours are rapidly progressing or who have bulky disease may benefit more from chemotherapy rather than everolimus, sunitinib or ^{177}Lu-DOTATATE as first line therapy, if the Ki67 labelling index is >5%. Everolimus and sunitinib are likely to be less toxic than chemotherapy and are likely to be used in patients who have disease progression following use of somatostatin anlalogue therapy as first line treatment. ^{177}Lu-DOTATATE is likely to be used in patients with somatostatin receptor positive disease which has progressed following somatostatin analogue therapy.

Patients with tuberous sclerosis represent a very small proportion of patients with NET, however this group of patients are much more likely to benefit from everolimus (an mTOR inhibitor) than other forms of systemic therapy for their disease.

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Multiple Technology Appraisal (MTA)

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

All three of these technologies should be used only in the context of specialised clinics in secondary care.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

There is use of sunitinib in England under the cancer drugs fund list published in November 2015 for patients with PNETs. The CDF did not recommend the use of everolimus for these patients, however there may be use in some areas of England under local arrangements or individual funding requests. Sunitinib and everolimus are used in patients with PNETS Scotland and Wales following SMC and AWMSG guidance. Sunitinb and Everolimus are used in Northern Ireland on a cost per case basis following the SMC guidance. This use is in line with licensed indications for these agents.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The European Neuro-endocrine Tumour Society published guidelines on the management of metastatic neuro-endocrine tumours in March 2016 (Pavel et al. Neuroendocrinology 2016: 103; 172-185.). These guidelines are based on RCT where these are available. NETs are relatively rare tumours, however and most data upn which these guidelines are based arise from single arm phase 2 trials or reports of large case series in single instiution studies. The data relating to the recommendations for the use of sunitinib everolimus and ^{177}Lu-DOTATATE are derived from RCT and are in line with the RCT findings.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

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Multiple Technology Appraisal (MTA)

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Sunitinib:

This represents a useful additional treatment for patients with progressive pancreatic NET. It is administered as a single daily dose continuously until there is evidence of progressive disease radiologically or clinically. The dose is modified, depending on the toxicity experienced by patients. Treatment is usually recommended after failure of a first line treatment, usually with a somatostatin analogue. The majority of patients do require dose modification or dose interruptions during treatment, however toxicity is usually manageable and less than would normally be expected with the use of systemic chemotherapy. Response to treatment is usually monitored radiologically with CT or MRI scans performed every 10 -12 weeks.

The use of this treatment is based on a RCT (Raymond et al. NEJM 2012) and the inclusion criteria for this study reflect the population of patients for whom this treatment is used in the UK. In the trial 66% of patients had received previous chemotherapy, however in UK practice, chemotherapy would usually be considered for those with rapidly progressive disease or with a relatively high mitotic index. It is likely, therefore, that fewer patients in UK practice, would receive chemotherapy prior to consideration of sunitinib treatment. The most common toxicities that impact on quality of life are fatigue, diarrhoea and hand-foot syndrome. As sunitinib has been used for many years in the management of renal cell carcinoma uncommon toxicities such as neurological toxicities are well described and understood.

Everolimus:

Everolimus results in a significant improvement in progression free survival in patients with metastatic PNET and also in patients with metastatic foregut and midgut NET (RADIANT4 trial). This is administered as a single daily oral dose of treatment and continued until disease progression is apparent clinically or radiologically. In patients with advanced progressive PNET, everolimus represents an important treatment alternative which can result in disease control and control of hormonal syndromes elated to these tumours. Major toxicities include stomatitis, diarrhoea and fatigue, however these are usually mild (Grade 1 or 2) and manageable without dose modification. Approximately 20% of patients develop pneumonitis related to everolimus which requires interruption of treatment. As everolimus is immunosuppressant, atypical pulmonary infections need to be considered in the differential diagnosis of pneumonitis and further investigation may be required. This

treatment is likely to be used in a similar group of patients for whom sunitinib is used and could be used in sequence with sunitinib in some patients as they have different molecular targets.

