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Abstract

Everolimus, lutetium-177 DOTATATE and sunitinib for advanced, unresectable or metastatic neuroendocrine tumours with disease progression: a systematic review and cost-effectiveness analysis

Ruben Mujica-Mota,[1]* Jo Varley-Campbell,[1] Irina Tikhonova,[1] Chris Cooper,[1] Ed Griffin,[1] Marcela Haasova,[1] Jaime Peters,[1] Stefano Lucherini,[1] Juan Talens-Bou,[1] Linda Long,[1] David Sherriff,[2] Mark Napier,[3] John Ramage[4] and Martin Hoyle[1]

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Background: Neuroendocrine tumours (NETs) are a group of heterogeneous cancers that develop in cells in the diffuse neuroendocrine system.

Objectives: To estimate the clinical effectiveness of three interventions [everolimus (Afinitor®; Novartis International AG, Basel, Switzerland), lutetium-177 DOTATATE (177Lu-DOTATATE) (Lutathera®; Imaging Equipment Ltd, Radstock, UK) and sunitinib (Sutent®; Pfizer Inc., New York, NY, USA)] for treating unresectable or metastatic NETs with disease progression and establish the cost-effectiveness of these interventions.

Data sources: The following databases were searched from inception to May 2016: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily, Epub Ahead of Print, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science.

Review methods: We systematically reviewed the clinical effectiveness and cost-effectiveness literature on everolimus, 177Lu-DOTATATE and sunitinib for treating advanced, unresectable or metastatic progressive NETs. The following NET locations were considered separately: pancreas, gastrointestinal (GI) tract and lung, and GI tract (midgut only). We wrote a survival partition cohort-based economic evaluation in Microsoft Excel® 2013 (Microsoft Corporation, Redmond, WA, USA) from the UK NHS and Personal Social Services perspective. This comprised three health states: (1) progression-free survival (PFS), (2) progressed disease and (3) death.

Results: Three randomised controlled trials (RCTs), RADIANT-3 [RAD001 in Advanced Neuroendocrine Tumors, Third Trial; pancreatic NETs (pNETs): everolimus vs. best supportive care (BSC)], A6181111 (pNETs: sunitinib vs. BSC) and RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial; GI and lung NETs: everolimus vs. BSC), met the inclusion criteria for the clinical effectiveness systematic review. The risk of bias was low. Although the NETTER-1 (Neuroendocrine Tumors Therapy) RCT, of 177Lu-DOTATATE plus 30 mg of octreotide (Sandostatin®, Novartis) compared with 60 mg of octreotide, was excluded from the review, we nonetheless present the results of this trial, as it informs our estimate of the cost-effectiveness of 177Lu-DOTATATE. The pNETs trials consistently found that the interventions improved PFS and overall

survival (OS) compared with BSC. Our indirect comparison found no significant difference in PFS between everolimus and sunitinib. Estimates of OS gain were confounded because of high rates of treatment switching. After adjustment, our indirect comparison suggested a lower, but non-significant, hazard of death for sunitinib compared with everolimus. In GI and lung NETs, everolimus significantly improved PFS compared with BSC and showed a non-significant trend towards improved OS compared with BSC. Adverse events were more commonly reported following treatment with targeted interventions than after treatment with BSC. In the base case for pNETs, assuming list prices, we estimated incremental cost-effectiveness ratios (ICERs) for everolimus compared with BSC of £45,493 per quality-adjusted life-year (QALY) and for sunitinib compared with BSC of £20,717 per QALY. These ICERs increased substantially without the adjustment for treatment switching. For GI and lung NETs, we estimated an ICER for everolimus compared with BSC of £44,557 per QALY. For GI (midgut) NETs, the ICERs were £199,233 per QALY for everolimus compared with BSC and £62,158 per QALY for a scenario analysis comparing 177Lu-DOTATATE with BSC. We judge that no treatment meets the National Institute for Health and Care Excellence's (NICE) end-of-life criteria, although we cannot rule out that sunitinib in the A6181111 trial does.

Limitations: A RCT with included comparators was not identified for 177Lu-DOTATATE. The indirect treatment comparison that our economic analysis was based on was of a simple Bucher type, unadjusted for any differences in the baseline characteristics across the two trials.

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

Future work: Further analysis of individual patient data from RADIANT-3 would allow assessment of the robustness of our findings. The data were not made available to us by the company sponsoring the trial.

Study registration: This study is registered as PROSPERO CRD42016041303.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

177Lu-DOTATATE	lutetium-177 DOTATATE
AAA	Advanced Accelerator Applications
AE	adverse event
AFT	accelerated failure time
AG	Assessment Group
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BNF	*British National Formulary*
BSC	best supportive care
CDF	Cancer Drugs Fund
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
COOPERATE-2	COmbination Of Pasireotide and evERolimus in Advanced Tumors of neuroEndocrine origin, second trial
CR	complete response
CRD	Centre for Reviews and Dissemination
CrI	credibility interval
CSR	clinical study report
CT	computed tomography
DIC	deviance information criterion
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	electronic market information tool
ENETS	European Neuroendocrine Tumor Society
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
FACT-G	Functional Assessment of Cancer Therapy – General
FDA	Food and Drug Administration
GEP	gastroenteropancreatic
GI	gastrointestinal
HPF	high-power field
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
ITT	intention to treat
LAR	long-acting release
MAIC	matched adjusted indirect comparison
MCMC	Markov chain Monte Carlo
MRI	magnetic resonance imaging
MTA	multiple technology appraisal
MTC	mixed treatment comparison
mTOR	mammalian target of rapamycin
NEC	neuroendocrine carcinoma
NET	neuroendocrine tumour
NETTER-1	Neuroendocrine Tumors Therapy
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence

OR	odds ratio
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PenTAG	Peninsula Technology Assessment Group
PET	positron emission tomography
PFS	progression-free survival
PHE	Public Health England
pNET	pancreatic neuroendocrine tumour
PPS	post-progression survival
PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality-adjusted life-year
RADIANT-3	RAD001 in Advanced Neuroendocrine Tumors, Third Trial
RADIANT-4	RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial
RCT	randomised controlled trial
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	rank-preserving structural failure time
RR	response rate
SAE	serious adverse event
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SMC	Scottish Medicines Consortium
SSA	somatostatin analogue
SSTR+	somatostatin receptor positive
SSTR2	somatostatin receptor type 2
UICC	Union for International Cancer Control
UKINETS	UK and Ireland Neuroendocrine Tumour Society
VIP	vasoactive intestinal peptide
WHO	World Health Organization

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Neuroendocrine tumours (NETs) usually occur in the intestine, but they are also found in the pancreas, the 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 clinical 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 (pNETs), everolimus for gastrointestinal and lung NETs and everolimus and lutetium-177 DOTATATE (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 pNETs 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 pNETs.

Two pharmaceutical companies also wrote mathematical models to estimate the cost-effectiveness of their drugs: Novartis Pharmaceuticals UK Ltd (Frimley, UK) for everolimus and Advanced Accelerator Applications Ltd (Saint-Genis-Pouilly, France) for 177Lu-DOTATATE.

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

Scientific summary

Background

Neuroendocrine tumours (NETs) are heterogeneous cancers that develop in the cells of the diffuse neuroendocrine system. The aetiology is poorly understood; however, NETs typically develop slowly and may remain undetected over a number of years.

The characteristics of a NET (e.g. location, grade and differentiation, stage of tumour and secretory profile) will determine the methods of treatment and affect prognosis. Prognosis is generally better with an early diagnosis; however, NETs are commonly diagnosed at a later stage when they have already metastasised.

Between 2013 and 2014, 8726 neoplasms were diagnosed in England. Diagnosing NETs can be difficult as they are often small tumours (< 1 cm in size) and they can occur almost anywhere in the body and present with a vast array of symptoms (typically non-specific symptoms such as pain, nausea or vomiting) or no symptoms at all.

The aim of treatment should always be curative. However, in the majority of cases it is most likely to be palliative. As metastatic disease is common, improving quality of life is often the primary aim of treatment. Individuals with NETs can maintain a good quality of life for a long period of time.

There are many treatment options for NETs. Initial treatment starts with surgery and symptom management, after which treatment may include liver transplant, interferon alpha (Roferon-A, Roche Products Ltd), chemotherapy, ablation therapies, targeted radionuclide therapy [including lutetium-177 DOTATATE (177Lu-DOTATATE) Lutathera®; Imaging Equipment Ltd, Radstock, UK)], transhepatic artery embolisation/chemoembolisation, external-beam radiotherapy and emerging therapies [including everolimus (Afinitor®; Novartis International AG, Basel, Switzerland) and sunitinib (Sutent®; Pfizer Inc., New York, NY, USA)].

Objectives

The objectives of this study were to, first, estimate the clinical effectiveness of three interventions (everolimus, 177Lu-DOTATATE and sunitinib) for treating unresectable or metastatic NETs with disease progression and, second, establish the cost-effectiveness of these interventions.

Changes in project scope

During the course of this project, the National Institute for Health and Care Excellence (NICE) consulted on amendments to the original project scope. The revised scope was agreed on 18 August 2016 and the intervention lanreotide (Somatuline Autogel®; Ipsen, Paris, France) and the comparator octreotide (Sandostatin®; Novartis) were removed.

Methods

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

Clinical effectiveness systematic review

A systematic review, following methodological guidance from the Centre for Reviews and Dissemination, was used to assess the clinical effectiveness evidence on everolimus, 177Lu-DOTATATE and sunitinib for treating unresectable or metastatic NETs with disease progression.

Identification of studies

Literature searching of seven bibliographic databases (including MEDLINE and EMBASE), four trial registries (including Current Controlled Trials and ClinicalTrials.gov) and two websites [the European Neuroendocrine Tumor Society [see www.enets.org/ (accessed 19 May 2016)] and the UK and Ireland Neuroendocrine Tumour Society [see www.ukinets.org/ (accessed 19 May 2016)], and additional supplementary search methods, were used for the identification of clinical effectiveness studies.

Study selection

- Population: people with progressed unresectable or metastatic NETs in locations covered by existing and anticipated marketing authorisations for the interventions.
- Interventions: everolimus [pancreatic, gastrointestinal (GI) or lung NETs], 177Lu-DOTATATE (pancreatic or GI NETs) and sunitinib [pancreatic NETs (pNETs)].
- Comparator: another intervention or interferon alpha, chemotherapy regimens and/or best supportive care (BSC).
- Outcomes: overall survival (OS), progression-free survival (PFS), response rates (RRs), symptom control, adverse events (AEs) and health-related quality of life (HRQoL).

Titles and abstracts were independently double-screened by two reviewers for inclusion and disagreements were resolved by discussion. Studies meeting the inclusion criteria at the title and abstract stage were double-screened at the full-text stage.

Data analysis/synthesis

The methodological quality of each included study was assessed and data were extracted, tabulated and narratively synthesised. When the data allowed, indirect treatment comparisons (ITCs) were performed using the Bucher method.

Cost-effectiveness systematic review

Cost-effectiveness studies were reviewed in accordance with the methods used in the systematic review of clinical effectiveness, extended to include electronic searches 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 relevant UK studies reported in conference posters were considered as supplementary information.

Results

Clinical effectiveness systematic review

Number and quality of effectiveness studies

Of 6209 titles/abstracts screened, three trials, RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial), A6181111 and RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial), met the inclusion criteria for the review.

A fourth trial, NETTER-1 (Neuroendocrine Tumors Therapy), was identified under the original scope but excluded under the revised scope as it no longer met the inclusion criteria. This randomised controlled trial (RCT) compared 177Lu-DOTATATE with 60 mg of octreotide. The Assessment Group appreciate that this trial might be of interest to the committee and, following a request from NICE, the results and comparative analysis are presented within the report.

The risk of bias in all three included studies was low.

Summary of benefits and risks

Pancreatic neuroendocrine tumours

Evidence consistently suggested a treatment effect for pNETs in favour of both everolimus (RADIANT-3; $n = 410$) and sunitinib (A6181111; $n = 171$) compared with placebo for the outcomes of interest. Treatment switching from the placebo arm to the treatment arm occurred in 73% of participants in RADIANT-3 and 69% in A6181111. The treatment switching significantly compromised the OS results. Overall, AEs were more commonly reported following treatment with everolimus and sunitinib than following treatment with placebo.

Indirect treatment comparison for pancreatic neuroendocrine tumours

The ITC for PFS from central radiology review suggests that there is no difference between the treatments [hazard ratio (HR) 1.06, 95% confidence interval (CI) 0.57 to 1.97], whereas the ITC for PFS from local review suggests that everolimus is associated with a 17% decrease in disease progression or death compared with sunitinib (HR 0.83, 95% CI 0.49 to 1.42). However, the 95% CI is consistent with there being no difference in PFS effectiveness between everolimus and sunitinib.

For OS, the ITC suggests that there is a 2.56 times greater hazard of dying in the everolimus treatment group than in the sunitinib treatment group, which is statistically significant. However, these analyses were not adjusted for treatment switching after disease progression and should not be relied on.

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

Gastrointestinal and lung neuroendocrine tumours

Evidence consistently suggested a treatment effect for GI and lung NETs in favour of the use of everolimus (RADIANT-4; $n = 302$) compared with placebo for the outcomes of interest. A limitation was the immaturity of the OS data and bias from treatment switching in the control arm.

Cost-effectiveness systematic review

Four studies were identified, all of which were carried out with patients with advanced pNETs. Two studies were model-based cost–utility analyses of sunitinib plus BSC compared with BSC based on the A6181111 trial data. Another study was a model-based cost–utility analysis of everolimus compared with sunitinib, 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 compared with BSC. 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 the manufacturers of the respective treatments under evaluation.

The study of everolimus compared with sunitinib found that the incremental cost-effectiveness ratio (ICER) for everolimus compared with sunitinib was equivalent to £30,524 at 2010 US prices, whereas the studies that compared sunitinib plus BSC with BSC found that sunitinib plus BSC had a discounted cost per quality-adjusted life-year (QALY) gained relative to BSC of £22,587. This result allowed for an adjustment for crossover to active treatment in the placebo plus BSC arm of A6181111.

The studies had severe limitations primarily as they were based only on Phase III trials with no active treatment comparators. The generalisability of these findings to the NHS remains in question, particularly as a conference abstract was the only identified report of a study in a UK setting.

Peninsula Technology Assessment Group de novo economic model and evaluation

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

- pNETs:
  - everolimus plus BSC
  - sunitinib plus BSC
  - BSC alone
- GI and lung NETs:
  - everolimus plus BSC
  - BSC alone
- GI (midgut) NETs:
  - everolimus plus BSC
  - 177Lu-DOTATATE plus 30 mg of octreotide (included as an intervention in scenario analyses)
  - BSC alone.

The choice of these tumour locations was determined by the available effectiveness data identified in the published literature. We did not perform subgroup analyses specified in our protocol because of the lack of data reported in suitable form from effectiveness sources. We did not have access to individual patient data (apart from A6181111) but extracted them from Kaplan–Meier curves.

We assumed that patients started treatment aged 60 years and assumed a 40-year time horizon. Costs and QALYs were discounted at 3.5% per annum. Analyses were undertaken using the same three-health-state model structure used in the economic evaluation literature and we assumed partitioned survival using summary data on PFS, OS and time on treatment outcomes in RADIANT-3 and A6181111 (pNETs), RADIANT-4 [GI and lung NETs and GI (midgut) NETs] and NETTER-1 [scenario analysis of GI (midgut) NETs 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. For the indirect comparison in pNETs, we adjusted the PFS and OS for sunitinib by the relative difference in the restricted mean time to event for the respective outcome between the placebo arm in RADIANT-3 and the placebo arm in A6181111.

We measured the costs of drug administration and acquisition, AEs, health-care resource use and post-progression therapy. 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. We also excluded subsequent treatment costs from the base-case analysis of GI and lung and GI (midgut) NETs and explored their likely importance in sensitivity analyses.

In the base-case analysis of pNETs, sunitinib produced the most life-years per patient at 6.39, followed by everolimus at 4.69 and BSC at 3.46. The expected discounted QALYs were 3.24, 2.51 and 1.91, respectively, and the respective discounted costs were £43,192, £42,646 and £15,761 respectively. Sunitinib (extendedly) dominated everolimus, that is, although both targeted treatments produced additional QALYs compared with BSC, sunitinib did so at a lower cost per QALY gained than everolimus and with a greater total number of

QALYs produced. At list prices, the ICER for everolimus compared with BSC was £45,493 per QALY and the ICER for sunitinib compared with BSC was £20,717 per QALY.

In the base-case analysis of GI and lung NETs, treatment with everolimus resulted in 6.21 life-years and 3.74 discounted QALYs per patient, whereas BSC yielded 4.82 life-years and 3.05 discounted QALYs per patient. The total per-patient discounted costs to the NHS for these two treatment options were £47,334 and £16,526 respectively. At list prices, the ICER was £44,557 per QALY gained for everolimus compared with BSC.

In the GI (midgut) population, in the base-case analysis, treatment with everolimus resulted in 7.50 life-years and 4.37 discounted QALYs per patient, whereas treatment with BSC resulted in 7.05 life-years and 4.19 discounted QALYs per patient. The total costs of these two treatment options were £55,842 and £21,119 respectively. Therefore, at list prices, the ICER was £199,233 per QALY for everolimus compared with BSC. This figure was highly uncertain because of the lack of midgut subgroup-specific OS data from RADIANT-4.

A range of scenario analyses were conducted. In pNETs, adjustment for the effect of crossover on OS had a large effect on cost-effectiveness. When relative effectiveness estimates from intention-to-treat OS data were used, treatment with everolimus resulted in higher costs and fewer QALYs than sunitinib and the ICER relative to BSC was £136,455 per QALY (compared with £45,493 in the base case), whereas the ICER for sunitinib compared with BSC was £37,217 per QALY (compared with £20,717 in the base case), at current list prices.

In the GI (midgut), applying background mortality produced ICERs for everolimus that were > £40,000 per QALY (compared with £199,000 in the base case). Another scenario involved the indirect comparison of everolimus and BSC with 177Lu-DOTATATE for GI (midgut) NETs. In analyses restricted to costs and benefits accrued up to disease progression, 177Lu-DOTATATE (extendedly) dominated everolimus (which had an ICER of £90,181 relative to BSC at list prices) and had an ICER of £30,115 relative to BSC.

End-of-life criteria

Based on the data from the three included trials (RADIANT-3, A6181111 and RADIANT-4), only sunitinib plus BSC in the pNETs population of A6181111 may meet the end-of-life criteria.

Conclusions

There is a high degree of uncertainty around the clinical effectiveness and cost-effectiveness of everolimus, 177Lu-DOTATATE and sunitinib in the treatment of advanced, progressive pNETs 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 for PFS but the effects on OS are uncertain because of the immaturity of some of the OS data and because of substantial treatment switching by patients on disease progression in some trials.

Another area of uncertainty is the relative effects of targeted treatments on HRQoL. Although some of the trials underpinning this technology assessment review have measured this outcome, they tend to cover only the phase while patients are on treatment and it is therefore not known how HRQoL evolves over time or towards the end of life. Even while patients are on active targeted treatment, the available HRQoL data are inadequate to differentiate between treatments.

Seeking to address uncertainties in the evidence, we requested data from sponsors of the main trials; however, we obtained data that were outdated and that related to only one trial. Further valuable research would use individual patient data from RADIANT-4 to explore (1) the effect of adjustment for crossover from placebo to active treatment on OS and cost-effectiveness and (2) the robustness of the results of indirect comparisons with the NETTER-1 trial using methods ranging from simple Bucher-type methods to

more elaborate matching methods, such as those reviewed and investigated in this assessment. Similar analyses for pNETs using updated OS data are also warranted.

Nevertheless, in pancreatic NETs, at current list prices, the ICERs relative to BSC 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 for GI and lung NETS, but is unlikely to be cost-effective for GI (midgut) NETs. The effectiveness evidence on 177Lu-DOTATATE is still too 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 based on these outcomes, its ICER compared with BSC is approximately £35,000 per QALY.

Study registration

This study is registered as PROSPERO CRD42016041303.

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Chapter 1 Background

Description of the health problem

'Neuroendocrine tumours' (NETs) is the overarching term for the group of heterogeneous cancers that develop in cells in the diffuse neuroendocrine system. The diffuse neuroendocrine system is made up of neuroendocrine cells found in the respiratory and digestive tracts. As 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 (GI) system. NETs also encompass carcinoids and may be referred to as neuroendocrine carcinoids, which leads to substantial confusion over their name.[2]

Aetiology, pathology and prognosis

The aetiology of NETs is poorly understood.[1] Predominantly, NETs are sporadic in nature (i.e. they 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 (i.e. spread to other organs or tissues in the body).