In both of the registration trials for sunitinib and everolimus in PNETs, patients receiving placebo were allowed to cross over onto the active treatment on the demonstration of disease progression, as a result overall survival differences in these trials are likely to underestimate the true survival benefit of these agents, however analyses to correct for cross over has been performed for both trials using the RPSFT method and suggest that both of these agents do result in a significant survival improvement (HR 0.43 for sunitinib and 0.61 for everolimus)

^{177}Lutetium-DOTATATE

I do not treat patients with ^{177}Lutetium-DOTATATE and am not best placed to discuss the relative toxicities and complexities of this treatment. It does represent an important treatment option for patient with metastatic midgut NETS withprogressive disease for whom few other treatment options exist as patients with these tumours do not benefit from chemotherapy treatment. In the NETTER 1 trial, there was a significant improvement of PFS in favour of ^{177}Lutetium-DOTATATE treatment (HR 0.21, p<0.0001), interim analysis also suggests an improvement in OS (HR 0.398, p=0.0043), however these data are at present immature and may change. Serious toxicities are uncommon and in the trial the most common toxicities experienced were nausea, vomiting, fatigue and diarrhoea.

Equality and Diversity

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 this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

No issues identified.

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Multiple Technology Appraisal (MTA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None identified

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There may be issues with access to ^{177}Lutetium-DOTATATE**.** This is currently provided in a small number of specialist centres and it may be appropriate this remains the case for this specialist treatment. Sunitinib and everolimus are routinely used in the treatment of other cancers and, other than the additional cost associated with acquisition should not be associated with a significant service impact if recommended.

1. About you

Your name: *Mark Zwanziger*

(Please note: I've submitted three sub-appendixes that go into further detail)

Appendix D(S1) ID858 Patient Personal Statement (Zwanziger) – Which goes into the "my cancer story detail" including my search for treatment in America.

Appendix D(S2) ID858 Patient ICER Statement (Zwanziger) – Covers the details from an "Incremental Cost Effectiveness Ratio" standpoint. I'm a private patient who has all the costs of a treatment year and followup year.

Appendix D(S3) ID858 Zwanziger – IECR Workbook – Pivot Table – Which shows my work for figuring QALY, ICER, Private to NHS Ratio, Treatment and Follow-up years exact costs, and a model of reducing the ICER.

Name of your nominating organisation: *NET Patient Foundation*
Do you know if your nominating organisation has submitted a statement?

☒ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☒ Yes ☐ No

ANSWER: Their point jumps out when you click on the links, as it quickly becomes evident how important their request of having a NET specialist on the MTA panel becomes. Their link **http://www.ukinets.org/net-clinics-research/** *takes you to their website which also shows very quickly how well organized they are for the UK & Ireland NETs. Their website also includes a map of the current "Centre's of Excellence" for the UK.*

Are you:

- a patient with the condition?

☒ Yes ☐ No

ANSWER: Well differentiated Neuroendocrine Tumours NET cancer with Liver Metasis, hindgut with 3% prolifereation index. Diagnosed 2007, Liver Resection/Microwave Albation 2008, 3 rounds of Y-90 PRRT 2011, and 3 rounds of Lu-177 PRRT 2015.

- a carer of a patient with the condition?

☐ Yes ☒ No

- a patient organisation employee or volunteer?

☐ Yes ☒ No

Do you have experience of the treatments being appraised?