Characteristics of neuroendocrine tumours

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

Location

Most NETs have been generally classified as foregut (including those in the lungs), midgut or hindgut, as it was thought that they were derived from embryonic neural crest cells. However, this theory is not now accepted and classification should be based on the site of origin of the tumour, that is, pancreas, lung, stomach, small bowel or large bowel (colon). The term 'carcinoid' is outdated but colloquially refers to NETs of the small bowel that secrete 5-hydroxytryptamine; the term 'carcinoid' is also still in common usage for NETs of the lung. 'NET' is the preferred term for all of these tumours. NET tumours may be grouped together as gastroenteropancreatic (GEP) NETs. Typically, the locations of these tumours 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 a tumour is located. An analysis of 13,715 carcinoid tumours over a 5-decade period in the USA found that the best 5-year survival rates were found in patients with rectal (88.3%), bronchopulmonary (73.5%) and appendicle (71.0%) NETs.[3] The lowest 5-year survival rates were found in patients with pancreatic NETs (pNETs) (37.5%).[3]

Pancreatic neuroendocrine tumours Neuroendocrine tumours 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 somatostatinomas (which produce the hormone somatostatin). However, the majority of pNETs are non-functioning and do not produce measurable levels of hormones that give symptoms.

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

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

Tumour grade/degree of differentiation

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 World Health Organization (WHO) introduced a new system for grading cancer tumours.[4] This grading system is also endorsed by the European Neuroendocrine Tumor Society (ENETS) grading schemes.[5,6] The grading scheme is as follows:

- NET grade 1 (low grade)
  - well-differentiated tumour with a low number of cells actively dividing
  - Ki-67 index of $\leq 2\%$
  - mitotic count of < 2 per 10 high-power field (HPF)
- NET grade 2 (intermediate grade)
  - well-differentiated tumour, but with a higher number of cells actively dividing
  - Ki-67 index of 3–20%
  - mitotic count of 2–20 per 10 HPF
- neuroendocrine carcinoma (NEC) grade 3 (high grade)
  - poorly differentiated, malignant carcinoma (most aggressive form of NET)
  - Ki-67 index of $> 20\%$
  - mitotic count of > 20 per 10 HPF.

Stage of tumour (see Appendix 20*)*

Determination of the size of a tumour and whether or not it has spread beyond its original site is known as staging 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's (UICC's) *TNM Classification of Malignant Tumours*, Seventh Edition[7] (see *Appendix 19*, *Table 133*) and the ENETS staging system[5,6] (see *Appendix 20*, *Table 134*). The Royal College of Pathologists[8] recommended both the WHO and the ENETS systems for assessing the grade/stage of a NET. In current practice, both systems are used together with the UICC grading system above. The difference between the UICC grading system and the ENETS grading systems is not great and would not affect outcomes relating to this report.

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 that may themselves need treating in addition to treating the cancer. For example, hormones released by a pNET include insulin, glucagon and pancreatic polypeptide, whereas hormones released by an appendix NET include serotonin and somatostatin. Tumours that are not releasing hormones, and, therefore, that have no hormone-related clinical features, are known as non-functioning tumours.

Epidemiology

Incidence and prevalence

In October 2016, Public Health England (PHE)[9] published the first data briefing on the incidence and survival in NETs and NECs in England. In 2013 and 2014, 8726 neoplasms were diagnosed, equating to 4000 per year or an approximate rate of 8 per 100,000 people per year (not age standardised). Although the annual incidence of NETs is low, because of the long survival of individuals with NETs, the prevalence is much greater and has been calculated as 35 per 100,000 people.[10]

Incidence trends for NETs were compared between a Norwegian registry and an American registry.[11] From the time period 1993–7 to 2000–4, there was an incidence rate increase of 72% for NETs in Norway (from 2.35 to 4.06 per 100,000 people). Over the same time period in America, the increase was 37% (from 4.22 to 5.79 per 100,000 people) for the white population and 40% (from 5.48 to 7.67 per 100,000 people) for the black population. In a Canadian population, between 1994 and 2009, the incidence rates for NETs at all locations increased by 138% (from 2.46 to 5.86 per 100,000 people).[12]

More specifically, for the subgroup of GI NETs, Ellis *et al.*[13] reviewed incidence rates in the UK between 1971 and 2006. In 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 (1971–8) to 1.32 in men and 1.33 in women (2000–6). This is equivalent to an increase in incidence rates for GI NETs from 1971 to 2006 of 392% for men and 282% for women.[13]

However, these incidence rates for the diagnosis of NETs do not account for the overall prevalence of NETs. As the delay in diagnosis is typically 5–7 years after the appearance of the first symptoms, many cases of NETs are undiagnosed.[1]

Public Health England[9] produced a diagram depicting the morphology (form of the neuroendocrine neoplasms) and topography (location of the neuroendocrine neoplasms) of 8726 individuals diagnosed with NETs and NECs in 2013 and 2014. Low-grade (grade 1) NETs and not-otherwise-specified NECs make up the predominant morphology of neuroendocrine neoplasms in England. PHE went on to describe some characteristics of the cohort:

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

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 US populations and Asian populations.[14] In the former countries, a midgut origin represented 30–60% of new NETs, whereas in Asian populations the midgut was the origin of < 10% of new NETs. In a parallel way, the hindgut was the origin of a higher proportion of new NETs in Asian populations.[14] A case–control study of risk factors for NETs of the small intestine, stomach, lung, pancreas and rectum in 740 individuals with NETs and 924 healthy control subjects in the USA indicated an increased risk for women with a family history of cancer and diabetes mellitus.[15] In contrast, in the UK, PHE[9] found no association of ethnicity and sex with NET prevalence.

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 (VHL) syndrome.

Survival

Although prognosis is generally better with an early diagnosis, the majority of NETs are diagnosed at a later stage when the tumour has already metastasised.

In data collected between 1986 and 1999 for 4104 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%), whereas small-cell tumours had the lowest 5-year survival rate (5.2%). Survival rates were higher for women and young people (15–54 years vs. 55–74 years and 75–99 years) and the overall prognosis was dependent on the features (e.g. tumour differentiation, anatomical site, histological type) of the NET.[16]

Although it is impossible to compare accurately different countries with the data available, median 5-year survival varied from 38% to 61% across Europe,[17] Taiwan[18] and Canada.[12] Whether or not survival has improved over time remains debated. Korse *et al.*[19] reported in the Netherlands an ongoing improvement in survival for well-differentiated NETs and suggested that the introduction of somatostatin analogues (SSAs) and their long-acting forms may explain this change in survival over time. However, other research groups in the USA and France have not confirmed this trend.[20,21]

Impact of the health problem

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

Although prognosis is better with an early diagnosis, NETs are generally diagnosed at a late stage when the tumour has already metastasised. In such cases, treatment is rarely curative, although individuals can live and maintain a good quality of life for a number of years (e.g. 68–77% of people diagnosed with a carcinoid tumour will survive for $\geq$ 5 years[22]). The primary management strategy for NETs is managing symptoms originating from the tumour. The onset of symptoms, however, may take between 3 and 5 years from the development of the tumour. Symptoms can vary widely and some patients may have no symptoms or non-specific and vague symptoms (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, because of intestinal blood loss. Most GEP 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, in which hormones are significantly elevated.

In total, 20% of well-differentiated endocrine tumours of the jejunum or ileum (midgut NETs) 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]

Measurement of disease

A number of outcomes 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 the time from randomisation until disease progression or death.
- Objective response rate (ORR), defined as either a partial response or a complete response:
    - Complete response – all detectable tumour has disappeared.
    - Partial response – roughly corresponds to a $\geq 50\%$ decrease in the total tumour volume but with evidence of some residual disease still remaining.
    - Stable disease – includes either a small amount of growth (typically $< 20\%$ or $< 25\%$) or a small amount of shrinkage.
    - Progressive disease – means that the tumour has grown significantly or that new tumours have appeared. The appearance of new tumours is always defined as progressive disease regardless of the response of other tumours. Progressive disease normally means that 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 has the most impact on a patient's day-to-day life.

Current service provision

Management of disease

Diagnosis

Diagnosis of NETs can be difficult as they are often small tumours (some may be < 1 cm in size), they can occur almost anywhere in the body and they can result in 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 often occurs at quite a late stage in the disease.

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 primarily occurs following detailed histology. Other tests may include urine tests, blood tests, ultrasound scans, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, radioactive scans and positron emission tomography (PET)/CT scans. 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 for diagnosis, to assess the efficacy of subsequent treatment and to assess changes in prognosis.[1] Similarly, imaging is used not only for detecting the primary tumour, but also for screening at-risk populations, assessing the extent of the disease and assessing the response to treatment at follow-up.[1]

Treatment

The aim of treatment, when 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). As metastatic disease is common for individuals with NETs, often improving 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 treatment often starts with surgery and symptom management. Surgery is the only curative treatment for NETs. Symptom treatment, particularly with hormonal hypersecretion in functional NETs, can have a significant impact on an

individual's quality of life as the symptoms themselves, as opposed to the cancer, may be life-threatening (e.g. severe diarrhoea and hypokalaemia).[1] Symptom control is often manged with a SSA, for example octreotide (Sandostatin®; Novartis International AG, Basel, Switzerland) or lanreotide (Somatuline Autogel®; Ipsen, Paris, France). Available treatments that follow surgery and initial symptom control include:

- liver transplant
- interferon alpha (Roferon-A, Roche Products Ltd)
- chemotherapy
- ablation therapies
- targeted radionuclide therapy, including one of the interventions of interest in this assessment report: lutetium-177 DOTATATE [(177Lu-DOTATATE) Lutathera®; Imaging Equipment Ltd, Radstock, UK]
- transhepatic artery embolisation/chemoembolisation
- external-beam radiotherapy
- emerging therapies, including two of the interventions of interest in this assessment report: everolimus (Afinitor®; Novartis) and sunitinib (Sutent®; Pfizer Inc., New York, NY, USA).

Describing an overarching treatment pathway for NETs is challenging as there are many different options depending on the characteristics of the NET (e.g. location, grade, differentiation, secretory profile).

Current service cost

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

Public Health England[9] has reported that approximately 4000 new cases of neuroendocrine neoplasms are diagnosed each year. From a budgetary perspective this is a small subgroup of the 300,000 new cancer diagnoses registered annually in England,[25] but with the arrival of new high-cost targeted therapeutic treatments, 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. measurement of blood markers and CT, MRI and PET), the cost of acquiring and administering active and supportive treatments (in particular long-acting repeat SSA therapy but also chemotherapy), the cost of managing symptoms (if the tumour is functioning), the cost of managing adverse events (AEs) and the cost of human resources for patient consultation, multidisciplinary team meetings and hospitalised care.

Relevant national guidelines, including National Service Frameworks

Guidelines for the management of GEP NETs (including carcinoid tumours) were published in 2012 by a group of authors who are members of the UK and Ireland Neuroendocrine Tumour Society (UKINETS).[1]

There is a related guideline from the National Institute for Health and Care Excellence (NICE) from 2010 that focuses on tumours of unknown origin[26] that fall under the NETs umbrella. This guideline is distinct from the work in this report, which focuses on pancreatic, lung and GI NETs.

Description of the technology under assessment

Summary of interventions

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

Everolimus[27]

Everolimus is an orally active agent that is able to slow down the growth and spread of a tumour. It acts by binding to FK506-binding protein-12 (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.*
>
> *European Medicines Agency.[27] © EMA [1995–2018]*

It also has a marketing authorisation for NETs of GI or lung origin:

> *Afinitor is indicated for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours.*
>
> *European Medicines Agency.[27] © EMA [1995–2018]*

Everolimus is an oral drug that is typically given at a dose of 10 mg a day. It is recommended that treatment is 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 every day at the same time of day.

The most common side effects of everolimus (affecting > 1 in 10 people) are 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 count), fatigue (tiredness), diarrhoea, asthenia (weakness), infections, stomatitis (inflammation of the lining of the mouth), hyperglycaemia (high blood glucose level), hypercholesterolaemia (high blood cholesterol level), 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 Drugs Fund (CDF) on 12 March 2015; it was previously available for the treatment of progressive unresectable or metastatic well-differentiated NETs of the pancreas.

177Lu-DOTATATE[28]

Lutetium-177 DOTATATE is a radiolabelled SSA. It is made up of 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 somatostain receptor type 2 (SSTR2)]. Once bound, the 177Lu-DOTATATE accumulates within the tumour cells, delivering cytotoxic radiation that kills them.

As of December 2016, 177Lu-DOTATATE does not have marketing authorisation in the UK for any indication.

Administration of 177Lu-DOTATATE is through an intravenous infusion and involves 3 days of hospital appointments, including an overnight stay. Typically, four cycles are administered over a total of 8 to 10 months.

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

Lutetium-177 DOTATATE was removed from the CDF on 4 November 2015. It was previously available for the treatment of advanced NETs after sunitinib/chemotherapy, pNETs and midgut carcinoid tumours (after octreotide/somatostatin therapies).

Sunitinib[29]

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 enzymes known as protein kinases that are 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 protein kinases and it is through the blocking of these enzymes that sunitinib is able to slow the growth and spread of the tumours.

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.*
>
> *European Medicines Agency.[27] © EMA [1995–2018]*

Sunitinib is an oral drug and is 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 occurs. 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), GI disorders (such as diarrhoea, feeling sick, inflammation of the lining of the mouth, indigestion and vomiting), respiratory disorders (such as shortness of breath and cough), 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 count), anaemia (low red blood cell count) and leukopenia (low white blood cell count).

Sunitinib is available on the CDF for the treatment of pNETs when all of the following criteria are met:

- application made, and first cycle of systemic anticancer therapy to be prescribed, by a consultant specialist specifically trained and accredited in the use of systemic anticancer therapy
- biopsy-proven well-differentiated pNET
- first-line indication or second-line indication or third-line indication
- no previous vascular endothelial growth factor (VEGF)-targeted therapy.

Identification of important subgroups

From the NICE scope,[30] the following subgroups were identified as being important in the treatment of NETs:

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

Further information on these subgroups can be found in *Characteristics of neuroendocrine tumours*.

Current usage in the NHS

It was difficult to ascertain the current usage of everolimus, sunitinib and 177Lu-DOTATATE in the NHS. In its submission, Advanced Accelerator Applications (AAA) Ltd[31] (Saint-Genis-Pouilly, France) reported that, although unlicensed, 177Lu-DOTATATE has been used to treat patients in England through the CDF (confidential information has been removed). Likewise, Pfizer[32] 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[33] did not report in its submission the estimated use of everolimus within the NHS in England; however, our clinicians suggest that the rate of use of everolimus is higher than that of sunitinib.

Anticipated costs associated with the interventions

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 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial)[34] and RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial)[35] trials of NET patients is about 9 months, with a range of 1 week to 2 years.[34] 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 and so the cost of drug delivery is limited to the time needed by hospital pharmacy staff to dispense the drugs. 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. In addition, in comparison to the oral preparations of everolimus and sunitinib, the delivery of 177Lu-DOTATATE is more resource intensive. 177Lu-DOTATATE is a radiolabelled intravenous preparation and so administration involves careful handling, specialist staff and post-administration observation, which for most patients means an overnight hospital stay. Beyond acquisition and administration, the remaining treatment-related costs arise from disease monitoring and the medical management of AEs, which will of course differ across treatments but which are less substantial components of the overall cost.

We expect that all of these cost components will vary between individuals and hence they were subject to modelling, but the acquisition costs of treatments are presented in *Table 23* for simple comparative purposes.[36]

Chapter 2 Changes to the project scope

During the course of this review, NICE consulted on amendments to the original project scope. The revised scope was agreed on 18 August 2016[30] and the differences between the original and the revised scope are provided in *Table 1*.

TABLE 1 Original and revised scope

Characteristic	Old scope	New scope
Intervention(s)	• Everolimus (NETs of GI, pancreatic or lung origin) • *Lanreotide (neuroendocrine tumours of mid-gut, pancreatic or unknown origin)* • 177Lu-DOTATATE (NETs of GI or pancreatic origin) • Sunitinib (pNETs)	• Everolimus (NETs of GI, pancreatic or lung origin) • Lutetium-177 DOTATATE (NETs of GI or pancreatic origin) • Sunitinib (pNETs)
Population(s)	People with progressed unresectable or metastatic NETs According to the specific locations covered by *the marketing* authorisations of the interventions	People with progressed unresectable or metastatic NETs According to the specific locations covered by *existing and anticipated* marketing authorisations of the interventions
Comparators	• The technologies listed above will be compared with each other when appropriate • *Octreotide (long-acting release formulation)* • Interferon alpha • Chemotherapy regimens {including but not restricted to combinations of streptozocin [Zanosar; TEVA Pharmaceuticals, Petah Tikva, Israel], 5-FU [fluorouracil sodium, Pfizer Inc., New York, NY, USA], doxorubicin [Adriamycin; Pfizer], temozolomide [Temodal, Merck Sharp & Dohme Limited, Kenilworth, NJ, USA] and capecitabine [Dr Reddy's Laboratories (UK) Ltd, Beverly, UK]} • Best supportive care	• The technologies listed above will be compared with each other when appropriate • Interferon alpha • Chemotherapy regimens (including but not restricted to combinations of streptozocin 5-FU, doxorubicin, temozolomide and capecitabine) • Best supportive care
Outcomes	The outcome measures to be considered include: • OS • PFS • RRs • symptom control • AEs • HRQoL	The outcome measures to be considered include: • OS • PFS • RRs • symptom control • AEs • HRQoL
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 be issued only 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 be issued only in accordance with the marketing authorisation

continued

TABLE 1 Original and revised scope (*continued*)

Characteristic	Old scope	New scope
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 effectiveness 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 a NHS and Personal Social Services perspective *The use of 177Lu-DOTATATE is conditional on the presence of somatostatin receptor-positive GEP NETs. The economic modelling should include the costs associated with diagnostic testing for somatostatin receptor-positive GEP NETs 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[37]	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 effectiveness 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 a NHS and Personal Social Services perspective

5-FU, fluorouracil; RR, response rate.
Differences between the original and the revised scope are highlighted in italics.

What is the impact of the changes in scope?

- The population and outcomes under review were unchanged from the original scope.
- The following intervention was removed: lanreotide (NETs of mid-gut, pancreatic or unknown origin).
- The following comparator was removed: octreotide (long-acting release formulation).

Chapter 3 Definition of the decision problem

Decision problem

Population

The population specified in the final scope issued by NICE[30] is people with progressed unresectable or metastatic NETs. In addition, the population must be in accordance with 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.

Interventions

- Everolimus – for NETs of GI, pancreatic or lung origin.
- Lutetium-177 DOTATATE – for NETs of GI or pancreatic origin.
- Sunitinib – for NETs of pancreatic origin.

Comparators

Interventions should be compared with each other and with:

- interferon alpha
- chemotherapy regimes (including but not restricted to combinations of streptozocin, fluorouracil (5-FU), doxorubicin, temozolomide and capecitabine)
- best supportive care (BSC).

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

Outcomes

The outcomes of interest based on the NICE scope include:

- OS
- PFS
- response rates (RRs: including complete response, partial response, stable disease, progressive disease, tumour shrinkage and ORR)
- symptom control
- AEs
- HRQoL.

Key issues

The primary factors that may influence the clinical effectiveness of treatment for individuals with NETs are predominantly covered within the population subgroups listed in *Population*.

In addition to the number of previous treatments, covered as a population subgroup, the use of concomitant treatment (primarily SSA use) while taking part in 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.

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

Overall aims and objectives of the assessment

The aim of this report was 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). We carried out a systematic review of clinical effectiveness studies to assess the medical benefit and risks associated with these treatments, and compared the treatments against available alternative standard treatments. We also assessed whether or not these drugs are likely to be considered good value for money for the NHS using a model-based economic evaluation.

Note

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 4 Assessment of clinical effectiveness

Methods for reviewing effectiveness

Evidence for the clinical effectiveness of everolimus, 177Lu-DOTATATE and sunitinib within their marketing authorisations for treating unresectable or metastatic NETs with disease progression was obtained 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).[38]

Changes to the protocol

As discussed in *Chapter 2*, NICE issued a revised scope for this project on 18 August 2016.[30] The revised scope necessitated a change to our published protocol[39] as lanreotide was removed as an intervention and octreotide was removed as a comparator. A revised protocol was drafted (PROSPERO CRD42016041303); there were no other changes to the published protocol.

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 NETs 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 databases and databases of ongoing trials

The following bibliographic databases were searched: MEDLINE (Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Ovid), MEDLINE Daily (Ovid), MEDLINE Epub Ahead of Print (Ovid), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (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). The searches were not limited by study design, language or date.

The following trial registries were handsearched: Current Controlled Trials, ClinicalTrials.gov, the US Food and Drug Administration (FDA) website and the European Medicines Agency (EMA) website[40] [including European Public Assessment Reports (EPARs)].

The full search strategies are provided in *Appendix 1*.

Website searching

The following websites were searched:

- ENETS [www.enets.org/ (accessed 19 May 2016)]
- UKINETS [www.ukinets.org/ (accessed 19 May 2016)].

Deduplication

All references were exported into EndNote X7 (Clarivate Analytics, Philadelphia, PA, USA), where automatic and manual deduplication was performed.

Screening

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

Citation searching, appraisal of company submissions and identification of systematic reviews of randomised controlled trials

All studies meeting the 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 randomised controlled trials (RCTs) from identified systematic reviews 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.

Inclusion and exclusion criteria

Inclusion and exclusion criteria for the selection of clinical effectiveness studies were defined exactly as per the decision problem (see *Chapter 3*). Studies identified prior to the publication of the revised scope[30] were rechecked for inclusion against this revised scope.

The inclusion and exclusion criteria for the original and revised scope are summarised in *Table 1*. Studies were also required to be in the English language.