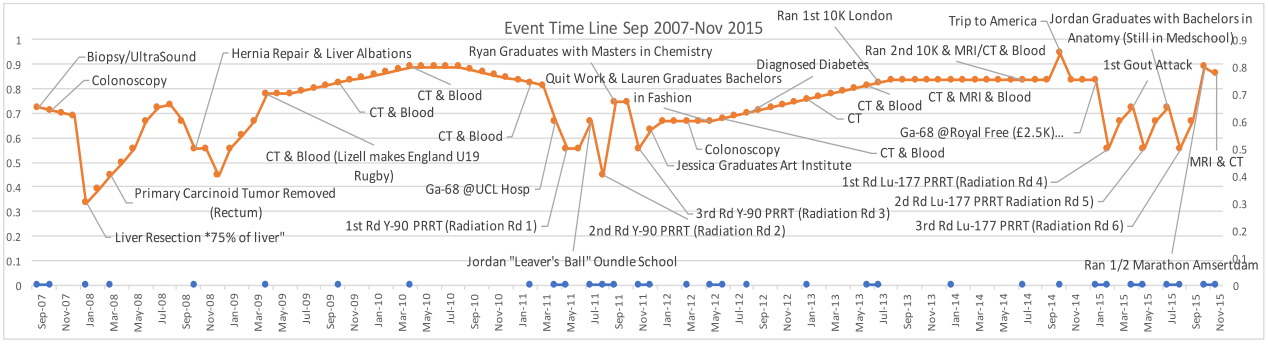
☒ Yes ☐ No

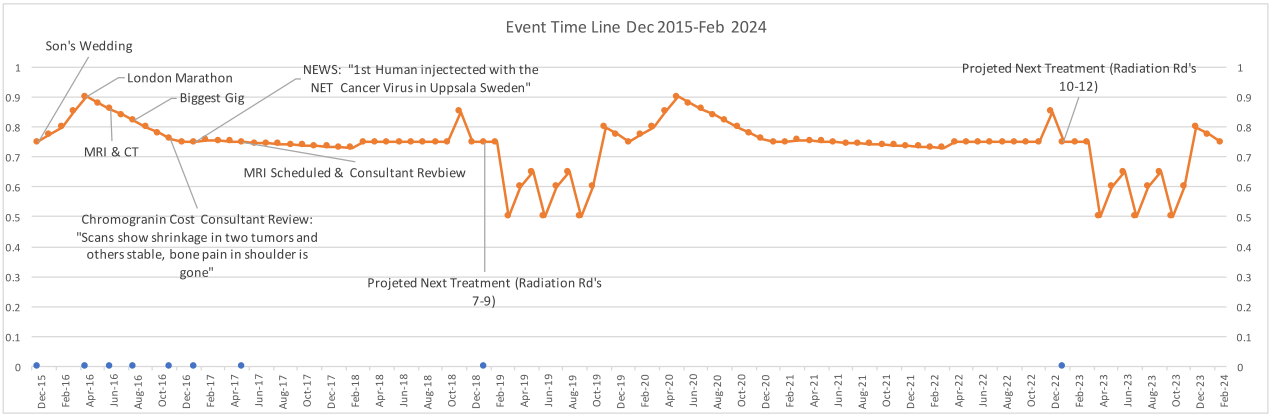
ANSWER: Approximately 100 shots of Lanreotide since February 2008 through today with only about 6 months where we switched to octreotide. Lu-177 (3 rounds) in 2015

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

In my sub appendix "Appendix D(S2) ID858 Patient ICER Statement (Zwanziger)", I have charted out the Quality of Life against a scale of 1=best & 0=worst. The treatment years are broken out on the diagram below:





- ***Pre-diagnosis***: *Approximately ten years ago (2005-2006), I started to notice a series of symptoms, including diarrhoea, night-sweats, unexplained rashes, panic attacks, inability to concentrate, pain in my right side, and tiredness. I was undergoing treatment for glaucoma in one eye (2005), and an acoustic neuroma (2006) that was effecting my hearing. These issues were cluing me in on listening to what my body was telling me.*

- ***Diagnosis:*** *A year after first seeing a doctor (Nov 2007), I received a diagnosis and discovered I had cancerous neuroendocrine tumours (NET cancer) with metastasis in the liver. Just as the many who receive this diagnosis I had never heard of NET, a type of cancer that occurs in the cells of the neuroendocrine system (the system which makes the hormones that regulate the organs of the body, controlling growth, reproduction, metabolism, mood and blood pressure). I'm grateful to never have received a prognosis attached to a timeline, but it was difficult to not focus on the statistics.*

- ***Surgery and Treatment***: *My treatment plan consisted of a right hemi-hepatectomy and a 75% liver resection (RLI – Leicester Jan 2008). In Oct 2008 I was started on a low dose of Lanreotide (samostatin), which seemed to instantly clear the carcinoid syndrome (diarrhoea, night-sweats, and unexplained rashes). In December 2008, hernia repair meant the surgeon could give an eyes on look and microwave ablation on the liver. From there, I was "stable" for three years before discovering the cancer was active again by CT*

and MRI scans. But, this time it was spreading and was now "inoperable". I tried very hard not to focus on "wouldn't that mean more than 75% of the liver is bad?". My options were very limited.

- ***PRRT Y-90**: I was referred to a NET specialist team at The Royal Free Hospital in London, the first of ten centres of excellence around the UK that lead the world in the treatment of this type of cancer. Due to the exponential demand on the NET centre at the Royal Free, it would be a few months before I would hear confirmation of an appointment. The centre was stood up in the late 90's with 20 patients, but by 2011, there were 1500 patients on the books (over 2000 patients today).*

I first underwent highly specialised imagery from a "Gallium-68" scan confirmed the spread outside the liver and my options were limited to a type of highly targeted treatment known as PRRT (Peptide Receptor Radionuclide Therapy) which uses an octreotide labelled with nuclear material to attack tumours in a very targeted way by attaching the radioactive material to the peptide receptors (a type of protein) of the tumours.

I consider myself very fortunate to have receive my first set of PRRT with 3 rounds of Ÿttrium 90 in 2011 at the Royal Free in London as a private patient under my corporate medical insurance. Spaces had been opened up to the private insurance patient due to some reason on the NHS side "|rumoured" as a "post code" lottery. I know this was extremely lucky for me, but I feel bad for whoever it was that had to go without or had to wait.

After the first set of PRRT (From 2011 to 2015) I lived a very normal life as a father, husband, and IT manager/technician on some of the most critical US Defense Department Satellite imagery systems in the Intelligence Community. I did leave work in 2012, but it was also the time before I was diagnosed with diabetes. Most of the effects I attributed to the cancer were actually diabetes.

- ***PRRT Lu-177**: Routine scans in 2015 found the cancer was back on the move again, and the spread to the spine, neck, shoulder, groin, lung and abdomen were confirmed with another Ga68 scan. The symptoms of carcinoid weren't back, but new pains in the shoulder and spine clued me in that something was different. The pain was like a mild cramp in the back of the right shoulder that couldn't be stretched out. The course action was another set of PRRT. This time the isotope would be Lutetium 177 over 4 rounds of treatment.*

The treatments went well (Feb, May, Aug 2015). They were quite easy, with just a little nausea and tiredness. The worst issue seemed to be the steroids for pain management. They were pushing my sugar levels into the mid 20's. Which would either require insulin or stop taking the steroids. We opted for the latter, and I was able to handle the pain with paracetamol. I think this is a sign of how tolerable this treatment can be.

Treatment since the Lu-177 PRRT has been the monthly shots of Lanreotide and MRI's and CT scans every six months for review. The latest review (Nov 2016) review has shown my cancer is stable disease, with a couple liver lesions continuing to reduce in size. We are back in control. As a side note: my diabetes is also under control with diet, exercise and metformin. I'm feeling quite well! Even the bone pain in the shoulder is gone!

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Lanreotide and PRRT (Lu-177) are the most important to me. They work hand in hand to control the carcinoid syndrome and control the tumors.

I can tell the Lanreotide LAR (120mg every 4 weeks) is doing its job as at the end of the 4 weeks I start to get mouth sores, a little more tired, and less sharp mentally.

I've asked my consultant if we should cut back on the Lanreotide when we are "in control", and he does not think that is wise. Citing "anti-tumour" statistics of the Lanreotide.

To me, the Lu-177 is like a Lanreotide shot with a nuclear bomb on it's back. Taking the radiation straight to the tumors. Stunning them hard for a few years.

During the last Lu-177 treatment, the nuclear pharmacist told me he has patients who have tolerated upto 13 rounds of radiation. What a huge shift from the maximum of six I was told during the Y-90 PRRT. This was a huge boost to my outlook.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

I don't have experience with any other care offered by the NHS for NET cancer instead of Surgery, Lanreotide, and PRRT.

Surgery (including microwave ablation) has come a long way from 2008 when I had mine. The microwave ablation "microwave on a stick" is now down to 1.5mm wires that can be guided into the turmours via ultrasound and literally cook the tumours.

My spreadsheet analysis in "Appendix D(S2) ID858 Patient ICER Statement (Zwanziger)" did show the ICER for surgery was possibly higher than PRRT. I'm not saying to skip surgery, but it might be worth a look. Especially, when you are looking at patients who may be closer to their life expectancy.