The systematic review of clinical effectiveness focused only on RCTs. When no RCTs were identified for an intervention of interest, a non-systematic review of non-randomised evidence was conducted (see *Appendix 2*). Non-randomised evidence included prospective observational cohort studies (both comparative and single-arm studies). Case reports were not included.

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 providing efficacy evidence.

Studies published as abstracts or conference presentations were included if they linked to included full-text papers, in which appraisal of the methodology and an assessment of the results could be undertaken.

Data extraction and management

Studies included at the full-text stage were shared between three reviewers for the purposes of data extraction. A standardised data specification form was used and extracted data were double-checked by a second reviewer. When 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 the study design and methodology, the baseline characteristics of participants and the following outcomes; PFS, OS, RRs, AEs and HRQoL. Definitions of the outcomes are provided in *Chapter 1* (see *Measurement of disease*).

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

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 CRD for RCTs.[38] An additional question (question 10; see *Table 4*) was added to assess the applicability of the study to the NHS in England.

Methods of data analysis/synthesis

Data were tabulated and narratively synthesised. If sufficient evidence was available and study designs were homogeneous, meta-analysis would be performed. In addition, when the data allowed, an indirect treatment comparison (ITC) would be performed.

The 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, as this was how the included studies were published. Additional data were subsequently made available so that GI NETs and lung NETs could be assessed as isolated tumour locations.

Indirect treatment comparisons

When data were available, the Bucher *et al.*[41] method was used for an ITC for the outcomes of PFS, OS, RR and AEs. This method was best suited for this assessment given that the available data were only in summary form and were limited to a handful of studies. More sophisticated methods were explored in the economic analysis described in *Chapter 6* using individual patient data, which highlight the limitations of the Bucher *et al.*[41] method, but resource limitations prevented this evidence being incorporated in the clinical effectiveness review. Further details can be found in *Indirect treatment comparison: pancreatic neuroendocrine tumours*.

Results

The results of study identification in accordance with the updated NICE scope are discussed first in this section, followed by a description of the quality of the evidence and overview tables of the included trials. When available, outcomes (PFS, OS, RRs, HRQoL and AEs) are then reported by tumour location and by subgroup. The subgroups considered were based on the NICE scope (see 'Other considerations' in *Table 1*).

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

Quantity and quality of research available (randomised controlled trial evidence)

Studies identified

Titles and abstracts were screened for 6209 unique references identified by the searches, after which 273 full-text papers were retrieved for detailed consideration. A total of 217 full texts were excluded (a table of these excluded references, along with the reasons for exclusion can be found in *Appendix 3*). The Cohen's kappa for full-text screening was 0.579 [standard error 0.045, 95% confidence interval (CI) 0.491 to 0.667].

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[42–47] were retained for scrutiny and three trials were included in the review: RADIANT-3 (four full texts[34,48–50] and 22 abstracts[51–72]), RADIANT-4 (one full text[35] and eight abstracts[73–80]) and A6181111 (one full text,[81] 19 abstracts[82–100] and erratum to the full text[81]). Following scrutiny of the included studies from the six systematic reviews, no further evidence was identified. A table of all of the included citations is provided in *Appendix 4*.

Of note, two citations related to a study by Yao *et al.*[101] This study met our inclusion criteria; however, it was excluded as the paper was retracted because 'the authors discovered statistical errors which need further validation'. The study compared everolimus ($n = 44$) with 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:

- 177Lu-DOTATATE compared with any of the included comparators
- everolimus compared with interferon alpha or chemotherapy
- sunitinib compared with interferon alpha or chemotherapy.

The AG ran an additional search (see *Appendix 5* for the search strategy) with the aim of identifying any RCTs that compared chemotherapy with BSC or placebo in the NETs population. Identified studies would help inform discussions around the clinical effectiveness of the interventions in comparison to chemotherapy through an ITC. 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 with BSC or placebo, as interferon alpha is not commonly used in UK clinical practice.

Neuroendocrine Tumors Therapy trial

The NETTER-1 (Neuroendocrine Tumors Therapy) trial[102] was identified as an includable trial through four published abstracts[103–106] identified in the systematic review in accordance with the original NICE scope. However, it was not included in this systematic review as it did not meet the revised inclusion criteria of the updated scope issued by NICE on 18 August 2016.[30]

The NETTER-1 trial is a RCT that compares 177Lu-DOTATATE plus 30 mg of octreotide long-acting release (LAR) with 60 mg of octreotide LAR. Whether or not octreotide LAR could be deemed a concomitant treatment, as the doses were different in each treatment arm, was explored.

The AG sought consultation from our clinicians, who were unable to confirm whether or not the different dosing of octreotide LAR would result in different clinical effectiveness results. Therefore, the AG searched for RCT dosing studies (see *Appendix 5* for the search strategy) to ascertain whether or not 30 mg of octreotide LAR had the same clinical effectiveness as 60 mg of octreotide LAR in the NETs population. Following screening of 180 citations, no studies were identified.

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

Taken from the company submission,[31] AAA reports that the rationale for treating the comparator arm with a high dose of octreotide (60 mg) 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.*
>
> *p. 44*[31]

The AG appreciate that, as the only RCT of 177Lu-DOTATATE identified, this trial may be of interest to the committee and so the main outcomes are presented in *Appendix 6* along with the results of an ITC with everolimus from RADIANT-4.[35]

The study selection process is outlined in *Figure 1*.

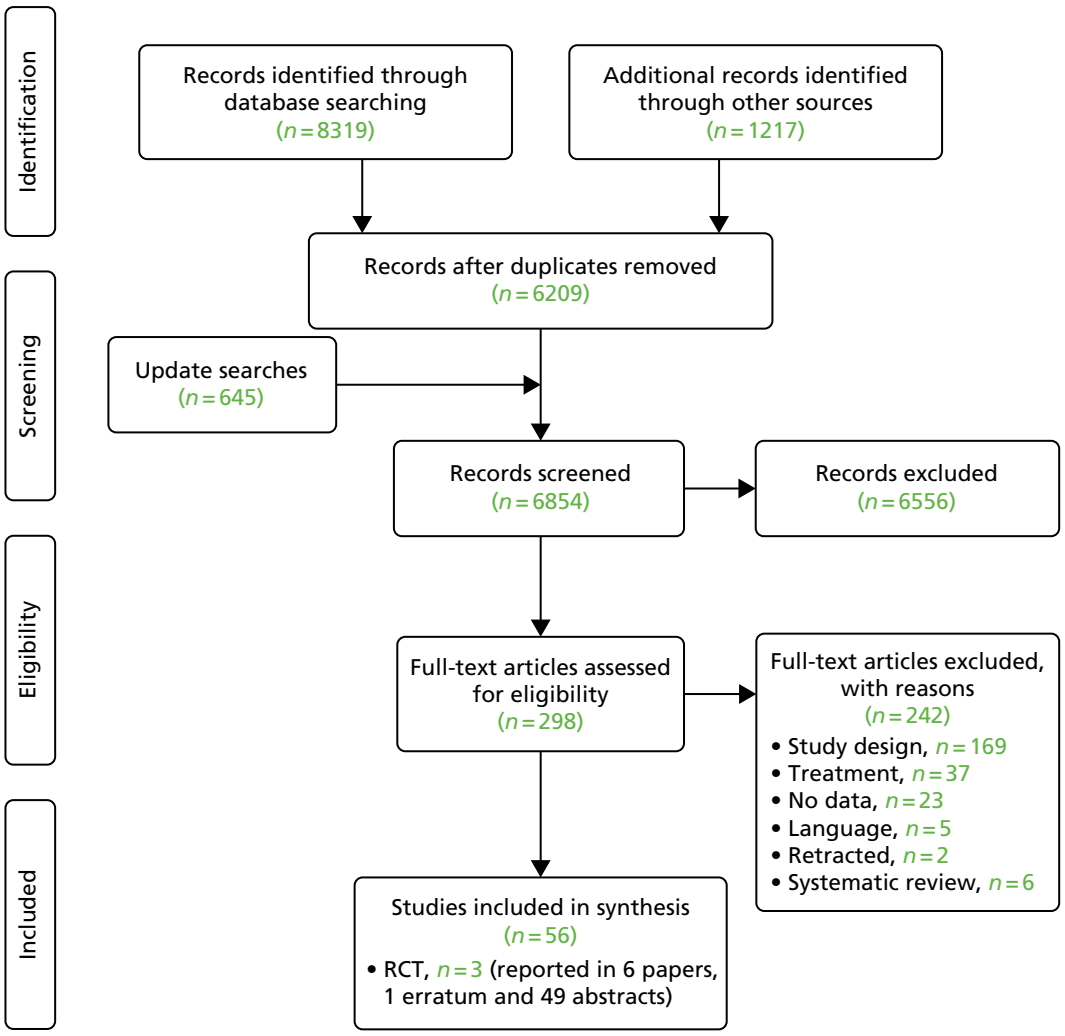


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Ongoing trials

The following trials registries were handsearched for ongoing trials: Current Controlled Trials, ClinicalTrials.gov; the FDA website and the EMA website (including EPARs) (see *Appendix 1* for the search strategy). All searches were carried out in May 2016. Three trials were considered relevant to this review:

1. NCT02687958: Study of Everolimus as Maintenance Therapy for Metastatic NEC with Pulmonary or Gastroenteropancreatic Origin. $N = 30$, currently recruiting, sponsored by the Gruppo Oncologico Italiano di Ricerca Clinica.
2. NCT02358356: Capecitabine ON Temozolomide Radionuclide Therapy Octreotate Lutetium-177 NeuroEndocrine Tumours Study (CONTROL NETs). $N = 165$, currently not open for recruitment, sponsored by the Australasian Gastro-Intestinal Trials Group.
3. NCT02230176: 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). $N = 80$, currently recruiting, sponsored by Gustave Roussy, Cancer Campus, Grand Paris.

As two of the trials were investigating 177Lu-DOTATATE, the intervention that we were unable to provide relevant RCT evidence for, we contacted the study organisers and received replies from both. The CONTROL NETs trial is in progress and data are not expected until 2018/19. The OCCLURANDOM study has recruited a total of 13 individuals and data are not expected to be ready before submission of this assessment report.

Study design and participant characteristics: pancreatic neuroendocrine tumours

This review includes the two trials that evaluated treatments in pNETs (RADIANT-3[34] – everolimus; A6181111[81] – sunitinib). The characteristics of the study designs are summarised in *Table 2*. In both trials, participants were randomised 1 : 1 to the intervention or placebo and BSC was given in both the intervention arm and the placebo arm. Both trials measured the following outcomes: PFS, OS, RR (to include complete response, partial response, stable disease, progressive disease and ORR) and AEs. A6181111[81] also reported HRQoL.

The primary end point was the same (PFS) for both trials. Median treatment duration was 4.6 months in the treatment arm in A6181111[81] and (confidential information has been removed) in RADIANT-3[34] for the treatment arm and (confidential information has been removed) for the placebo/BSC arm. Median follow-up was reported to be 17 months for RADIANT-3[34] and 34.1 months for A6181111.[81]

A summary of information relating to drug administration is also provided in *Table 2*. The mean relative dose intensity (RDI) of the active treatment was slightly lower in the everolimus studies (0.86 in RADIANT-3[34]) than in the sunitinib study (0.91 in A6181111[81]). The use of SSAs was 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 a 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.*
>
> *Raymond* et al.[81]

The statistical power of the study was reduced because of the early termination of the trial. Only 171 individuals were randomised rather than the target of 340.

To achieve sufficient statistical power in RADIANT-3,[34] it was estimated that 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.

Population characteristics: pancreatic neuroendocrine tumours

The baseline demographic and disease characteristics for RADIANT-3[34] and A6181111[81] are reported in *Table 3*.

RADIANT-3[34] and A6181111[81] recruited participants of a similar age (median age ranged from 56 to 58 years). There was a slightly higher proportion of men recruited to RADIANT-3[34] (53% to the everolimus arm and 58% to the placebo arm) than to A6181111[81] (49% to the sunitinib arm and 47% to the placebo arm). Both studies recruited individuals with pNETs only.

The functionality of the tumour was not reported in RADIANT-3,[34] whereas A6181111[81] recruited a mixture of functioning (> 30%) and non-functioning (≈50%) individuals (the functionality of the remaining ≈20% was not clarified).

A6181111[81] recruited individuals with well-defined or moderately defined tumours, whereas RADIANT-3[34] recruited around 80% of individuals with well-defined tumours, with the remainder having moderately defined tumours.

RADIANT-3[34] measured performance status (PS) using the WHO PS score system, whereas A6181111[81] measured PS using the Eastern Cooperative Oncology Group (ECOG) PS system. Our clinicians suggested that there is little difference between PS measured by either system. The majority of individuals had a PS

TABLE 2 Study characteristics and drug administration: pNETs

Study ID	ITT population (*n*)	Intervention	Tumour locations included	Inclusion criteria	Randomisation stratification factor	Primary end point	Secondary end points	Median (range) treatment duration (months)	Median follow-up (months)
RADIANT-3[33,34] (NCT00510068)	207	Everolimus + BSC	Pancreas	Low or intermediate grade, advanced (unresectable or metastatic), disease progression in previous 12 months	Stratified according to status with respect to previous chemotherapy (receipt vs. no receipt) and according to WHO PS (0 vs. 1 or 2) at baseline	PFS	OS, ORR, duration of response, safety	(Confidential information has been removed	17
	203	Placebo + BSC						(Confidential information has been removed	
A6181111[81] (NCT00428597)	86	Sunitinib + BSC	Pancreas	Pathologically confirmed, well differentiated, advanced and/or metastatic, disease progression in previous 12 months	NR	PFS	OS, ORR, time to response, duration of response, safety, patient-reported outcomes	4.6 (0.4–17.5)	34.1
	85	Placebo + BSC						3.7 (0.03–20.2)	
RADIANT-4[35] (NCT01524783)	205	Everolimus + BSC	Lung + GI (Ileum, rectum, unknown origin, jejunum, stomach, duodenum, colon, other, caecum, appendix)	Pathologically confirmed, advanced (unresectable or metastatic), non-functional, well differentiated (grade 1 or 2), disease progression in previous 6 months	Stratified by previous SSA 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 (0.1–27.7)[a]	21
	97	Placebo + BSC						4.5 (0.9–30.0)[b]	

continued

TABLE 2 Study characteristics and drug administration: pNETs (*continued*)

Study ID	ITT (*n*)	Interventions evaluated (dose)	Mean relative dose intensity[c]	Dose reductions/ interruptions, *n*/*N* (%)	Treatment switching, *n*/*N* (%)	SSA use during study
RADIANT-3[34] (NCT00510068)	207	10 mg of oral everolimus once daily; BSC (confidential information has been removed)[a]	0.86	(59)	NA	Approximately 40% of individuals: everolimus arm 37.7%,[d] placebo arm 39.9%[e]
	203	Matching placebo; BSC (includes SSAs)[a]	0.97	(28)	148/203 (73)	
A6181111[81] (NCT00428597)	86	37.5 mg of oral sunitinib once daily;[f] BSC	0.91	(30)	NA	*n* = 23 (*n* = 22 were already on SSAs; *n* = 1 started following study enrolment)
	85	Matching placebo; BSC	1.01	(12)	59/85 (69)[g]	*n* = 25 (*n* = 20 were already on SSAs; *n* = 5 started following study enrolment)
RADIANT-4[35] (NCT01524783)	205	10 mg of oral everolimus once daily; BSC	0.90[h]	135/202 (67)	NA	NR[i]
	97	Matching placebo; BSC	1.00[j]	29/98 (30)	Not permitted	

ID, identification; ITT, intention to treat; NA, not applicable; NR, not reported; PS, performance status.
a Converted into months by the AG [reported as 40.4 weeks (range 0.7–120.4 weeks)].
b Converted into months by the AG [reported as 19.6 weeks (range 4.0–130.3 weeks)].
c Ratio of administered to planned doses.
d Percentage reported as 39.7% in Yao *et al.*[48]
e Percentage reported as 41.4% in Yao *et al.*[48]
f Treatment interruptions and a dose reduction to 25 mg per day were permitted to manage AEs. 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-haematological AEs of higher than grade 1 or haematological AEs of greater than grade 2.
g *n* = 38 patients at disease progression before study termination and *n* = 21 at disease progression after study closure.
h Reported as 0.794 in the company submission.
i SSAs were allowed only for the control of emergent carcinoid symptoms.
j Reported as 0.962 in the company submission.
Confidential information has been removed.
Source: Yao *et al.*[34] and Novartis[33] (RADIANT-3); Raymond *et al.*[81] and Pfizer[32] (A6181111); and Yao *et al.*[35] (RADIANT-4).

TABLE 3 Baseline characteristics

Study ID	Intervention	Tumour location	*n*	Age (years), median (range)	Male, *n*/*N* (%)	Tumour functioning, *n*/*N* (%)		Tumour differentiation, *n*/*N* (%)			WHO PS, *n*/*N* (%)	Previous treatments, *n*/*N* (%)
						Yes	No	Well differentiated	Moderately differentiated	Unknown		
RADIANT-3[34]	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); SSAs: 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); SSAs: 102/203 (50)
A6181111[81]	Sunitinib + BSC	Pancreas	86	56 (25–84)	42/86 (49)	25/86 (29)	42/86 (49)	86/86 (100)[a]		(0)	ECOG PS: 0: 53/86 (62); 1: 33/86 (38); 2: 0/86 (0)	Surgery: 76/86 (88); radiation therapy: 9/86 (10); chemoembolisation: 7/86 (8); radiofrequency ablation: 3/86 (3); percutaneous ethanol injection: 1/86 (1); SSAs: 30/86 (35)
	Placebo + BSC		85	57 (26–78)	40/85 (47)	21/85 (25)	44/85 (52)	85/85 (100)[a]		(0)	ECOG PS: 0: 41/85 (48); 1: 43/85 (51); 2: 1/85 (1)[b]	Surgery: 77/85 (91); radiation therapy: 12/85 (14); chemoembolisation: 14/85 (16); radiofrequency ablation: 6/85 (7); percutaneous ethanol injection: 2/85 (2); SSAs: 32/85 (38)
RADIANT-4[35]	Everolimus + BSC	Lung, GI	205	65 (22–86)	89/205 (43)	0/205 (0)	205/205 (100)	205/205 (100)[a]		(0)	0: 149/205 (73); 1: 55/205 (27)	Surgery: 121/205 (59); chemotherapy: 54/205 (26); radiotherapy: 44/205 (22); locoregional + ablative therapy: 23/205 (11); SSAs: 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); SSAs: 54/97 (56)

ECOG, Eastern Cooperative Oncology Group; NR, not reported; PS, performance status.
a Assumed from the inclusion criterion requiring individuals to present with well-differentiated NETs; poorly differentiated NETs was an exclusion criterion.
b Enrolment of this individual was a protocol violation.
Source: Yao *et al.*[34] and Table 4.2 (p. 37) from Novartis[33] (RADIANT-3); Raymond *et al.*[81] (A6181111) and Yao *et al.*[35] (RADIANT-4).

score of 0 in RADIANT-3[34] (66–67%), with the majority of the remaining individuals having a PS score of 1 (30–32%) and the remainder having a PS score of 2 (3%). A6181111[81] had a lower proportion of individuals with a PS score of 0 (62% in the sunitinib arm and 48% in the placebo arm) and a higher proportion of individuals with a PS score of 1 (38% in the sunitinib arm and 51% in the placebo arm) than RADIANT-3.[34] One individual was recruited with a PS score of 2 in the placebo arm; this was a protocol deviation for A6181111.[81]

The proportions of individuals who had received previous treatments were variable between RADIANT-3[34] and A6181111[81] (see *Table 3*). Of particular note, SSA use prior to treatment was around 50% in RADIANT-3[34] and between 35% and 38% in A6181111.[81]

Study design and participant characteristics: gastrointestinal and lung neuroendocrine tumours

This review includes RADIANT-4,[35] which evaluated everolimus in individuals with GI and lung NETs. The characteristics of the study design are summarised in *Table 2*. Participants were randomised 2 : 1 to everolimus or placebo. BSC was given in both the intervention (everolimus) arm and the placebo arm. RADIANT-4[35] measured the following outcomes: PFS, OS, RR (to include complete response, partial response, stable disease, progressive disease and ORR) and AEs. The primary end point 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 provided in *Table 2*. The use of SSAs was permitted in both treatment arms. Treatment switching (from placebo to active treatment) was not allowed in RADIANT-4.[35]

For RADIANT-4[35] it was estimated that 285 individuals would need to be randomised at a ratio of 2 : 1. This requirement was met as 302 individuals were randomised.

Population characteristics: gastrointestinal and lung neuroendocrine tumours

Baseline demographic and disease characteristics for RADIANT-4[35] are reported in *Table 3*.

The median age of participants ranged from 60 to 65 years in RADIANT-4.[35] There was a slightly lower proportion of men recruited to the everolimus arm (43%) than to the placebo arm (55%). Only individuals with non-functioning, well-defined tumours were recruited to RADIANT-4.[35] PS was measured using the WHO PS scoring system. The majority of individuals had a PS score of 0 (73–75%), with the remaining having a PS score of 1 (27–25%). The proportions of individuals who had received previous treatments were variable between the arms (see *Table 3*).

Quality appraisal

The three identified RCTs were appraised for quality (*Table 4*). When necessary for clarification purposes, published protocols available as online supplementary material for 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.

Treatment allocation

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

RADIANT-3,[34] A6181111[81] and RADIANT-4[35] all used a centralised internet or telephone registration system for determining treatment allocation. RADIANT-3[34] and RADIANT-4[35] based their stratification on prognostic factors (tumour location,[35] WHO PS,[34,35] previous chemotherapy use[34] and previous SSA use[35]). A6181111[81] stratified by country/region only.

TABLE 4 Quality appraisal

Item	RADIANT-3[34]	A6181111[81]	RADIANT-4[35]
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	Low risk[d]	Low risk
9. Did the analyses include an ITT analysis?	Low risk	Low risk	Low risk
10. Are there any specific limitations that might limit the applicability of this study's findings to the current NHS in England?	Unclear risk[e]	Unclear risk[d]	Unclear risk

ITT, intention to treat.
a Baseline characteristics of time from initial diagnosis and number of disease sites.
b Baseline characteristics of ECOG PS, Ki067 index, median time since diagnosis and number of sites of disease.
c Baseline characteristics of sex and previous surgical treatment.
d Around 67% of the participants were European.
e Around 38% of the participants were European.
Note
Criteria were based on CRD guidance.[38]

Similarity of groups

Baseline characteristics were predominantly similar between the two arms for all of the trials. However, there were some differences between arms in the trials:

- RADIANT-3[34] – participants in the everolimus arm tended to have a shorter time from initial diagnosis at baseline than participants in the placebo arm (6 months to < 2 years: 31% vs. 21% respectively; 2 years to ≤ 5 years: 26% vs. 40% respectively). The proportion of individuals with two disease sites was higher in the everolimus arm than in the placebo arm (41% vs. 32%).
- A6181111[81] – there was a higher proportion of participants with an ECOG PS of 0 in the sunitinib arm than in the placebo arm (62% vs. 48%), whereas the proportion of participants with a PS of 1 was lower in the sunitinib arm than in the placebo arm (38% vs. 51%).
- RADIANT-4[35] – there was a higher proportion of women in the everolimus arm than in the placebo arm (57% vs. 45%). In addition, fewer individuals had been treated with surgery prior to entering the study in the everolimus arm than in the placebo arm (59% vs. 72%).

The difference in ECOG PS between arms in A6181111[81] is the difference most likely to affect the clinical effectiveness results, with those receiving sunitinib having a proportionally better PS than those receiving placebo. Otherwise, it was considered by the clinicians that these baseline differences between the treatment arms were unlikely to affect significantly the clinical effectiveness outcomes reported in the trials.

Implementation of masking

RADIANT-3,[34] A6181111[81] and RADIANT-4[35] were all double-blind trials 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[34] and RADIANT-4;[35] these outcome assessors were also blinded to treatment allocation. Information obtained from the protocols indicated that both everolimus and placebo had an identical appearance, identical packaging and labelling and an identical scheduling of administration in both RADIANT-3[34] and RADIANT-4.[35] Information on the appearance of the placebo medication was not provided for A6181111.[81]

It was assessed that there was a low risk of bias with regard to the blinding of outcome assessors, participants and care providers.

Completeness of trial data

All a priori outcomes reported in the protocols were reported in the trial publications.[34,35,81] Intention-to-treat (ITT) analysis was carried out in each of the trials. Discrepancies in participant numbers in reports of AEs were poorly explained in all three trials. Both RADIANT-3[34] and A6181111[81] included fewer participants in their AE outcomes than the number of participants recruited, whereas RADIANT-4[35] included an additional participant in the placebo arm who was not accounted for ($n = 97$ randomised and $n = 98$ reported for AEs).

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

Generalisability

The populations evaluated by RADIANT-3,[34] A6181111[81] and RADIANT-4[35] were all in line with the licensed indication for each treatment and with the final scope issued by NICE.[30] All of the studies were multicentre studies including centres in both the UK and Europe. In total, 38% of the population in RADIANT-3[34] were European, whereas 67% of the population in A6181111[81] were European. It was not reported in RADIANT-4[35] what proportion of the population was European.

To assess the 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. In October 2016, PHE[9] published the first documentation of the incidences of and survival in NETs, based on a cohort of 8726 neoplasms diagnosed in England in 2013–14.[9]

In the UK, NETs were described by PHE as having a 50 : 50 male-to-female ratio, with no obvious variation by geographical region or ethnicity.[9] In the three trials included here there was an average split for male-to-female ratio, with the percentage of males recruited ranging from 43%[35] to 58%.[34]

Public Health England[9] deemed the age at which NETs are most prevalent to be similar to that for all other malignant cancers. The age range of participants in the three trials appears to be younger (median age ranging between 56 and 65 years) than the age range of 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 to the UK.

Assessment of effectiveness: randomised controlled trial evidence

The following outcomes were assessed:

- PFS
- OS
- RRs: complete response, partial response, stable disease, progressive disease, ORR and tumour shrinkage
- AEs
- HRQoL.

Outcomes from randomised controlled trial evidence for pancreatic neuroendocrine tumours

Progression-free survival

In RADIANT-3[34] and A6181111[81] the primary outcome was PFS. Disease progression was defined by both trials as the time from randomisation to the first evidence of progression or death from any cause.[34,81] Both trials used the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0[107] to define disease progression. In RADIANT-3,[34] PFS was obtained from central radiology review and also local investigator review, whereas in A6181111[81] PFS was obtained only from local investigator review in the published paper.[81] PFS from the assessment of an independent review was available from the company submission.[33]

In RADIANT-3,[34] median PFS as assessed by central review was 11.4 months (95% CI 10.8 to 14.8 months) in the everolimus plus BSC arm and 5.4 months (95% CI 4.3 to 5.6 months) in 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 with placebo [hazard ratio (HR) 0.34, 95% CI 0.26 to 0.44; *Table 5*].

In the submission from Pfizer,[32] PFS from the assessment of an independent review was 12.6 months (95% CI 11.1 to 20.6 months) for sunitinib plus BSC and 5.8 months (95% CI 3.8 to 7.2 months) for placebo plus BSC. Sunitinib was associated with a 68% reduction in the risk of disease progression or death for people with pNETs compared with placebo (HR 0.32, 95% CI 0.18 to 0.55; see *Table 5*).

Locally assessed PFS in RADIANT-3[34] was 11.0 months (95% CI 8.4 to 13.9 months) in the everolimus plus BSC arm compared with 4.6 months (95% CI 3.1 to 5.4 months) 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 with placebo (HR 0.35, 95% CI 0.27 to 0.45; see *Table 5*). The A6181111[81] trial reported locally assessed PFS to be 11.4 months (95% CI 7.4 to 19.8 months) in the sunitinib plus BSC arm and 5.5 months (95% CI 3.6 to 7.4 months) 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 with placebo (HR 0.42, 95% CI 0.26 to 0.66; see *Table 5*). Both trials reported a shorter time for PFS in both arms for locally assessed PFS than for central/independent review.

Kaplan–Meier curves for progression free survival Kaplan–Meier curves are presented for RADIANT-3[34] (local and central review) and A6181111[81] (local review) in *Figures 2* and *3* respectively.

Overall survival

Both of the pNET studies (RADIANT-3[34] and A6181111[81]) reported some data relating to OS.

It was reported for RADIANT-3[34] that the OS data were 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'.[34] In addition, of the 203 people initially assigned to receive placebo in RADIANT-3,[34] 172 (85%) received open-label everolimus and 148 (73%) crossed over from placebo to everolimus following disease progression. By individuals crossing over from placebo to everolimus, the detection of a treatment-related survival benefit is confounded in ITT analysis. In RADIANT-3[34] the HR for OS was 1.05 (95% CI 0.71 to 1.55; see *Table 5*).

As it had not been reached, median OS was not reported for A6181111;[81] instead, survival probability at month 6 was reported. Survival was predicted to be higher in the sunitinib arm (92.6%, 95% CI 86.3% to 98.9%) than in the placebo arm (85.2%, 95% CI 77.1% to 93.3%). Survival was improved by 59% following sunitinib treatment compared with placebo (HR 0.41, 95% CI 0.19 to 0.89; see *Table 5*).

Both companies [Novartis[33] for everolimus (RADIANT-3[34]) and Pfizer[32] for sunitinib (A6181111[81])] presented updated OS data in their submission.

TABLE 5 Outcome results

Outcome	RADIANT-3[34]			A6181111[81]		
	Everolimus + BSC ($n = 207$)	Placebo + BSC ($n = 203$)	HR (95% CI)	Sunitinib + BSC ($n = 86$)	Placebo + BSC ($n = 85$)	HR (95% CI)
Tumour location	Pancreas			Pancreas		
PFS (central radiology review) (months), median (95% CI)	($n = 95/207$) 11.4 (10.8 to 14.8)	($n = 142/203$) 5.4 (4.3 to 5.6)	0.34 (0.26 to 0.44), $p < 0.001$	12.6 (11.1 to 20.6)	5.8 (3.8 to 7.2)	0.32 (0.18 to 0.55), $p < 0.001$
PFS (local review) (months), median (95% CI)	($n = 109/207$) 11.0 (8.4 to 13.9)	($n = 165/203$) 4.6 (3.1 to 5.4)	0.35 (0.27 to 0.45), $p < 0.001$	($n = 30/86$) 11.4 (7.4 to 19.8)	($n = 51/85$) 5.5 (3.6 to 7.4)	0.42 (0.26 to 0.66), $p < 0.001$
OS (months), median (95% CI)	Not reached	Not reached	1.05 (0.71 to 1.55),[a] $p = 0.59$	($n = 77/86$) 92.6 (86.3 to 98.9)[b]	($n = 64/85$) 85.2 (77.1 to 93.3)[b]	0.41 (0.19 to 0.89),[c] $p = 0.02$
Final OS (months), median (95% CI)	($n = 81/207$)[d] 44.0 (35.6 to 51.8)	($n = 73/203$)[d] 37.7 (29.1 to 45.8)	0.94 (0.73 to 1.20), $p = 0.30$	($n = 31/86$)[d] 38.6 (range 25.6–56.4)	($n = 27/85$)[d] 29.1 (range 16.4–36.8)	0.73 (0.50 to 1.06), $p = 0.094$
Complete response, *n/N* (%)	0/207 (0)	0/203 (0)		2/86 (2)	0/85	
Partial response, *n/N* (%)	10/207 (5)	4/203 (2)		6/86 (7)	0/85	
Stable disease, *n/N* (%)	151/207 (73)	103/203 (51)		54/86 (63)	51/85 (60)	
Progressive disease, *n/N* (%)	29/207 (14)	85/203 (42)		12/86 (14)	23/85 (27)	
Tumour shrinkage, *n/N* (%)	123/191[e] (64)	39/189[e] (21)		12/86 (14)	11/85 (13)	
ORR, *n/N* (%)	10/207 (5)	4/203 (2)	9.3 (3.2 to 15.4), $p = 0.007$	8/86 (9.3)[f]	0/85 (0)[f]	

a Median OS was not reached at the time of analysis.
b Survival probability (%) at month 6.
c Most individuals were in follow-up at the data cut-off point – HR for death.
d Calculated from the total number of participants minus the number of deaths.
e Data on 30 patients with lesions that could be evaluated in the everolimus arm and 42 patients with lesions that could be evaluated in the placebo arm were not included in the analysis for the following reasons: 14 in the everolimus arm and 28 in the placebo arm showed a change in the available target lesion that contradicted the overall response of progressive disease; one patent in the everolimus arm 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 arm and 14 in the placebo arm.
f Complete response combined with partial response.
Sources: Yao *et al.*[34,48] and company submission from Novartis[33] for RADIANT-3 data; Novartis; Pfizer submission[32] for A6181111.

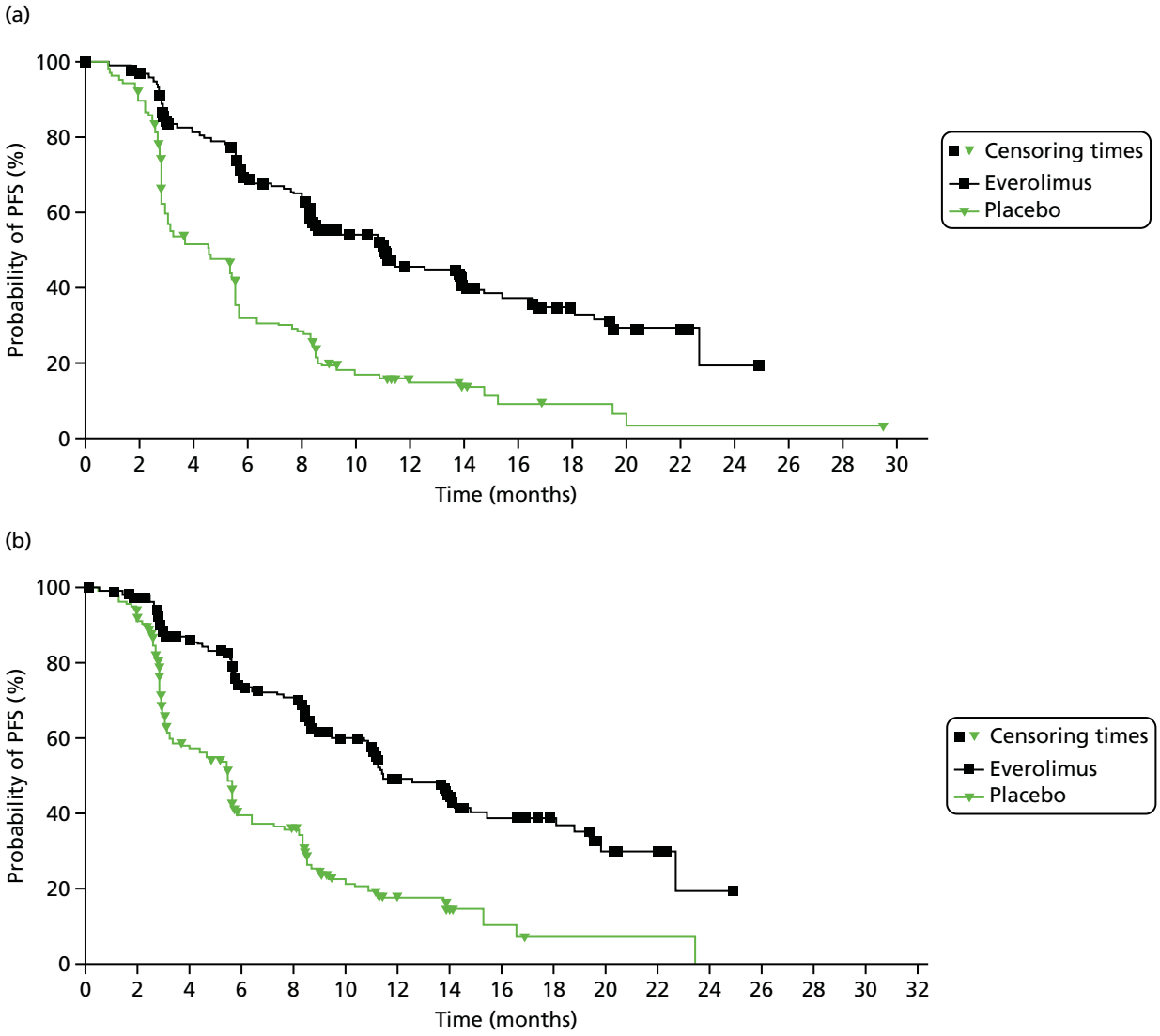


FIGURE 2 Kaplan–Meier plots for PFS in RADIANT-3.[34] (a) PFS assessed by local review – Kaplan–Meier medians: everolimus 11.0 months, placebo 4.6 months; HR 0.35 (95% CI 0.27 to 0.45; $p < 0.001$ by one-sided log-rank test); (b) central review – Kaplan–Meier median: everolimus 11.4 months, placebo 5.4 months; HR 0.34 (95% CI 0.26 to 0.44; $p < 0.001$ by one-sided log-rank test). Source: figure 4.3 (p. 39) of the Novartis submission.[33]

For everolimus, the initial data presented in Yao *et al.*[34] were analysed on 28 February 2010. In its submission, Novartis[33] presented interim OS analysis from 23 February 2011 and final OS analysis from 5 March 5. The final OS data are also available in the published paper by Yao *et al.*[48] 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 to 1.23). At the final OS time point, the median OS for everolimus plus BSC was 44.0 months (95% CI 35.6 to 51.8 months) and for placebo plus BSC was 37.68 months (95% CI 29.1 to 45.8 months), indicating an overall improvement in median OS of 6.3 months (HR 0.94, 95% CI 0.73 to 1.20; $p = 0.30$; see *Table 5*). In its submission, Novartis[33] commented that 'the results may be confounded due to the high level of treatment switching from placebo to everolimus and the receipt of subsequent anti-neoplastic therapies' (p. 43). Novartis accounted for the treatment switching from placebo to everolimus using the rank-preserving structural failure time (RPSFT) model. The RPSFT results are shown in *Appendix 7* (see *Table 49*) and suggest a 40% reduction in OS with everolimus compared with placebo (HR 0.60, 95% CI 0.09 to 3.95).

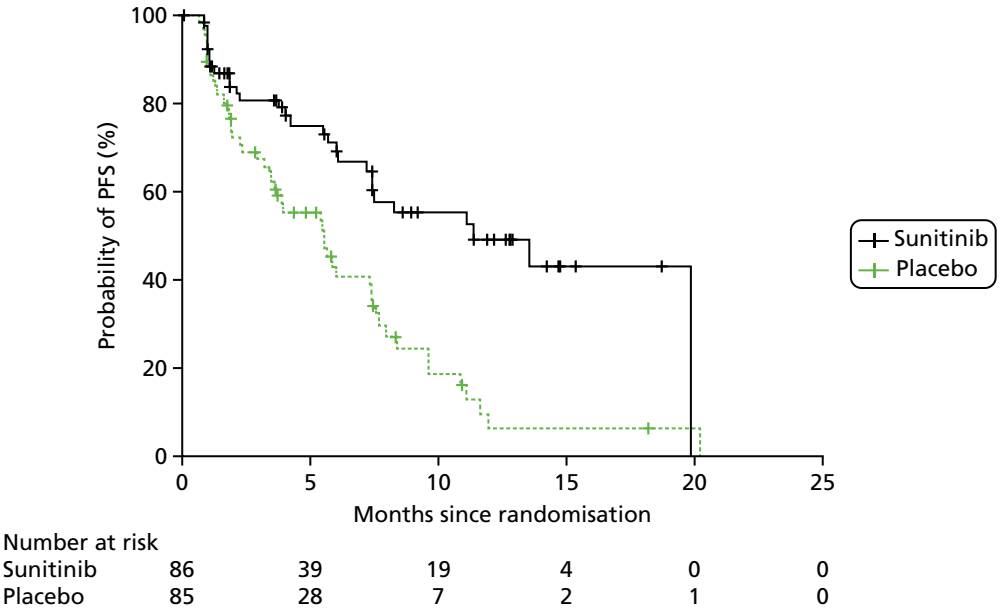


FIGURE 3 Kaplan–Meier plots for PFS (local review) in A6181111.[81] HR 0.42 (95% CI 0.26 to 0.66; $p < 0.001$). Note: ITT population. Source: figure 4 (p. 45) of the Pfizer submission.[32]

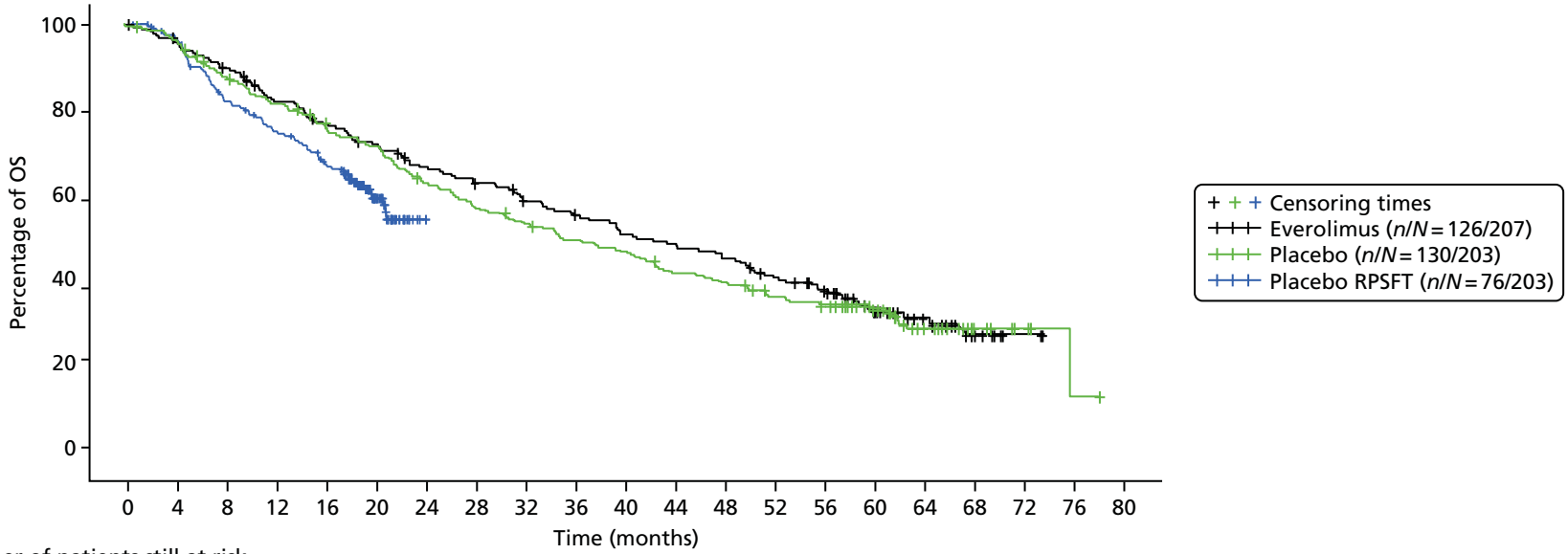
Additional OS data were also available in the submission from Pfizer[32] (pp. 45–9). Pfizer performed final OS analysis in A6181111[81] after 5 years of follow-up post study closure. From the ITT population, median OS was 38.6 months (range 25.6–56.4 months; $n = 55$ deaths) in the sunitinib plus BSC arm and 29.1 months (range 16.4–36.8 months; $n = 58$ deaths) in the placebo plus BSC arm, an improvement of 9.5 months (HR 0.73, 95% CI 0.50 to 1.06; $p = 0.094$; see *Table 5*). After accounting for treatment switching 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 as 13.2 months (range 11.3–16.5 months) (HR 0.34, 95% CI 0.14 to 1.28; $p = 0.094$) (it should be noted that the 95% CI was also reported as 0.15 to 1.28 in the company submission).