For the monthly samostatin analogue, Octreotide vs Lanreotide, the only difference I noticed was the packaging. I preferred the packaging of the Lanreotide (it comes pre-mixed and preloaded into a syringe), but I don't consider that significant.

I have taken over 100 shots of Lanreotide to date, and only 1 of mine has ever went wrong. I felt the needle go in, and then it felt like it came back out about halfway. So, the injection wasn't subcutaneous. It became infected, and took several rounds of antibiotics to clear it up. I have no proof, but would consider the risk of this type of failure more likely in the Octreotide where it has to be mixed before injection.

4. What do you consider to be the advantages of the treatment(s) being appraised?

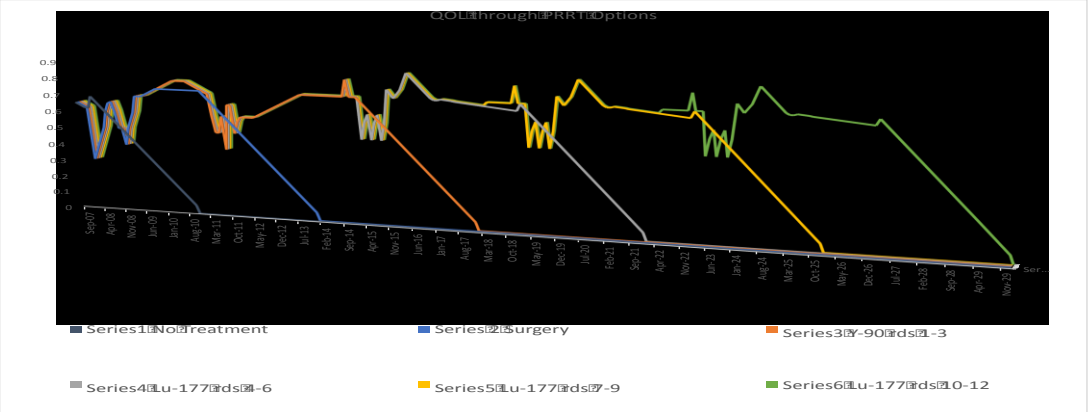
Benefits of a treatment might include its effect on:

- **the course and/or outcome of the condition:** *The average of progression free survival (PFS) is 40 months for PRRT, but this could be much longer. I'm banking on a strong wellness regime of diet, exercise and mindfulness to take it longer.*
- **physical symptoms:** *For me, my symptoms have been very similar to diabetes. Which are tiredness, irritability, and numbness. Lanreotide helps, and PRRT has even relieved the overall effects of the cancer. The treatments are quiet easy for me, and very tolerable. PRRT has even relieved bone pain I was experiencing in my shoulder and spine.*
- **pain**: *The pain of both shots isn't very significant for me considering the alternative.*
- **level of disability**: *There is no level of disability to the Lanreotide. A round of Lu-177 is 24 hours in the hospital to monitor and isolate the effects of the radiation. Quite serious tiredness after a round, but back to normal after a couple weeks. Better than normal after a couple months.*
- **mental health**: *The thought of not getting PRRT was probably the biggest impact on my state. NET cancer itself throws chemicals that can make you question your own sanity, but the key to dealing with this cancer is knowing your endocrine system doesn't produce normal hormonal levels when put under stress, and to take an appropriate action. This may be rest, waiting the sensation out, or maybe exercise if you need to burn off blood sugar or adrenaline.*
- **quality of life** (such as lifestyle and work) *Please see the "time line" chart above, the quality of life PRRT and Lanreotide has provided me has been excellent! I was able to run a half-marathon two months after Lu-177 and the London marathon 6 months after that. I'm not a runner. The longest I'd ran up until these was the 10Km runs I did for the charity before.*
- **other people** (for example, family, friends and employers) *I have a friend who is a couple years behind me on the treatment schedule, and it would be devastating to his family should he not be provided the treatment.*
- **ease of use** (for example, tablets rather than injection) *I consider Lanreotide and PRRT very easy. For me, a key to PRRT is that you are given enough time between the amino acids and Lu-177 to protect the kidneys.*
- **where the treatment has to be used** *(for example, at home rather than in hospital) The Lanreotide can be given at home, self administered in the USA. PRRT needs a lead-lined room to provide isolation.*
- **any other issues not listed above** *I don't think these rooms are turned back over to the hospital should they need beds during a bed-shortage crisis. It may not be as much of a savings to not provide the treatment as it is a waste of resources by not using them. For example; the special rooms and the nuclear pharmacy.*

Please list the benefit that you expect to gain from using the treatment(s) being appraised.