Kaplan–Meier curves for overall survival Kaplan–Meier curves for OS and RPSFT-adjusted OS were presented for both RADIANT-3[34] (see *Appendix 7*, *Figure 29*, and *Figure 4* respectively) and A6181111[81] (see *Appendix 7*, *Figure 30*, and *Figure 5* respectively).

Response rate

Both studies used RECIST version 1.0[107] to assess tumour response. Response rate was assessed by local investigators in RADIANT-3.[34] It was unclear whether response rate was assessed locally or centrally in A6181111;[81] however, as PFS was assessed only locally,[81] it might be assumed that the response rate was also assessed locally. In A618111,[81] clinical assessments were performed at screening, during weeks 5 and 9 and every 8 weeks thereafter, whenever progression was suspected and at the end of treatment or withdrawal from the study, whereas in RADIANT-3[34] assessments were performed at baseline and every 12 weeks thereafter.

Complete response, partial response, stable disease and progressive disease were reported by both studies (see *Table 5*). In RADIANT-3[34] tumour shrinkage was also reported, whereas in A6181111[81] the proportion of individuals who could not be evaluated and ORR were also reported (see *Table 5*). Complete response was achieved by only two individuals in A6181111[81] following treatment with sunitinib and BSC. Complete response was not achieved by any participants receiving placebo (both trials), nor following treatment with everolimus (RADIANT-3[34]). The numbers of individuals achieving a partial response or stable disease were higher in the treatment arms (everolimus and sunitinib) than in the placebo arms in both trials. Likewise, there were higher proportions of individuals with progressive disease in the placebo arms than in the treatment arms.



Number 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

FIGURE 4 Kaplan–Meier plot of the final OS analysis from RADIANT-3[34] adjusted using RPSFT (everolimus vs. placebo). Kaplan–Meier medians (95% CI): everolimus 44.02 (35.61 to 51.57) months, placebo 37.68 (29.14 to 45.77) months, placebo RPSFT (reconstructed placebo data as if the treatment crossover to open-label everolimus had not occurred): not available (20.61 to not available) months. Source: figure 4.7 (p. 45) of the Novartis submission.[33]

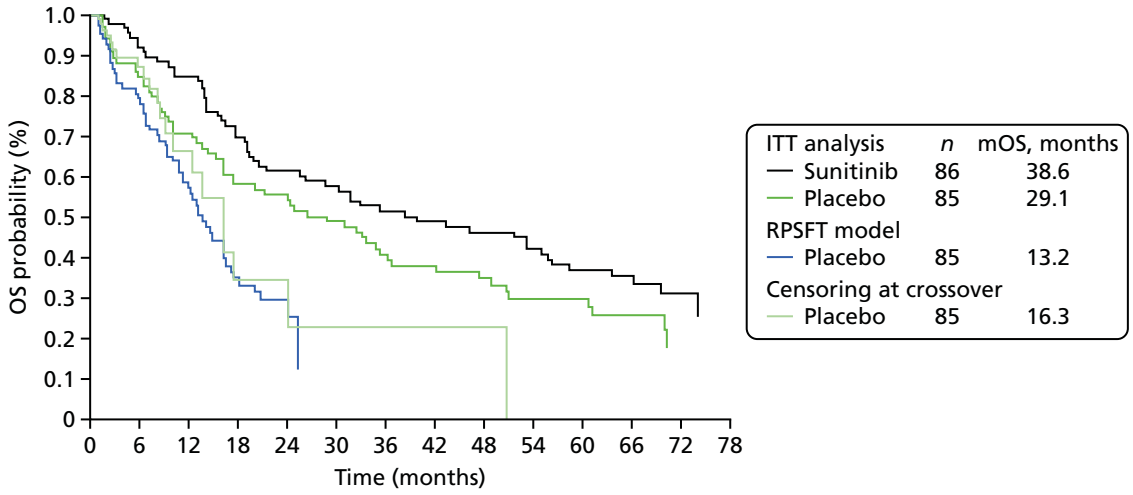


FIGURE 5 Kaplan–Meier estimates of OS from A6181111[81] with and without adjustment for treatment switching: final analysis, ITT population (sunitinib vs. placebo). mOS, median overall survival. Source: figure 6 (pp. 48–9) of the Pfizer submission.[32]

Novartis[33] reported in its submission that (confidential information has been removed). Novartis[33] also reported central investigator RRs and adjudicated central investigator RRs from RADIANT-3.[34]

Although relevant outcome data were reported, this information was designated as commercial-in-confidence.

Adverse events

In both RADIANT-3[34] and A6181111[81] AEs were assessed in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[108]

Treatment-related AEs (all grades and grades 3 and 4 combined) are reported for both trials in *Table 6*. In RADIANT-3,[34] AEs were reported that occurred in at least 10% of the safety population, whereas, in A6181111,[81] AEs were reported that occurred in > 15% of the safety population. AEs were more commonly reported following treatment with everolimus and sunitinib than following treatment with placebo. The five most common all-grade AEs following treatment with everolimus (RADIANT-3[34]) were stomatitis (64%), rashes (49%), diarrhoea (34%), fatigue (31%) and infections (23%). Following treatment with sunitinib (A6181111[81]), the five most common all-grade AEs were diarrhoea (59%), nausea (45%), vomiting (34%), asthenia (34%) and fatigue (32%).

Treatment-related AEs occurring in ≥ 20% of patients in RADIANT-3[34] at the latest cut-off (5 March) were presented in the company submission from Novartis[33] (see *Appendix 7*, *Table 50*). These AE rates are different (predominantly higher) from the rates published by Yao *et al.*[34] The AEs published in the paper by Yao *et al.*[34] were coded using the *Medical Dictionary for Regulatory Activities*, version 16.1.[109]

Health-related quality of life

IN A6181111[81] the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) version 3.0 was used to measure HRQoL. The EORTC QLQ-C30 was available for 73 out of 86 (85%) individuals treated with sunitinib and 71 out of 85 (84%) individuals treated with placebo. The EORTC QLQ-C30 includes one global health scale, 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 the 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 for diarrhoea (21.4-point difference; $p < 0.001$) and insomnia (7.8-point difference; $p = 0.04$), which were higher in the sunitinib arm than in the placebo arm.

TABLE 6 Adverse events: all grades and grades 3 + 4 only – pancreatic NETs

AE	All grades				Grades 3 + 4			
	[a]RADIANT-3[34]		[b,c]A6181111[81]		[a]RADIANT-3[34]		[b,c]A6181111[81]	
	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	12/204 (6)	4/203 (2)	5/83 (6)	9/82 (11)				
Treatment discontinuation	13/204 (6)	2/203 (1)	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)

continued

TABLE 6 Adverse events: all grades and grades 3 + 4 only – pancreatic NETs (*continued*)

AE	All grades				Grades 3 + 4			
	[a]RADIANT-3[34]		[b,c]A6181111[81]		[a]RADIANT-3[34]		[b,c]A6181111[81]	
	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* (%)
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 erythrodysaesthesia	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)

NR, not reported.

a Most common AE with a frequency of ≥ 10%.

b Most common AE with a frequency of > 15.

c Pfizer, in its submission,[32] reported AEs from its clinical study report,[110] in which incidence rates are lower than the incidence rates reported in Raymond *et al.*[81] These AEs are reported in *Appendix 7* (see *Table 52*).

More detailed results were available for HRQoL from Pfizer's submission.[32] The mean baseline global HRQoL score was 67.0 (95% CI 62.0 to 72.0) in the sunitinib plus BSC arm compared with 64.0 (95% CI 58.4 to 69.6) in the placebo plus BSC arm. Post-baseline scores were 62.44 for sunitinib and 61.28 for placebo. Overall differences in the EORTC QLQ-C30 for each item on the scale between the two arms are shown in *Table 53* (see *Appendix 7*). Changes in global HRQoL scores over time in the two arms are shown in *Figure 31* (see *Appendix 7*).

Subgroup analysis

Progression-free survival A6181111[81] reported Cox proportional hazards analysis of PFS for the subgroups tumour functioning, number of previous systemic regimes and previous use of SSAs (see *Appendix 7*, *Table 54*), whereas RADIANT-3[34] reported PFS for subgroups based on tumour grade, previous chemotherapy use and previous long-acting SSA use (see *Appendix 7*, *Table 55*).

Overall survival Novartis (A6181111[81]) also reported covariate analysis of OS using a Cox's proportional hazards model for previous use of SSAs and previous use of chemotherapy (see *Appendix 7*, *Table 56*).

Indirect treatment comparison: pancreatic neuroendocrine tumours

Two RCTs were used to compare everolimus with sunitinib: RADIANT-3[34] (everolimus plus BSC vs. placebo plus BSC) and A6181111[81] (sunitinib plus BSC vs. placebo plus BSC; *Figure 6*).

The Bucher method[41] was used to indirectly compare everolimus with sunitinib in individuals with pNETs for the following outcomes: PFS, OS, RR (not including complete response as there were zero responses in both treatment arms of RADIANT-3[34] and a zero response in the placebo arm of A6181111[81]) and various AEs. Because there were only two relevant trials for this synthesis we could not undertake any analyses for heterogeneity between the trials or inconsistency in the network. As we used only aggregate summary data, other more complex methods of indirect comparison were not considered [e.g. matched adjusted indirect comparisons (MAICs) using individual patient data]. After we had conducted these analyses, the AG requested individual patient data from the companies, and obtained data on the A6181111[81] trial, for the purposes informing de novo economic analysis. However, limited resources prevented us from updating the indirect comparison reported in this section using matched adjusted Bucher methods.

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

An assessment of the characteristics of the two trials (RADIANT-3[34] and A6181111[81]) suggested that they were comparable to allow an ITC. Both trials compared the active treatment with placebo plus BSC and included only participants with advanced or metastatic disease. A slightly higher proportion of participants used SSAs in RADIANT-3[34] (≈40%) than in A6181111[81] (≈28%); however, it was not thought that this would affect the relative effectiveness of the treatments.

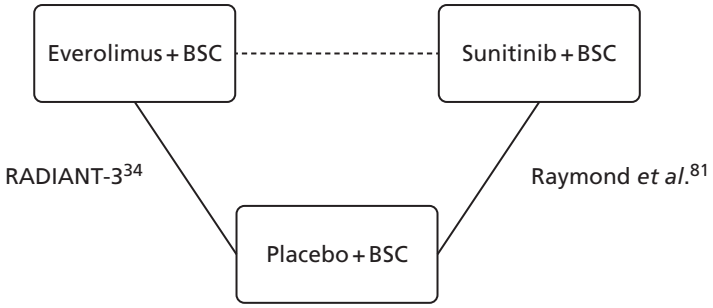


FIGURE 6 Diagram of the ITC for pNETs.

Treatment switching from the active arm to the placebo arm was permitted in both trials after disease progression. For OS, ITCs were conducted using ITT analyses and analyses adjusted for treatment switching (using the RPSFT method). Methods other than the RPSFT were considered by one of the companies A6181111,[81] including the inverse probability of censoring weights. The RPSFT method relies on the common treatment effect assumption, that is, that the effectiveness of targeted treatment is the same in patients in the targeted intervention arm and patients in the control arm who switch over to the targeted treatment on disease progression. This assumption was considered to pose less practical problems than the inverse probability of censoring weights method, which requires censoring of the data at the time of crossover and adjusting the remaining data using all relevant confounders affecting both the decision to switch and the outcome (PFS, OS).

Progression-free survival

Table 7 shows the evidence used from RADIANT-3[34] and A6181111[81] to inform the indirect comparison between everolimus and sunitinib for PFS assessed by local review. The analysis suggests that everolimus is associated with a 17% decrease in disease progression or death compared with sunitinib (HR 0.83, 95% CI 0.49 to 1.42). The 95% CI is wide and includes the null hypothesis that there is no difference in PFS effectiveness between everolimus and sunitinib.

Further data available from the company submissions[32,33] enabled an indirect comparison for PFS assessed by central radiology review to be carried out. The ITC between everolimus and sunitinib for PFS based on central radiology review suggests no difference between the treatments (see *Table 7*).

Overall survival

Table 7 shows the evidence used to inform the indirect comparison between everolimus and sunitinib for OS. The analysis suggests that there is a 2.56 times greater hazard of dying associated with treatment with everolimus than treatment with sunitinib, which is statistically significant. However, as these analyses are

TABLE 7 Hazard ratios (95% CIs) for outcomes following ITC in pNETs

	Everolimus + BSC vs. placebo + BSC		Sunitinib + BSC vs. placebo + BSC		Everolimus + BSC vs. sunitinib + BSC	
AE	HR (95% CI)	Data source	HR (95% CI)	Data source	HR (95% CI)	Data source
Disease progression or death (local radiology review)	0.35 (0.27 to 0.45)	RADIANT-3[34]	0.42 (0.26 to 0.66)	A6181111[81]	0.83 (0.49 to 1.42)	Calculated by AG
Disease progression or death (central radiology review)	0.34 (0.26 to 0.44)	RADIANT-3[34]	0.32 (0.18 to 0.55)	From Pfizer submission[32] (A6181111[81])	1.06 (0.57 to 1.97)	Calculated by AG
OS	1.05 (0.71 to 1.55)	RADIANT-3[34]	0.41 (0.19 to 0.89)	A6181111[81]	2.56 (1.08 to 6.08)	Calculated by AG
Final OS	0.94 (0.73 to 1.20)	RADIANT-3[34]	0.73 (0.50 to 1.06)	From Pfizer submission[32] (A6181111[81])	1.26 (0.82 to 2.02)	Calculated by AG
OS accounting for treatment switching	0.60 (0.09 to 3.95)	RADIANT-3[34]	0.34 (0.14 to 3.95)	From Pfizer submission[32] (A6181111[81])	1.76 (0.20 to 15.78)	Calculated by AG
Partial response	OR 2.53 (0.78 to 8.19)	RADIANT-3[34]	OR 13.81 (1.65 to 115.85)	A6181111[81]	OR 0.18 (0.02 to 2.08)	Calculated by AG
Stable disease	OR 2.62 (1.73 to 3.95)	RADIANT-3[34]	OR 1.13 (0.61 to 2.07)	A6181111[81]	OR 2.33 (1.11 to 4.86)	Calculated by AG
Progressive disease	OR 0.23 (0.14 to 0.37)	RADIANT-3[34]	OR 0.44 (0.20 to 0.95)	A6181111[81]	OR 0.52 (0.21 to 1.30)	Calculated by AG

based on published HRs from RADIANT-3[34] and A6181111,[81] which were not adjusted for treatment switching after disease progression, these results should not be relied on.

Final follow-up data for OS available from the company submissions[32,33] enabled an indirect comparison between everolimus and sunitinib for this outcome to be carried out, which suggests a lower hazard of death associated with sunitinib than with everolimus. However, the 95% CI includes the null effect, suggesting that this is not a statistically significant effect (see *Table 7*). This analysis does not account for the fact that approximately 70% of participants in the placebo plus BSC arms of these two trials switched to receive the active treatment after disease progression and so it should be interpreted with caution.

Overall survival accounting for treatment switching using the rank-preserving structural failure time method The indirect comparison of everolimus with sunitinib for OS in which the companies have used the RPSFT method to adjust for treatment switching suggests a lower hazard of death associated with sunitinib than with everolimus (as in the ITT analyses above); however, the 95% CI is very wide and includes the null effect (see *Table 7*).

Response rate

All ORs reported in *Table 7* for the intervention compared with placebo were calculated by the AG, based on the numbers of individuals reported to have experienced the different outcomes in RADIANT-3[34] and A6181111.[81] The ITCs for everolimus and sunitinib were based on the AG-calculated ORs from RADIANT-3[34] and A6181111.[81] The indirect analysis suggests that there is an 82% increase in the odds of a partial response in individuals treated with sunitinib compared with everolimus. However, sunitinib was associated with a 52% increase in the odds of progressive disease compared with everolimus. Everolimus was associated with a 2.3 times greater odds for disease stability than sunitinib. However, all of these ITCs were associated with wide 95% CIs, suggesting that there is little evidence of a difference in RRs between everolimus and sunitinib.

Adverse events

An ITC was completed only for those AEs for which data were available from both trials. All ORs reported in *Appendix 7* (see *Table 57* for all grades of AE and *Table 58* for grade 3/4 AEs) were calculated by the AG based on the numbers of participants experiencing these AEs reported in A6181111[81] and RADIANT-3.[34] For all grades of AE, the ITC suggests that there is a 19% increase in the odds of experiencing stomatitis and a 42% increase in the odds of experiencing nausea associated with sunitinib compared with everolimus. For the other AEs (all grades), the evidence suggests an increase in the odds of experiencing the AE with everolimus compared with sunitinib. However, except for decreased appetite, all of these ITCs 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 with sunitinib.

For the grade 3/4 AEs, the ITC could consider only seven AEs based on the data available from the two trials. The evidence suggests an increased odds of experiencing grade 3/4 stomatitis, fatigue, diarrhoea, nausea and thrombocytopenia with everolimus compared with sunitinib and an increased odds of experiencing decreased appetite and asthenia with sunitinib compared with everolimus. However, all of the ITCs 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.

Subgroup analysis

Subgroup analysis based on whether or not participants had previously received SSAs suggests very little difference in time to disease progression or death for everolimus compared with sunitinib (see *Appendix 7*, *Table 59*).

Outcomes from randomised controlled trial evidence for gastrointestinal and lung neuroendocrine tumours

Progression-free survival

In RADIANT-4,[35] PFS was the primary outcome, with disease progression defined as 'the time from randomisation to death or progression as per modified RECIST version 1.0 criteria'.[35] In RADIANT-4,[35] PFS was reported according to both central radiology review and local investigator review.

Median PFS in RADIANT-4,[35] assessed by central review, was 11.0 months (95% CI 9.2 to 13.3 months) in the everolimus plus BSC arm and 3.9 months (95% CI 3.6 to 7.4 months) in 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 with placebo (HR 0.48, 95% CI 0.35 to 0.67; *Table 8*).

In RADIANT-4,[35] locally assessed PFS was longer in duration in both arms than PFS assessed by central review, at 14.0 months (95% CI 11.2 to 17.7 months) in the everolimus plus BSC arm compared with 5.5 months (95% CI 3.7 to 7.4 months) 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 with placebo (HR 0.39, 95% CI 0.28 to 0.54; see *Table 8*).

The company submission from Novartis[33] made available secondary analysis of PFS (1 year and 2 days after the PFS analysis presented in the published paper[35]). Median PFS from central review was 14.39 months (95% CI 11.24 to 17.97 months) for the everolimus plus BSC arm and 5.45 months (95% CI 3.71 to 7.39 months) 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 with placebo (HR 0.41, 95% CI 0.30 to 0.56).

Kaplan–Meier curves were produced for PFS in RADIANT-4[35] from both central review and local review (*Figure 7*) with data from the primary cut-off point.

Overall survival

Interim OS analysis was carried out for RADIANT-4[35] once 70 deaths had been reached. Data were not sufficiently mature to provide an estimation of median OS. In individuals with lung and GI NETs, Kaplan–Meier estimates for OS at the 25th percentile – 25% of individuals having died – were 23.7 months (95% CI 17.6 to 27.3 months) for everolimus and 16.5 months (95% CI 9.0 to 21.0 months) for placebo. Everolimus was associated with a 36% improvement in OS for individuals with lung and GI NETs compared with placebo (HR 0.64, 95% CI 0.40 to 1.05; see *Table 8*).

In its company submission, Novartis[33] presented secondary analysis of OS from RADIANT-4,[35] which was performed 1 year and 2 days after the published analysis presented by Yao *et al.*[35] This analysis was based on 101 deaths, corresponding to a 52.9% information fraction, and the 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 compared with placebo (HR 0.73, 95% CI 0.48 to 1.11).

A Kaplan–Meier plot was produced for OS in RADIANT-4[35] at both the primary data cut-off point (see *Appendix 7*, *Figure 32*) and the secondary data cut-off point (*Figure 8*).

Response rate

In RADIANT-4,[35] a modified version of RECIST version 1.0[107] was used 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.

Complete response, partial response, stable disease, progressive disease, ORR, disease control rate and tumour shrinkage, following central radiology review, were reported (see *Table 8*). For all RR outcomes,

TABLE 8 Outcome results

Outcome	RADIANT-4[35]								
	Everolimus + BSC (*n* = 205)	Placebo + BSC (*n* = 97)	HR (95% CI)	Everolimus + BSC (*n* = 118)	Placebo + BSC (*n* = 57)	HR (95% CI)	Everolimus + BSC (*n* = 118)	Placebo + BSC (*n* = 57)	HR (95% CI)
Tumour location	Lung and GI			GI only			Lung only		
PFS (central radiology review) (months), median (95% CI)	(*n* = 113/205) 11.0 (9.2 to 13.3)	(*n* = 65/97) 3.9[a] (3.6 to 7.4)	0.48 (0.35 to 0.67), $p < 0.00001$	(*n* = NR/118) 13.1 (9.2 to 17.3)	(*n* = NR/57) 5.4 (3.6 to 9.3)	0.56 (0.37 to 0.84)	*n* = 42/63	*n* = 18/27	0.50 (0.28 to 0.88)
PFS (local review) (months), median (95% CI)	(*n* = 98/205) 14.0 (11.2 to 17.7)	(*n* = 70/97) 5.5 (3.7 to 7.4)	0.39 (0.28 to 0.54), $p < 0.00001$	NR	NR	NR	NR	NR	NR
OS (primary cut-off point) (months), median (95% CI)	(*n* = 42/205) 23.7 (17.6 to 27.3)[b]	(*n* = 28/97) 16.5 (9.0 to 21.0)[b]	0.64 (0.40 to 1.05),[c] $p = 0.037$	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
OS (secondary cut-off point) (months), median (95% CI)	(*n* = 66/205) 25.7 (18.4 to 28.6)	(*n* = 35/97) 16.5 (9.0 to 20.2)[d]	0.73 (0.48 to 1.11), $p = 0.071$	NR	NR	NR	NR	NR	NR
Complete response, *n/N* (%)	0	0		Confidential information has been removed	Confidential information has been removed	NR	Confidential information has been removed	Confidential information has been removed	NR
Partial response, *n/N* (%)	4/205 (2)	1/97 (1)				NR	Confidential information has been removed	Confidential information has been removed	NR
Stable disease, *n/N* (%)	165/205 (80)	62/97 (64)		Confidential information has been removed	Confidential information has been removed	NR	Confidential information has been removed	Confidential information has been removed	NR

continued

TABLE 8 Outcome results (*continued*)

Outcome	RADIANT-4[35]								
	Everolimus + BSC (*n* = 205)	Placebo + BSC (*n* = 97)	HR (95% CI)	Everolimus + BSC (*n* = 118)	Placebo + BSC (*n* = 57)	HR (95% CI)	Everolimus + BSC (*n* = 118)	Placebo + BSC (*n* = 57)	HR (95% CI)
Progressive disease, *n/N* (%)	19/205 (9)	26/97 (27)		Confidential information has been removed	Confidential information has been removed	NR	Confidential information has been removed	Confidential information has been removed	NR
Unknown response, *n/N* (%)				Confidential information has been removed	Confidential information has been removed	NR	Confidential information has been removed	Confidential information has been removed	NR
ORR, *n/N* (%) [95% CI]	4/205 (2) [0.5 to 4.9]	1/97 (1) [0.0 to 5.6]		NR	NR	NR	Confidential information has been removed	Confidential information has been removed	NR
Disease control rate, *n/N* (%) [95% CI]	169/205 (82.4) [76.5 to 87.4]	63/97 (64.9) [54.6 to 74.4]		Confidential information has been removed	Confidential information has been removed	NR	Confidential information has been removed	Confidential information has been removed	NR
Tumour shrinkage, *n/N* (%)	117/184 (64)	22/85 (26)		Confidential information has been removed	Confidential information has been removed		NR	NR	NR

NR, not reported.
a This was reported as both 3.0 and 3.9 months in the company submission;[33] in Yao *et al.*[35] it was reported as 3.9 months.
b Kaplan–Meier estimates for OS at the 25th percentile.
c Interim OS analysis from a total of 70 deaths.
d Reported in the company submission[33] as 2.18; assumed to be 20.18.
Source: Yao *et al.*[35] and Novartis[33] (RADIANT-4).

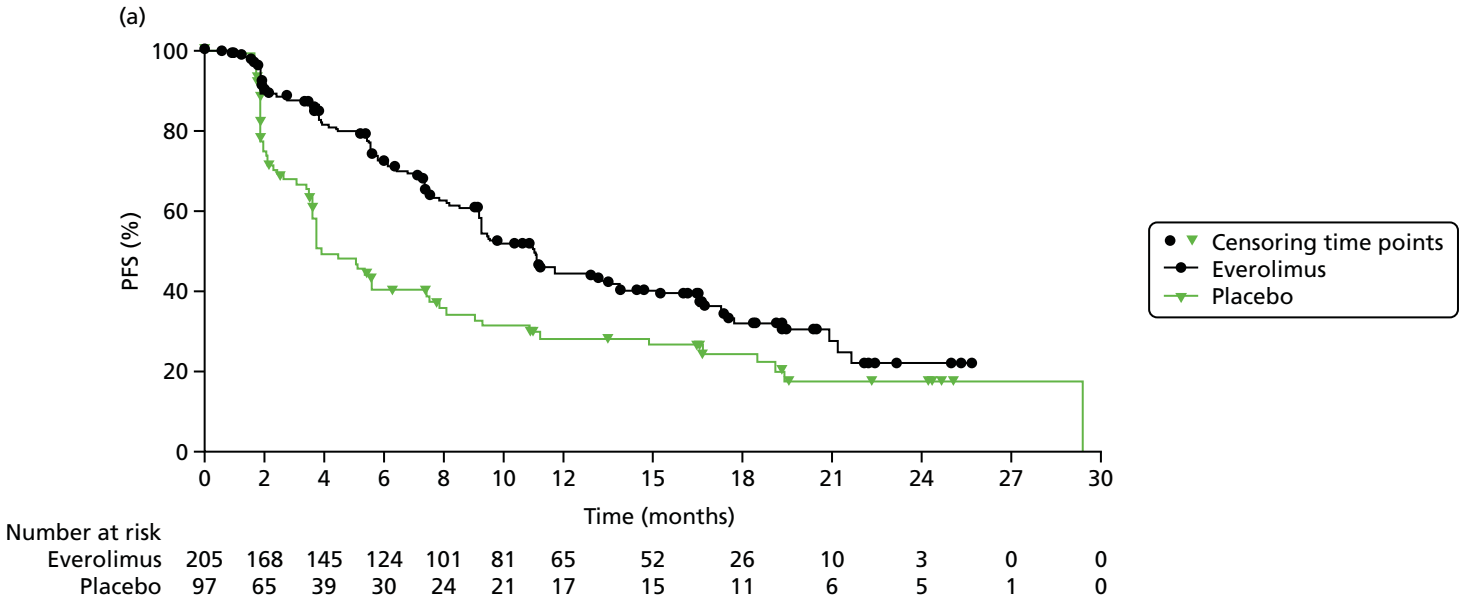


FIGURE 7 Kaplan–Meier plots for PFS (primary cut-off point) in RADIANT-4[35] (everolimus vs. placebo). (a) PFS assessed by central review – Kaplan–Meier medians: everolimus 11.0 (95% CI 9.2 to 13.3) months, placebo 3.9 (95% CI 3.6 to 7.4) months; HR 0.48 (95% CI 0.35 to 0.67; $p < 0.00001$ by stratified one-sided log-rank test); and (b) PFS assessed by local review – Kaplan–Meier medians: everolimus 14.0 (95% CI 11.2 to 17.7) months, placebo 5.5 (95% CI 3.7 to 7.4) months; HR 0.39 (95% CI 0.28 to 0.54; $p < 0.00001$ by stratified one-sided log-rank test). Source: figures 5.3 (p. 67) and 5.4 (p. 68) of the Novartis submission.[33] (*continued*)

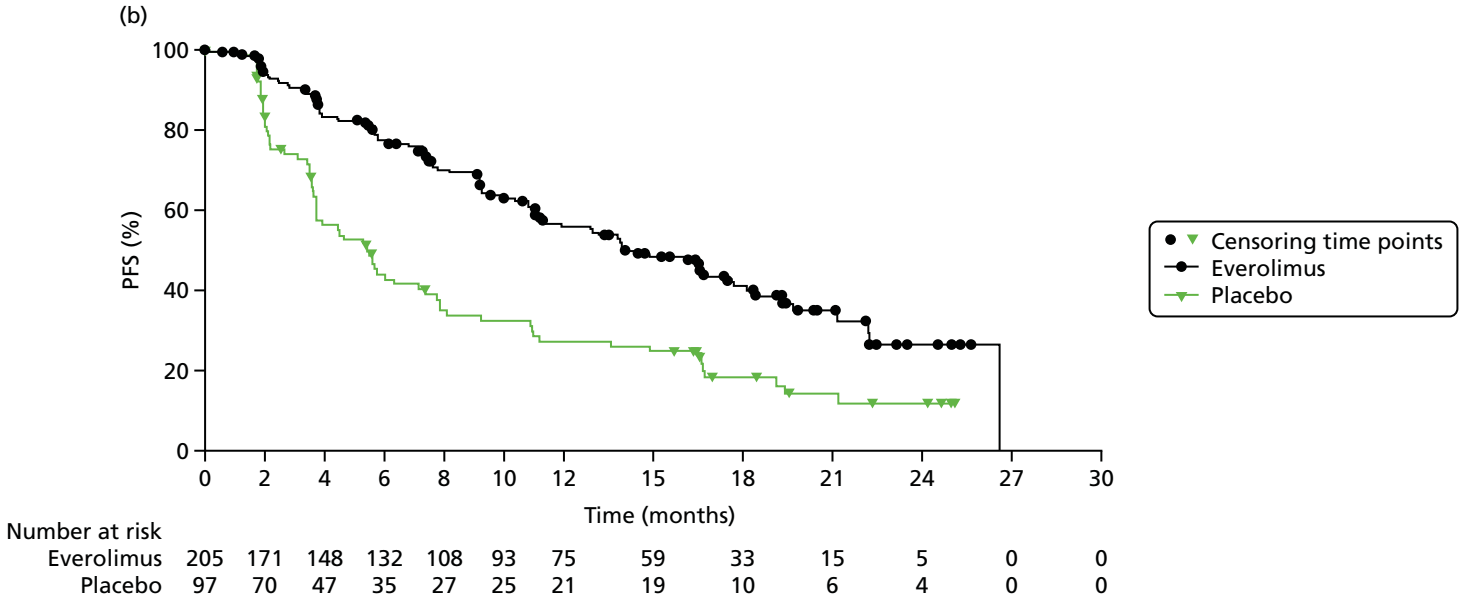
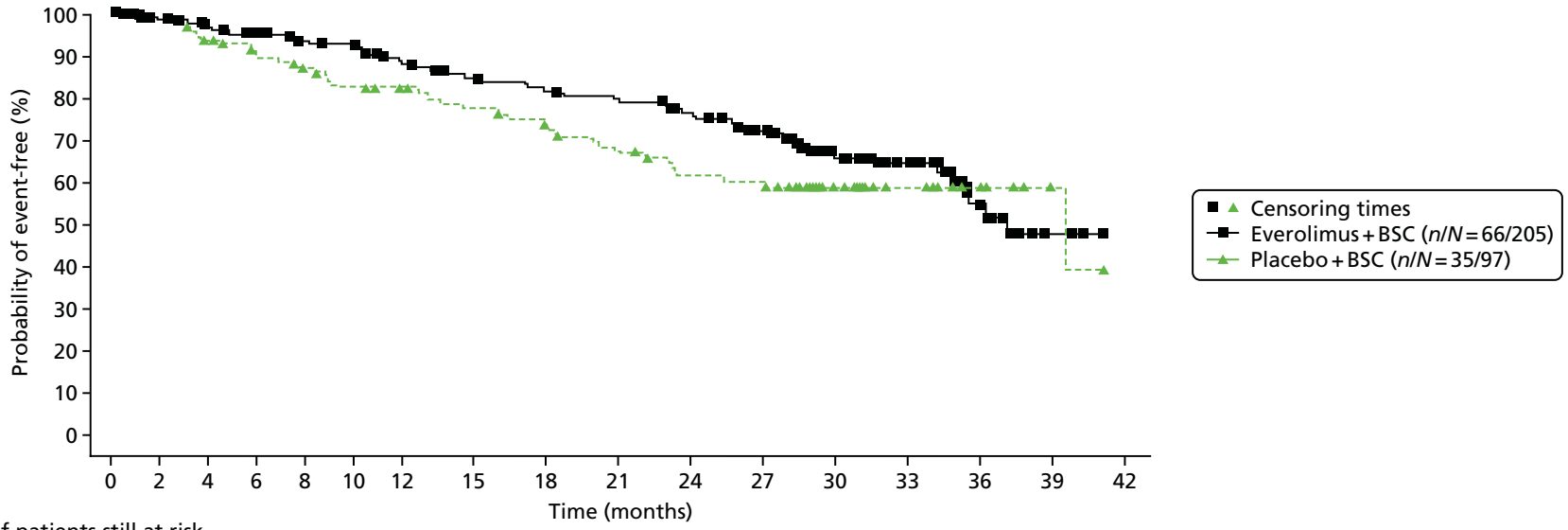


FIGURE 7 Kaplan–Meier plots for PFS (primary cut-off point) in RADIANT-4[35] (everolimus vs. placebo). (a) PFS assessed by central review – Kaplan–Meier medians: everolimus 11.0 (95% CI 9.2 to 13.3) months, placebo 3.9 (95% CI 3.6 to 7.4) months; HR 0.48 (95% CI 0.35 to 0.67; $p < 0.00001$ by stratified one-sided log-rank test); and (b) PFS assessed by local review – Kaplan–Meier medians: everolimus 14.0 (95% CI 11.2 to 17.7) months, placebo 5.5 (95% CI 3.7 to 7.4) months; HR 0.39 (95% CI 0.28 to 0.54; $p < 0.00001$ by stratified one-sided log-rank test). Source: figures 5.3 (p. 67) and 5.4 (p. 68) of the Novartis submission.[33]



Number 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	90	67	62	57	51	45	43	28	18	10	3	0

FIGURE 8 Kaplan–Meier plot for OS estimates in RADIANT-4:[35] secondary data cut-off point. Kaplan–Meier medians: everolimus + BSC 37.16 (95% CI 35.35 to not evaluable) months, placebo + BSC 39.56 (95% CI 23.46 to not evaluable) months; HR 0.73 (95% CI 0.48 to 1.11; log-rank *p*-value = 0.071). *p*-value is obtained from the stratified log-rank test. Source: figure 5.11 (p. 75) of the Novartis submission.[33]

treatment with everolimus for lung and GI NETs resulted in a favourable response compared with treatment with placebo, except for complete response, which was not achieved in either arm.

Adverse events

In RADIANT-4[35] AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[111] Treatment-related AEs (all grades and grades 3 and 4 combined), reported in ≥ 10% of the safety population, are presented in *Table 9*. AEs were more commonly reported following treatment with everolimus than following treatment with placebo. The five most common all-grade AEs following treatment with everolimus were stomatitis (63%), diarrhoea (31%), fatigue (31%), infections (29%) and rash (27%).

In its submission, Novartis[33] also reported AEs in patients regardless of the study drug relationship of the safety population. This table can be found in *Appendix 7* (see *Table 51*).

TABLE 9 Adverse events: lung and GI NETs

	Grades, *n*/*N* (%)			
	All		3 + 4	
AE	Everolimus + BSC	Placebo + BSC	Everolimus + BSC	Placebo + BSC
On-treatment deaths	7/202 (4)	3/98 (3)		
Treatment discontinuation	59/202 (29)[a]	7/98 (7)[b]		
Any AE	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)

a Reported as 24/202 (12%) in Yao *et al.*[35]
b Reported as 3/98 (3%) in Yao *et al.*[35]
Source: Novartis submission, table 5.8 (p. 82).[33]

Health-related quality of life

In its submission, Novartis[33] presented data on HRQoL from RADIANT-4[35] using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire.[112] The FACT-G is based on 27 items in four domains: physical well-being, social/family well-being, emotional well-being and functional well-being. Participant completion rates for the FACT-G questionnaire in RADIANT-4 are provided in *Table 60* (see *Appendix 7*).

Mean total score over time for the FACT-G questionnaire is presented in *Figure 34* (see *Appendix 7*). The HR for definitive deterioration of the total FACT-G score was (confidential information has been removed) *Figure 34* (see *Appendix 7*).

In its submission, Novartis[33] reported 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' (p. 77).

Subgroup analysis

Progression-free survival (based on central review) in RADIANT-4[35] was reported for everolimus compared with placebo based on treatment naivety, previous chemotherapy use and previous long-acting SSA use (see *Appendix 7*, *Table 61*). There is little evidence of a difference in PFS within subgroups.

Outcomes from randomised controlled trial evidence for gastrointestinal neuroendocrine tumours

Following a data request to Novartis, some of the outcomes from RADIANT-4[35] were provided for individuals with GI NETs alone and for individuals with lung NETs alone. The following sections report the baseline characteristics and outcomes provided by Novartis for individuals with GI NETs from RADIANT-4.[35] Tumour locations included under the GI umbrella were stomach, colon, rectum, appendix, caecum, ileum, duodenum, jejunum and small intestine.

Baseline characteristics

Baseline characteristics for individuals with GI NETs only are presented in *Table 62* (see *Appendix 7*).

Progression-free survival

Novartis provided data for PFS from the RADIANT-4[35] trial for patients with GI NETs. Median PFS assessed by central review was 13.1 months (95% CI 9.2 to 17.3 months) for the everolimus plus BSC arm and 5.4 months (95% CI 3.6 to 9.3 months) 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 with placebo (HR 0.56, 95% CI 0.37 to 0.84; see *Table 8*).

Overall survival

Novartis provided data for OS and Kaplan–Meier estimates of OS at the 25th percentile from the RADIANT-4[35] trial for patients with GI NETs (see *Table 8*).

Response rate

Novartis provided data for RRs from RADIANT-4[35] for patients with GI NETs (see *Table 8*).

For all RR outcomes, treatment with everolimus plus BSC for GI NETs resulted in a favourable response compared with treatment with placebo plus BSC.

Adverse events

Novartis provided data for AEs from RADAINT-4 for individuals with GI NETs. AEs were more commonly reported following treatment with everolimus than following treatment with placebo (*Table 10*). The five most common all-grade AEs following treatment with everolimus were stomatitis (71.8%), infections (59%), diarrhoea (44.4%), peripheral oedema (40.2%) and fatigue (36.8%).

TABLE 10 Adverse events: GI NETs

AE	All grades		Grades 3 + 4	
	Everolimus + BSC (%) (n = 117[a])	Placebo + BSC (%) (n = 58[a])	Everolimus + BSC (%) (n = 117[a])	Placebo + BSC (%) (n = 58[a])
Abdominal pain	19.7	27.6	5.1	6.9
Anaemia	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
Diarrhoea	44.4	43.1	11.1	3.4
Dysgeusia	22.2	5.2	0.9	0
Dyspnoea	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]	59.0	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 oedema	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[d]	71.8	22.4	7.7	0
Weight decrease	18.8	10.3	0	0

a In the GI subgroup, one patient randomised to the everolimus arm inadvertently received only placebo treatment because of a dispensation error on site and was therefore included in the placebo arm.
b Includes all infections.
c Includes pneumonitis and interstitial lung disease.
d Includes stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration.
Source: Novartis.[33]

Outcomes from randomised controlled trial evidence for lung neuroendocrine tumours

Following a data request to Novartis, some of the outcomes from RADIANT-4[35] were provided for individuals with lung NETs alone. The following sections report the baseline characteristics and outcomes provided by Novartis for the individuals with lung NETs only from RADIANT-4.[35]

Baseline characteristics

Baseline characteristics for individuals with lung NETs only are reported in *Table 63* (see *Appendix 7*).

Progression-free survival

Novartis provided data for PFS from the RADIANT-4[35] trial for patients with lung NETs. There were 42 progression events for 63 individuals assigned to everolimus plus BSC compared with 18 events for 27 individuals in 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 with placebo (HR 0.50, 95% CI 0.28 to 0.88; see *Table 8*).

Overall survival

Novartis provided data for OS from the RADIANT-4[35] trial for patients with lung NETs (see *Table 8*). HRs were obtained from the unstratified Cox model.

Response rate

Novartis provided data for RRs from RADIANT-4[35] for patients with lung NETs (see *Table 8*).

For all RR outcomes, treatment with everolimus plus BSC for lung NETs resulted in a favourable response compared with treatment with placebo plus BSC.

Adverse events

Novartis provided data for AEs from RADIANT-4 for individuals with lung NETs. AEs were more commonly reported following treatment with everolimus than following treatment with placebo (see *Appendix 7*, *Table 64*). The five most common all-grade AEs following treatment with everolimus (RADIANT-4[35]) (confidential information has been removed).