Lanreotide and Lu-177 (used together) can set up a scenario to extend the outcome by many additional quality of life years (QALY's). For me, this means they may take me out to approximately 2027 when I'll need a treatment that hasn't been invented yet. (Versus possibly dying before Jan 2014 if I had never received PRRT)

Here is my plan. I'm currently between series4 and series 5. The plan to hit the tumors before we enter an "End of Life" down slope. Pushing the progression free survival out a few different times. (Please refer to Appendix D(S2))



Please explain any advantages for the treatment(s) being appraised compared with other NHS treatments in England.

I'm not aware of any other options, but suspect it would be with chemotherapy. Something that my general oncologist explained as a last option, and wasn't confident in its effectiveness.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

I've not seen any opinion against PRRT other than its cost effectiveness. It is effective and quite easily tolerated compared to surgery or chemotherapy.

5. What do you consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- **aspects of the condition that the treatment cannot help with or might make worse?** *Exposure to radiation can lead to other types of cancers or bone marrow, kidney or liver problems.*
- **difficulties in taking or using the treatment?** *I haven't experienced anything with Lanreotide other than one shot got infected.*
- **side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)** *With Lu-177; I did experience radiation sickness one time(severe cramping for a few hours), but mostly it was just tiredness.*
- **where the treatment has to be used**? *Lanreotide can be done anywhere, but Lu-177 needs to be at a treatment facility with a nuclear pharmacy. In my case that means a 3 hour trip into London (Royal Free or Wellington).*

- **impact on others** (for example, family, friends and employers) *My wife needed to come to the London hospital to drop me off and to pick me up. No visiting hours while in isolation.*
- **financial impact on the patient and/or their family** (for example, the cost of travel to hospital or paying a carer) *The impact for me has been about £3000 a year. My insurance deductible plus car journeys to London for treatment and checkups. I'm not complaining though.*
- **any other issues not listed above?** *This treatment is quite expensive, but the QALY's added is excellent, with the Quality of Life being exceptional. I've ran a marathon since having this treatment. Which was just as much a testament to being able to do the training. I had to get creative, but I did it.*

Please list any concerns you have about current NHS treatments in England.

The removal of several drugs and treatments (including PRRT) from the CDF in the Fall of 2015 due to the cash crisis of the NHS.

The rising age of the population, an increase in long term diseases like diabetes, dementia, and cancer are looming. These are dire times for the NHS, and there will be some tough choices.

I think the example Lu-177 can provide is a start in switching the mindset to using the NHS has an asset. Lu-177 is only finishing clinical trials in America, and it will likely be several times more expensive in the USA. The NHS could sell this treatment to cover its costs. I've given an example in the Appendix D(S2) ICER Statement.

Please list any concerns you have about the treatment(s) being appraised.

The treatment is expensive, but better isotopes are in the pipleline. And, as I indicated above it has the potential of being a resource (with a bigger profit margin).

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

The opinions I've spilled on this statement are very common on the patient forums and blogs I've read. Lanreotide and PRRT are the most important weapons for some of us.

6. Patient population

Do you think some patients might benefit more from the treatment(s) than others? If so, please describe them and explain why.

I think younger and stronger will be able to handle the treatment better, but that is probably true with all treatment. Looking at the ICER though, it might be better to offer PRRT versus major surgery for patients who's prognosis look appropriate.

Do you think some patients might benefit less from the treatment(s) than others? If so, please describe them and explain why.

Those who have tumors too bulky or not receptive to uptake wouldn't be the best use of this treatment.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment(s)?

☒ Yes ☐ No

The UK are participating with the NET Research Foundation out of Boston, MA to collaborate on research. This must be a critical example of success for the NHS and UK Healthcare as a whole. I think this is bigger than just NET.