Summary

Summary of the 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 reported in 56 citations (six full texts, one errata and 49 conference abstracts).
- The risk of bias within the trials was low and was found to be the same within the three studies with regard to selection, performance, detection, attrition and reporting bias.

Pancreatic neuroendocrine tumours

- Two trials provided evidence on the effectiveness of everolimus (RADIANT-332) and sunitinib (A618111145) in the treatment of pNETs. Both interventions were compared with placebo. BSC was also given in both the intervention arm and the placebo arm in both trials.
- Median PFS, assessed by central review, was 11.4 months for everolimus[34] and 12.6 months for sunitinib[81] compared with 5.4 months and 5.8 months, respectively, in the placebo arms of the trials. Locally assessed PFS was also reported.
- In the first publication for each trial, median OS was not reached or data were immature. Longer follow-up data were available from company submissions.[32,33] Median OS was 44.0 months for everolimus[34] and 38.6 months for sunitinib[81] compared with 37.7 months and 29.1 months, respectively, in the placebo arms. Treatment switching from the placebo arm to the treatment arm (73% in RADIANT-3[34] and 69% in A6181111[81]) significantly compromises the OS results.
- Tumour response rates were assessed locally for RADIANT-3[34] and were assumed to be locally assessed in A6181111.[81] Complete response was achieved by only two individuals receiving sunitinib;[81] complete response was not achieved in any of the other arms. Both trials reported higher rates for partial response and stable disease and lower rates for progressive disease in the treatment arms (everolimus and sunitinib) than in the placebo arms.
- Overall, AEs were more commonly reported following treatment with everolimus and sunitinib than following with placebo. The five most common all-grade AEs following treatment with everolimus[34] were stomatitis (64%), rashes (49%), diarrhoea (34%), fatigue (31%) and infections (23%). Following treatment with sunitinib,[81] the five most common all-grade AEs were diarrhoea (59%), nausea (45%), vomiting (34%), asthenia (34%) and fatigue (32%).
- Health-related quality of life was assessed in A6181111[81] (sunitinib) using the EORTC QLQ-C30. There were no overall differences between study groups, except for diarrhoea (21.4-point difference) and insomnia (7.8-point difference), which occurred with a higher frequency in the sunitinib arm than in the placebo arm. HRQoL data were not collected in RADIANT-3.[34]

Indirect treatment comparison: pancreatic neuroendocrine tumours

- RADIANT-3[34] and A6181111[81] were used to compare everolimus with sunitinib in an ITC using the Bucher method.
- The ITC for PFS from central radiology review suggests no difference between the treatments (HR 1.06, 95% CI 0.57 to 1.97).
- The ITC for PFS from local review suggests that everolimus is associated with a 17% decrease in disease progression or death compared with sunitinib (HR 0.83, 95% CI 0.49 to 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 a 2.56 times greater hazard of dying associated with treatment with everolimus than with sunitinib, which is statistically significant. However, as these analyses are based on published HRs from RADIANT-3[34] and A6181111,[81] which were not adjusted for treatment switching after disease progression, these results should not be relied on.
- The ITC for OS, in which the companies have used the RPSFT method to adjust for treatment switching, suggests a lower hazard of death associated with sunitinib than with everolimus (HR 1.76, 95% CI 0.20 to 15.78). However, the 95% CI is very wide and includes the null effect.
- For RRs, the ITC suggests that there is an 82% increase in the odds of a partial response in individuals treated with sunitinib compared with individuals treated with everolimus. However, sunitinib was associated with a 52% increase in the odds of progressive disease compared with everolimus. Everolimus was associated with a 2.3 times greater odds of disease stability than sunitinib. However, all of these ITCs were associated with wide 95% CIs, suggesting that there is little evidence of a difference in RRs between everolimus and sunitinib.
- An ITC was completed only for those AEs for which 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 with everolimus. For rash, fatigue, diarrhoea, dysguesia, epistaxis, loss of weight, thrombocytopenia, decrease in appetite, headache, vomiting and asthenia (all grades), the evidence suggests an increase in the odds of experiencing the AE with everolimus compared with sunitinib. However, except for decreased appetite, all of these ITCs 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 with sunitinib. For the grade 3/4 AEs, the ITC could consider only seven AEs based on the data that were available from the two trials. The evidence suggests an increased odds of experiencing grade 3/4 stomatitis, fatigue, diarrhoea, nausea and thrombocytopenia with everolimus compared with sunitinib and an increased odds of experiencing decreased appetite and asthenia with sunitinib compared with everolimus. However, all of the ITCs 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 and lung neuroendocrine tumours

- One trial, RADIANT-4,[35] provided evidence for the effectiveness of everolimus for treating GI and lung NETs. The intervention was compared with placebo and both arms received BSC.
- Median PFS for RADIANT-4[35], assessed by central review, was 11.0 months for treatment with everolimus and 3.9 months for treatment with placebo. Locally assessed PFS was also reported.
- Median OS was not reached. However, Kaplan–Meier estimates for OS at the 25th percentile were 23.7 months (95% CI 17.6 to 27.3 months) in the everolimus arm and 16.5 months (95% CI 9.0 to 21.0 months) in the placebo arm. In longer follow-up analysis of OS from the Novartis submission, OS was 25.7 months in the everolimus arm compared with 16.5 months in the placebo arm.[33] Treatment switching was not permitted in RADIANT-4.[35]

- Tumour RRs were assessed by central radiology review. No arm achieved a complete response. Individuals receiving everolimus had a favourable response for partial disease, stable disease, progressive disease and tumour shrinkage compared with those in the placebo arm.
- Overall, AEs were more commonly reported following treatment with everolimus than following treatment with placebo. The five most common all-grade AEs following treatment with everolimus[35] were stomatitis (63%), diarrhoea (31%), fatigue (31%), infections (29%) and rash (27%).
- HRQoL was reported in the company submission from Novartis[33] for RADIANT-4. The FACT-G questionnaire was used. Confidential information has been removed.

Gastrointestinal neuroendocrine tumours

- Following a data request from the AG to Novartis, results from RADIANT-4[35] were provided for individuals recruited with only GI NETs ($n = 118$ for everolimus vs. $n = 57$ for placebo).[33]
- Median PFS for participants with GI NETs from RADIANT-4[35] was 13.1 months for everolimus and 5.4 months for placebo.
- Median OS estimated from a Kaplan–Meier curve at the 25th percentile was (confidential information has been removed) in the everolimus arm compared with (confidential information has been removed) in the placebo arm.
- Confidential information has been removed. Individuals receiving everolimus (confidential information has been removed) response for stable disease, progressive disease and tumour shrinkage compared with those in the placebo arm.
- Overall, AEs were more commonly reported following treatment with everolimus than following treatment with placebo for individuals with GI NETs. The five most common all-grade AEs following treatment with everolimus were stomatitis (71.8%), infections (59%), diarrhoea (44.4%), peripheral oedema (40.2%) and fatigue (36.8%).

Lung neuroendocrine tumours

- Following a data request from the AG to Novartis, results from RADIANT-4[35] were provided for individuals recruited with only lung NETs ($n = 62$ for everolimus vs. $n = 27$ for placebo).
- There were (confidential information has been removed) assigned to everolimus compared with (confidential information has been removed) for the placebo arm. Everolimus was associated with a (confidential information has been removed) in the risk of disease progression compared with placebo.
- There were (confidential information has been removed) assigned to everolimus arm compared with (confidential information has been removed) for the placebo arm. Survival was (confidential information has been removed) following everolimus treatment compared with placebo.
- Rates of stable disease and progressive disease (confidential information has been removed) with everolimus.
- Overall, AEs were more commonly reported following treatment with everolimus than following treatment with placebo. The five most common all-grade AEs following treatment with everolimus[35] (confidential information has been removed).

Summary of the non-randomised 177Lu-DOTATATE studies

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

Chapter 5 Critical appraisal of the company submissions

Two companies submitted economic models to NICE: AAA and Novartis. Novartis submitted an economic evaluation in patients with pNETs and, separately, in patients with GI and lung NETs. AAA presented an economic evaluation in pNETs and another in midgut carcinoid tumours. The background safety and efficacy evidence supporting the companies' model submissions detailed model characteristics, and results are presented in *Appendix 8*. Pfizer did not submit a cost-effectiveness model; it stated that:

> *Previous technology appraisals (SMC [Scottish Medicines Consortium] and AWMSG [All Wales Medicines Strategy Group]) have challenged the data limitations relating to uncertainty associated with modelling the clinical OS benefits of sunitinib in PNET due to the extensive treatment switching 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*[32]

Novartis submission[33]

Economic evaluation of everolimus in pancreatic neuroendocrine tumours

Overview

In pNETs, the company evaluated everolimus plus BSC compared with sunitinib plus BSC. The company based this analysis on an ITC of the results of RADIANT-3,[34] a Phase III pivotal trial of 10 mg of everolimus once daily plus BSC compared with placebo plus BSC, and A6181111,[81] a Phase III RCT of sunitinib (confidential information has been removed) plus BSC compared with placebo plus BSC. These RCTs were the only available relevant evidence identified from a systematic review of RCTs and non-RCTs of everolimus, sunitinib and 177Lu-DOTATATE for treating patients with advanced, metastatic or inoperable pNETs, and 177Lu-DOTATATE for treating advanced, metastatic or unresectable GEP NETs. The company did not provide the reasons for omitting BSC from the analysis, for which head-to-head trial data were available compared with each of the targeted treatments from RADIANT-3[34] and A6181111.[81]

The ITC of everolimus and sunitinib found no statistically significant differences in PFS and OS outcomes, with estimated differences having wide CIs. The company found that everolimus was associated with a lower frequency of grade 3/4 AEs and a different tolerability profile (see *Chapter 4*, *Results*).

Everolimus was found to dominate sunitinib. It generated lower discounted costs and more discounted quality-adjusted life-years (QALYs), which were calculated on the assumption that the two treatments produced the same mean PFS and OS. As 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 HRQoL descriptors (vignettes) of stable disease in general and the impact of treatment-specific AEs, as opposed to HRQoL outcomes in actual patients.

Economic evaluation by the company

Novartis evaluated the costs and health benefits of everolimus plus BSC relative to sunitinib plus BSC in advanced, well-differentiated or moderately differentiated pNETs patients with progressive disease from a NHS or Personal Social Services (PSS) perspective. A semi-Markov model of monthly health state cycles experienced by a patient cohort was used to synthesise 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 ITC of PFS, OS, concomitant SSA use, treatment duration and grade 3/4 AEs in the A6181111[81] trial of sunitinib and the RADIANT-3[34] trial of everolimus (see *Chapter 4*, *Indirect treatment comparison: pancreatic neuroendocrine tumours*, and *Appendix 8*, *Novartis*). The model consisted of three health states, representing stable disease, disease progression and death, each associated with different costs and utilities, as illustrated in *Figure 9*.

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 the PFS rates was used as the estimator for the proportion of patients in the progressive disease phase.

The resource utilisation data were obtained from a survey of 32 clinical experts in the UK.[113] 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, as no HRQoL or utility data were recorded in RADIANT-3.[34] Sensitivity analyses adopted alternative values for the sunitinib arm derived from HRQoL outcomes measured in the A6181111[81] trial of sunitinib compared with placebo.

The model accounts for the costs of subsequent treatments after disease progression by including a fixed cost of radiotherapy, chemoembolisation and chemotherapy in the first cycle of the progressive disease state of the model. Similarly, a fixed cost of end-of-life care is included on transition to the death state.

Results

In the advanced pNETs patients with progressive disease, the base-case analysis found a life expectancy of 4.17 years over a 20-year time horizon after the start of treatment with everolimus or sunitinib in patients with a median age of 58 years (as in the everolimus arm of RADIANT-3[34]). Everolimus produced more QALYs than sunitinib (2.73 vs. 2.71, a difference of 0.02 QALYs discounted at 3.5%) (*Table 11*). As this analysis assumed equal PFS and OS outcomes between the two treatments, the QALY difference was purely the result of the impact on HRQoL of treatment differences in AEs.

Everolimus was associated with discounted health-care costs of £36,933 per patient, that is, an overall saving of £1636 relative to sunitinib, which had discounted health-care costs of £38,569 per patient. With a (confidential information has been removed) Patient Access Scheme (PAS) discount applied to the list price of everolimus and reimbursement of the first cycle of sunitinib, the total cost to the NHS of using

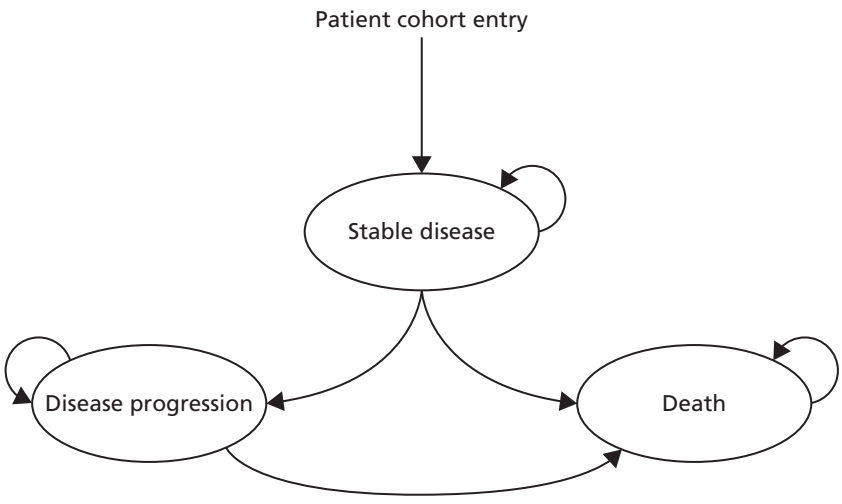


FIGURE 9 Model structure in pNETs. Source: reproduced from figure 6.1 of the Novartis submission.[33]

TABLE 11 Main results of the Novartis model submission for pNETs at current list prices (2015[114])

Treatment	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	1636	

ICER, incremental cost-effectiveness ratio.

everolimus was reduced to (confidential information has been removed) and of using sunitinib was reduced to £36,247, that is, a saving of (confidential information has been removed) per patient for everolimus. As PFS, OS and costs in the progressive disease state were the same across the two arms, the cost differences were the result of differences in the drug acquisition costs of the targeted therapies in the stable disease period. As a result, everolimus was found to be dominant over sunitinib.

Novartis [table 6.18 (p. 112) of the Novartis submission[33]] reports that the total cumulative time spent per patient in the stable disease health state is 0.899 years under everolimus and 0.878 years under sunitinib. This must be an error as the base-case model assumes equal PFS outcomes for both treatments and there is no accounting in the model for differences in grade 5 AEs (deaths).

Probabilistic sensitivity analyses (PSAs) of drug acquisition prices unadjusted for the PAS produced a mean cost saving estimate for everolimus of £2055 per patient and a QALY gain of 0.002. With the PAS, the mean cost saving with everolimus was increased to (confidential information has been removed). This result suggests that the main determining factor is costs, as the mean QALY difference of 0.002 is not considered to be clinically significant.[115] However, these PSAs by Novartis were not adequately performed as the PFS and OS and SSA use (set at zero) parameter values were 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 (confidential information has been removed) probability of everolimus being cost-effective when compared to sunitinib at their respective PAS prices' (Novartis submission, p. 114[33]) 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 in terms of the incremental cost-effectiveness ratio (ICER) is 'so marginal, it does not materially affect the model results' (Novartis submission, p. 116[33]). Similarly, positive rates of SSA use, use of PFS data assessed by local experts compared with centrally assessed data and choice of PFS distribution had a marginal impact. In scenario analyses, exploring the effects of changing clinical effectiveness, utility and cost parameter values, as well as structural assumptions about OS and PFS outcomes, everolimus was still dominant, except for the case in which the relative treatment effect on PFS was set to favour sunitinib according to estimates derived from the Bucher indirect comparison (HR: PFS 0.93, OS 0.72). In this instance, everolimus had lower costs and produced fewer QALYs than sunitinib and the ICER was found to be (confidential information has been removed). The interpretation of the ICER in this case reverses, that is, the higher the value the more cost-effective everolimus is; it may be reasonable to consider (confidential information has been removed) in this patient population. It must be noted that this is the result of everolimus saving £5963 (confidential information has been removed) at the expense of having 0.685 fewer QALYs per patient [table 6.23 (p. 117) of the Novartis submission[33]].

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 progressive disease and stable disease phases. Nevertheless, given the possibly clinically insignificant utility differences discussed earlier, or that Novartis may produce fewer

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.

Strengths and weaknesses of Novartis's evaluation of pancreatic neuroendocrine tumours

The model by Novartis follows the NICE reference case[37] (see *Appendix 9*) except for one major aspect, which was the lack of inclusion of BSC as a comparator. This omission is at odds with the fact that 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 justification given by Novartis for omitting the BSC-only treatment option in its 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 on disease progression.

This was a complex area to analyse because of 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, for which the quantities used in the model were based on expert opinion. Another major uncertainty in the evidence base is the lack of HRQoL data 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 AE outcomes complemented by clinical experts' views of quality of life in stable disease under different AEs.

A critical feature of the OS data used in the Novartis economic model was the adjustment for crossover from placebo to active treatment in the RCT data. In particular, the method used for such adjustment, the RPSFT model, 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 crossover, such as inverse probability of censoring weight[116] and censoring at crossover,[117] they are clearly inferior as the majority of cases of crossover in RADIANT-3[34] and A6181111[81] occurred following study termination, making the key assumption underlying these methods, either that crossover is 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 to be outdated on three fronts. First, Novartis estimated relative OS effectiveness using an indirect comparison (Bucher method) of placebo-adjusted HRs that corrected for crossover from the placebo to the active treatment arms in the two RCTs used in the indirect comparison. The crossover-adjusted OS HR estimate used for sunitinib compared with placebo in the indirect comparison by Novartis is lower than that in the final published results for OS for A6181111.[81] With these new data, we obtained a crossover-adjusted OS HR for everolimus compared with sunitinib of 0.51, instead of the OS HR of 0.72 derived by Novartis. Second, our updated searches of the literature conducted in September 2016 identified a forthcoming publication[48] 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 indirect comparison for the sunitinib and placebo arms were different from the corresponding data submitted by Pfizer[32] to NICE. When the Pfizer data are used instead, the pooled AE OR estimated by Novartis as 4.47 changes to 1.37, thus reducing the differences in costs and disutilities of AEs between sunitinib and everolimus.

The way that Novartis synthesised the effectiveness and safety evidence in its 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 CIs around the point estimates of relative effectiveness. This practice is clearly inadequate because it misrepresents the level of uncertainty in the data as evidence of lack of effect. This issue is made more serious in view of the direction and extent of possible bias resulting from 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 the same treatment duration for everolimus and sunitinib. As pointed out earlier, the mean number of treatment cycles of sunitinib is likely to be lower than that of everolimus, based on the Pfizer data[32] submitted to NICE and comparison of median treatment durations in the main publications of A6181111[81] and RADIANT-3.[34] On the other hand, Novartis did not account for the fact that the mean PFS (area under the Kaplan–Meier curve) in the placebo arm of the A6181111[81] trial of sunitinib was lower than the mean PFS of the placebo arm of the RADIANT-3[34] 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[34] and PFS of the placebo arm of A6181111.[81]

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 who were 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 were 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 currently 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. The disutility of AEs is unlikely to be a significant factor in that choice and determining its importance is hampered by the lack of data of sufficient quality for meaningful assessment.

Economic evaluation of everolimus in gastrointestinal and lung neuroendocrine tumours

Overview

The economic evaluation by Novartis of everolimus plus BSC compared with BSC alone in advanced, progressive, well-differentiated, non-functioning GI and lung NETs was based on the effectiveness, safety and quality of life evidence reported from a Phase III RCT, RADIANT-4.[35] As in its economic evaluation in pNETs, discussed in the previous section, Novartis relied on data from a resource use survey,[113] which was validated for the UK.

Economic evaluation by the company

Novartis evaluated the cost-effectiveness of 10 mg of everolimus daily plus BSC relative to BSC alone in patients with advanced, progressive, well-differentiated, non-functional GI and lung NETs. This evaluation 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[35] Phase III trial of everolimus plus BSC compared with placebo plus BSC. 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 was the same as that described in the Novartis pNETs model and that used by Ayyagari *et al.*[118] in GI locations (see *Figure 9*).

Results

Novartis reports that the life expectancy over a 30-year period for patients with advanced, progressive, well-differentiated, non-functional GI and lung NETs is 5.79 life-years for 10 mg of everolimus daily plus BSC compared with 4.77 life-years for BSC alone (*Table 12*). The respective total discounted costs are expected to be £59,720 and £25,817 and the total QALYs produced are 4.28 and 3.51. This results in an ICER of £43,642 per QALY gained for everolimus plus BSC compared with BSC alone. Under the (confidential information has been removed) PAS discount on the everolimus price, the cost per QALY gained with everolimus would be reduced to (confidential information has been removed). In total, 71% of the QALY gain for everolimus plus BSC compared with BSC takes place in the stable disease state and the share of the cost falling during the stable disease state is 98% at list prices. The costs of active initial treatment with everolimus and BSC costs represent 79% and 8%, respectively, of the total incremental costs of treatment with everolimus plus BSC. The mean PSA ICER for everolimus plus BSC compared with BSC was £45,385 without the PAS and (confidential information has been removed) with the PAS.