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment(s) as part of routine NHS care reflects the experience of patients in the clinical trials.

No personal experience

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

No personal experience, but I think the testing program has been very successful. The limitations I saw were in the effect the removal of PRRT from the CDF has had on the community. How could the UK NET Team advocate their primary weapon (PRRT) while having it removed from its arsenal.

The knock-on effect will likely never be measured, but I'd really like to see the NET specialist teams get the weapon back before they lose all momentum on fighting this disease. Apply restrictions as appropriate, but everybody I have talked to in the NET community feels it is absolutely crucial to reinstate it as a treatment option.

If already available in the NHS, are there any side effects associated with the treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

I'm not aware of any.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☒ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

I don't' know of any ethnic or gender difference in treating NETS, but I would expect age may be a factor.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

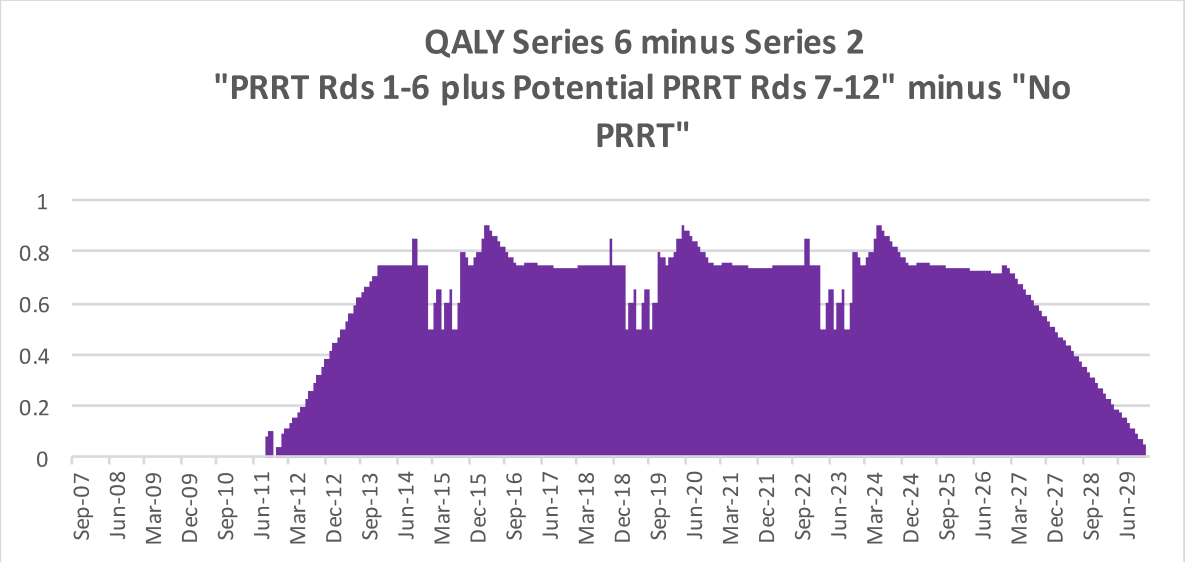
☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

The UK and Europe "E-nets" are the world leaders in treating NET cancer with PRRT. The USA is close to the FDA approving Lu-177. The FDA has only approved Ga-68 scanning a year ago, and is still only available in a limited number of zones by medicade insurance. There are several centers of expertise in the USA, but nothing quite like the UK.

Is there anything else that you would like the Appraisal Committee to consider?

I think I would have died by Jan 2014 with my first Y-90 PRRT. Now, I have a plan that could keep me going until 2024 before I need something that hasn't been invented yet. That's quite a significant QALY. This is what it could look like.



10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Lanreotide and Lu-177 are the state of the art, and work together
- Lu-177 is state of the art today, but other isotopes are in the pipeline
- NET Specialist Teams are absolutely crucial
- NET Cancer care in the NHS is a great model for the NHS
- PRRT can be used more than once. (Up to 13 rounds has been tolerated)

Thank you for this opportunity to provide my input into the MTA of Lanreotide and Lu-177. I'm literally here today because of them.

Respectfully,

Mark A. Zwanziger