Univariate deterministic sensitivity analyses found that the ICER was most sensitive to the choice of distribution for extrapolating OS. The ICER varied from £39,571 to £59,832 with different OS distributions and (confidential information has been removed) with the PAS. When treatment-specific utility values were applied, the ICER increased to £56,385 and (confidential information has been removed) under the PAS. The results were also sensitive to the RDI. Novartis also reports how extending the lifetime horizon and extrapolating outcomes beyond the trial period improved the cost-effectiveness of everolimus.

From the results reported by Novartis it is evident that, in the analysis of the PAS, the (confidential information has been removed) PAS discount was applied only to everolimus given as initial treatment, not as subsequent treatment. In principle, the discount should have been applied to subsequent treatment too.

The company concluded that the ICER (confidential information has been removed). 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, with there being approximately 936 patients in England across the two indications (pNETs and GI/lung) [table 3.1 (p. 27) of the Novartis submission[33]].

Strengths and weaknesses of Novartis's evaluation of gastrointestinal and lung neuroendocrine tumours

The economic evaluation by Novartis of everolimus in GI and lung NET patients relies on the quality of RADIANT-4,[35] which was the source of the effectiveness, AE 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 or not the differences captured may have been an artefact of the length of follow-up.

TABLE 12 Main results of the Novartis model submission for GI and lung NETs at current list prices (2015[114])

Treatment	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	

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 crossover from everolimus to placebo was not permitted in the trial, 10% (10/97) of patients in the placebo arm did cross over (four before and six after unmasking). In spite of this, the analysis of OS data in RADIANT-4[35] did not adjust for such treatment crossover. This limitation may slightly bias the results if the analysis is intended to inform the evaluation of two alternative states of the world, one in which everolimus is provided as initial treatment and another in which 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 a potential subsequent treatment, the lack of adjustment for crossover by Novartis may not need to be a source of bias per se.

Another minor limitation is the inaccuracy in estimating the costs of subsequent treatments in the Novartis GI and lung model. This issue is the same as that discussed in the previous section for the Novartis model in pNETs and is not repeated here.

On the other hand, data on BSC treatment use, everolimus treatment duration and intensity and the incidence of grade 3/4 AEs in RADIANT-4[35] are detailed and Novartis describes important sources of uncertainty in the evidence base.

Advanced Accelerator Applications submission[31]

Overview

In anticipation of European market authorisation, the company's submission considers the use of the radiolabelled SSA 177Lu-DOTATATE (7.4 GBq, equivalent to 200 mCi) for people with inoperable progressive somatostatin receptor-positive GEP NETS. The company separates the GEP NETs population into two subpopulations in the model:

1. (confidential information has been removed)
2. (confidential information has been removed).

Separation into these subpopulations was seen by AAA as appropriate as pNETs and GI NETs have different clinical profiles and undergo different management. It is also important to note that with the selection of this trial[102] the population considered in the economic evaluations was further restricted to the subpopulation of somatostatin receptor-positive (SSTR+) patients.

The comparators in the pNETs evaluation were everolimus (10 mg per day) and sunitinib (37.5 mg per day). The comparator in the GI NETs evaluation was everolimus (10 mg per day) only. BSC 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 for 177Lu-DOTATATE compared with everolimus was (confidential information has been removed). 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 compared with everolimus was estimated to be (confidential information has been removed).

Supportive arguments for these findings are not discussed except that it was stated that the result is driven by superior survival with 177Lu-DOTATATE. The company did not draw comparisons with existing published economic evidence as this is the first cost-effectiveness analysis of 177Lu-DOTATATE.

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 HRs applied proportionally through a 20-year time horizon. The evaluation utilises a three-health state cohort transition model to simulate survival and progression (*Figure 10*). The selected cycle length is 1 month. Costs and benefits were discounted at 3.5% in future years and are reported from the NHS/PSS and patient's perspective respectively.

Advanced Accelerator Applications conducted two mixed treatment comparisons (MTCs) for the outcomes of PFS and OS: one for pNETs comparing 177Lu-DOTATATE with everolimus and sunitinib, and one for GI NETs comparing 177Lu-DOTATATE with everolimus (see *Appendix 8*, *Advanced Accelerator Applications*).

The sources of evidence of health effects in the pNETs evaluation were the NETTER-1 study[102] for octreotide LAR (baseline reference) and 177Lu-DOTATATE;[102] RADIANT-3[34] for everolimus; and A6181111[81] for sunitinib. The sources of evidence of health effects in the GI NETs evaluation were the ERASMUS study for 177Lu-DOTATATE (Dutch pNETs subgroup) and RADIANT-4[35] for everolimus.

Result

Over a time horizon of 20 years, for people with inoperable progressive SSTR+ pNETs the use of 177Lu-DOTATATE was found to be cost-effective compared with both everolimus and sunitinib at a threshold of £20,000 per QALY gained (*Table 13*).

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 was found to be cost-effective compared with everolimus at a threshold of £20,000 per QALY gained (*Table 14*).

In a one-way deterministic sensitivity analysis in which individual parameter point estimates were varied to their upper and lower 95% CI or interquartile range boundaries (or, when not available, ±20% of the mean):

- the 177Lu-DOTATATE acquisition cost and RDI adjustment were identified as highly sensitive model input parameters
- PFS and post-progression survival (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 PSA. In 5000 iterations selected parameters were varied using conventional distributions. Parameters not included in the PSA were relative treatment effect (PFS, OS), drug acquisition costs and drug administration costs. The results revealed that PSA ICERs were consistently lower than deterministic ICERs (*Table 15*). 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 parameters in the model.

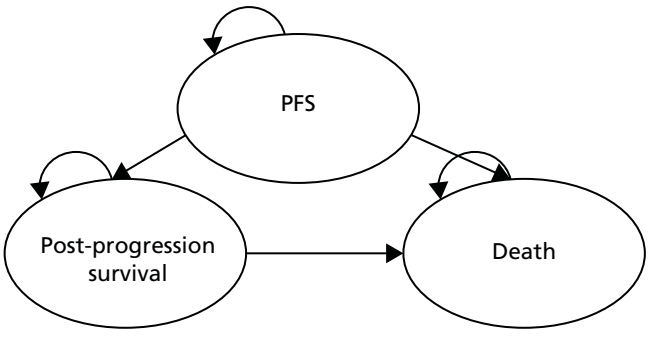


FIGURE 10 Decision-analytic model structure. Source: figure 15 (p. 114) of the AAA submission.[31]

TABLE 13 Incremental costs and effects from the deterministic evaluation of pNETs

Outcome	177Lu-DOTATATE	Everolimus	Sunitinib
PFS at 5 years (%)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
OS at 5 years (%)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Life-years (discounted)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
QALYs PFS (discounted)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
QALYs PPS (discounted)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Total QALYs	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Drug cost	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Drug administration	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Disease monitoring	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
AE management	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Total costs	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Incremental cost vs. 177Lu-DOTATATE (£)		21,489	–6648
Life-years gained by 177Lu-DOTATATE		2.75	0.07
QALYs gained by 177Lu-DOTATATE		2.18	0.10
ICER (£) (177Lu-DOTATATE vs. treatment in the respective column heading)		9847	Dominant (–68,916)

Summary results of scenario analyses

- Shortening the time horizon to 5 or 10 years reduced the ICERs, except for the 5-year comparison with everolimus in GI NETs, in which the ICER increased to £23,334.
- Discounting of costs and benefits to 6% and 1%, respectively, decreased all ICERs.
- Increasing the 177Lu-DOTATATE dose intensity to 100% increased all ICERs (pNETs: vs. everolimus £14,206 per QALY gained; pNETs: vs. sunitinib £29,686 per QALY gained; GI NETs: vs. everolimus £26,386 per QALY gained).
- Using alternative sources of utility for pre-progression in GI NETs:
  - using the NETTER-1 utility value (mean all patients: 0.750) rather than the utility value from Guy's and St Thomas' NHS Foundation Trust (0.793) resulted in an ICER of £21,295 for 177Lu-DOTATATE compared with everolimus
  - using the ERASMUS utility value (GI NETs subgroup: 0.773) rather than the utility value from Guy's and St Thomas' NHS Foundation Trust (0.793) resulted in an ICER of £20,931 for 177Lu-DOTATATE compared with everolimus (not £20,136 as reported by AAA).
- Including palliative care costs and an end-of-life utility decrement in the last 4 weeks of life has a negligible effect on ICERs in both the pNET and the GI NET evaluations.
- The inclusion of background mortality has a negligible effect on findings.

TABLE 14 Incremental costs and effects from the deterministic evaluation of GI NETs

Outcome	177Lu-DOTATATE	Everolimus
PFS at 5 years (%)	Confidential information has been removed	Confidential information has been removed
OS at 5 years (%)	Confidential information has been removed	Confidential information has been removed
Life-years (discounted)	Confidential information has been removed	Confidential information has been removed
QALYs PFS (discounted)	Confidential information has been removed	Confidential information has been removed
QALYs PPS (discounted)	Confidential information has been removed	Confidential information has been removed
Total QALYs	Confidential information has been removed	Confidential information has been removed
Drug cost	Confidential information has been removed	Confidential information has been removed
Drug administration	Confidential information has been removed	Confidential information has been removed
Disease monitoring	Confidential information has been removed	Confidential information has been removed
AE management	Confidential information has been removed	Confidential information has been removed
Total costs	Confidential information has been removed	Confidential information has been removed
Incremental cost vs. 177Lu-DOTATATE (£)		28,099
Life-years gained by 177Lu-DOTATATE		1.77
QALYs gained by 177Lu-DOTATATE		1.42
ICER (£) (177Lu-DOTATATE vs. treatment in the respective column heading)		19,816

TABLE 15 Incremental cost-effectiveness ratios in deterministic and probabilistic analyses

	ICER (£)	
Comparison	Deterministic result	Probabilistic result
pNETS: 177Lu-DOTATATE vs. everolimus	9847	Confidential information has been removed
pNETS: 177Lu-DOTATATE vs. sunitinib	–68,916 (dominant)	Confidential information has been removed
GI NETS: 177Lu-DOTATATE vs. everolimus	19,816	Confidential information has been removed

Strengths and weaknesses of Advanced Accelerator Applications's evaluation

Strengths

- The analysis separated the evaluation of pNETs from the evaluation of GI NETs.
- The structural methodology followed recommended approaches and was implemented correctly. The model was well presented, transparent and generally straightforward to understand.
- Serious AEs 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 BSC.
- The MTCs used to inform the relative treatment effect in each of the evaluations were premised on crucial yet unjustified assumptions:
  - that 60 mg of octreotide can be assumed to be equivalent to placebo and placebo plus 30 mg of octreotide in the GI NETs network
  - that 60 mg of octreotide is equivalent to placebo and placebo plus BSC in the pNETs network
  - that data from the NETTER-1 trial[102] can be used to inform the network for pNETs even though no participants in the NETTER-1 trial had pNETs.
- The MTCs used to inform the relative treatment effect in each of the evaluations were premised on weak methodology:
  - RADIANT-2[119] should be not have been included in the GI NETs MTC as the population in this trial all had functioning tumours, which is outside the marketing licence for everolimus for GI NETs
  - NETTER-1 should not have been included in the pNETs MTC as this trial did not include any patients with pNETs, meaning that AAA's pNETs evaluation is tenuous
  - there was no consideration of the extent of treatment switching in RADIANT-2 (58% switched to active treatment), RADIANT-3[34] (73% switched to active treatment) and A6181111[81] (69% switched to active treatment), which limits the interpretation of the results for OS.
- Treatment after progression was oversimplified to octreotide across all strategies, which was continued until death.
- Treatment with everolimus and sunitinib was assumed to continue until disease progression. This is an overestimate of usage and therefore cost as the average duration of treatment in trials was 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 was underestimated given that current practice as described by the AG clinical experts is for an overnight stay rather than day case administration and that there is a greater time requirement from clinical specialists. No alternative estimates of drug administration costs were tested. Exploratory univariate variations in the cost of 177Lu-DOTATATE administration carried out by the AG revealed that this may be an important area for scrutiny.
- The costing of serious adverse events (SAEs) was implemented poorly. On the one hand, costs were underestimated because of an overly low unit costing of SAEs, most of which require attention in the hospital setting, and, on the other hand, they were overestimated by their application well beyond the expected mean duration of treatment.

Chapter 6 Independent economic assessment

Methods

Model structure

Structure of relevant published models

In *Table 16* 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 (see *Appendix 10* for details). For comparison, we include characteristics of the Peninsula Technology Assessment Group (PenTAG) model.

Structure of the Peninsula Technology Assessment Group model

The majority of the studies, selected during the systematic review of cost-effectiveness (see *Chapter 5*, *Novartis submission*), reported models with three health states. The study by Casciano *et al.*[120] reported a four-state 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 three states: stable disease, disease progression and death.

In our analysis, we adopted the three-state model structure shown in *Figure 11*.

The model health states are defined as follows:

- pre progression
- post progression
- death.

The PenTAG cost-effectiveness model, implemented in Microsoft Excel® 2013 (Microsoft Corporation, Redmond, WA, USA), simulates a hypothetical cohort of 1000 patients with progressed unresectable or metastatic NETs. At the beginning of the simulation, all patients start in the pre-progression state; they then transition to the 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 state (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 the 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 11* 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 19* for a detailed description of the submitted models).

In the model we assumed that:

- patients receive active treatment until disease progression or earlier treatment discontinuation because of the onset of serious AEs or other reasons as observed in the RCT sources of effectiveness data
- on progression of disease, patients are treated with BSC.

TABLE 16 Structure of relevant published cost-effectiveness models compared with the PenTAG model

Model attribute	Casciano *et al.*[120]	Mucino Ortega *et al.*[121]	Johns *et al.*[122]	Walczak *et al.*[123]	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 NETs of pancreatic, GI or lung origin
Initial treatments	Everolimus vs. sunitinib (including SSAs)	Sunitinib + BSC vs. placebo + BSC	Sunitinib + BSC vs. placebo + BSC	Sunitinib + BSC vs. placebo + BSC (including SSAs)	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 AEs', 'stable disease with AEs', '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 and drug costs	PFS estimates were obtained from the indirect analysis (Signorovich *et al.*[124]) based on data from RADIANT-3[34] and A6181111.[81] Initial treatment assumed up to progression	PFS data used in the analysis were from A6181111.[81] Costs included the costs of drug acquisition and medical management, including specialist consultations, laboratory and imaging tests, pain management and palliative care	PFS data were from A6181111.[81] Cost components were not reported	PFS data from A6181111[81] were extrapolated using the Weibull and RPSFT methods (to allow for treatment switching between the arms of the clinical trial). Cost components were not reported	Initial treatment assumed up to progression
Subsequent treatments	BSC	BSC	BSC	BSC	BSC
Method of estimating OS	OS estimates were obtained from the indirect analysis (Signorovich *et al.*[124]) based on data from RADIANT-3[34] and A6181111[81]	OS data used in the analysis were from A6181111[81]	OS data from A6181111[81] were adjusted for treatment switching using the RPSFT method	OS data from A6181111[81] were extrapolated using the Weibull and RPSFT methods (to allow for treatment switching between the arms of the clinical trial)	Extrapolation of OS data 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

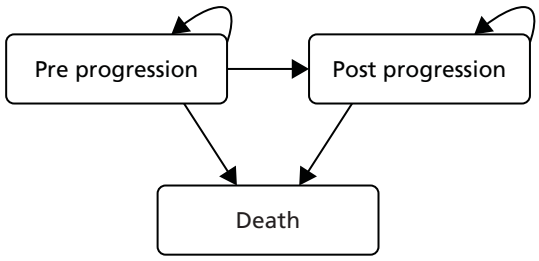


FIGURE 11 Structure of the PenTAG cost-effectiveness model.

See *Interventions and comparators* for further details of the treatments and comparators considered in our analysis.

Population

In line with the NICE scope, we considered people with progressed unresectable or metastatic NETs from three different patient populations according to tumour location:

1. patients with NETs of pancreatic origin
2. patients with GI and lung NETs
3. patients with GI (midgut) NETs.

The choice of these particular patient populations was determined by the available clinical effectiveness RCT data. Specifically, GI (midgut) NETs were assessed as the population recruited to the single RCT for 177Lu-DOTATATE (NETTER-1)[102] included only patients with midgut NETs. We did not consider any other subgroups in our analysis as no relevant clinical evidence was identified during the clinical effectiveness systematic review (see *Chapter 4*, *Outcomes for randomised controlled trial evidence for pancreatic neuroendocrine tumours*, *Subgroup analysis*, and *Outcomes for randomised controlled trial evidence for gastrointestinal and lung neuroendocrine tumours*, *Subgroup analysis*, for further details).

Interventions and comparators

Clinical data identified during the systematic literature review allowed the analyses shown in *Table 17* to be carried out. The treatments included in the model were:

- everolimus
- sunitinib
- 177Lu-DOTATATE (in scenario analyses only)
- BSC.

All included treatments are in the NICE scope.

TABLE 17 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[34]
	Everolimus	Sunitinib	Indirect comparison	RADIANT-3,[34] A6181111[81]
	Sunitinib	BSC	Head-to-head RCT	A6181111[81]
GI NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4[35]
	Everolimus	177Lu-DOTATATE	Indirect comparison	RADIANT-4,[35] NETTER-1[102]
	177Lu-DOTATATE	BSC	Head-to-head RCT	NETTER-1[102]
GI and lung NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4[35]

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 was identified during the clinical effectiveness systematic literature review (see *Chapter 4*, *Results*). Therefore, chemotherapy was not included in our analysis. Following the advice from our clinical experts, the AG did not consider interferon alpha in the economic analysis as it is not commonly used in UK clinical practice.

Perspective, time horizon and discounting

The model perspective was that of the NHS and PSS, in accordance with the NICE reference case.[37] In the base-case analysis, the model time horizon was 40 years, which reflects the lifetime horizon of patients with advanced NETs. Costs and benefits were discounted at 3.5% per annum. The model used a 4-weekly cycle length to facilitate the implementation of the costs of drug acquisition and administration for 177Lu-DOTATATE as these costs were incurred every 4 weeks.

A number of scenario analyses were performed to estimate the effect on outcomes of different survival model structures and data and assumptions around the discount rate and model time horizon (see *Appendix 11*, *Scenario analyses*, for further details).

Model parameters

Population characteristics

Mean age

We assumed that all patients were aged 60 years at the start of treatment. The estimate of the mean age of patients in the model population was based on the patient characteristics from the 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 varied from 61.7 to 63.7 years.

Sex composition

All analyses were performed assuming that the proportion of male patients is 53% (as in RADIANT-3[34]), which affects only background mortality (see *Appendix 11*, *Table 98*). The models in the company submissions used proportions of 50–51%.

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 were expected to account for background mortality. However, background mortality rises as the modelled cohort ages and, as in some analyses OS data were immature, in those cases the effect of background mortality was taken into account using data for the years 2012–14 from the Office for National Statistics.[125]

Models submitted by AAA for GEP NETs allow estimation of the ICER with and without general mortality. When general mortality was taken into account, it was modelled in the subpopulation of patients with stable disease; in the subpopulation of patients whose disease has progressed, background mortality was not modelled. Therefore, death events are double-counted during the stable disease stage and may be underestimated in the progressive disease subpopulation.

In contrast, none of the model-based analyses submitted by Novartis, which considered pancreatic and GI/lung locations, separately modelled background mortality.

Treatment effectiveness and extrapolation

Baseline randomised controlled trials

RADIANT-3[34] was chosen as the baseline trial for the pNETs population, whereas RADIANT-4[35] was chosen as the baseline trial for the GI (midgut) NETs and GI/lung NETs analyses. The size of the study populations in these trials was larger and the data were more mature than in A6181111[81] and NETTER-1.[102] In addition, the control arm in NETTER-1[102] received 60 mg of octreotide daily plus BSC, which is outside the NICE scope for this review.

Modelled progression-free survival and overall survival

A partitioned survival approach was used to populate the parameters of the semi-Markov model. PFS Kaplan–Meier curves for the trial arms of the main RCTs informing the company submissions on pNETs (including A6181111 and RADIANT-3), GI/lung NETs (RADIANT-4) and GI (midgut) NETs (RADIANT-4 midgut subgroup and NETTER-1) were extracted from graphs in the latest available source for each trial [peer-reviewed publications for A6181111,[81] RADIANT-3[34] and RADIANT-4;[35] a published conference abstract for the RADIANT-4 midgut subgroup;[74] and an industry submission (NETTER-1)] using digitising software (DigitizeIt version 2.2.2; Braunschweig, Germany). The extracted data were used to recreate the associated original individual patient data using the Guyot algorithm[126] implemented in R (The R Foundation for Statistical Computing, Vienna, Austria).

A range of parametric curves from the proportional hazards (Weibull, exponential and Gompertz), piecewise proportional hazards (restricted cubic splines with five pieces or knots) and accelerated failure time (AFT) (log-normal, log-logistic and generalised gamma) families were fit to the recreated individual patient data for each arm separately and evaluated for use in the base-case analysis according to goodness of fit criteria [Akaike information criterion (AIC) and Bayesian information criterion (BIC)], 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.[127] We relaxed 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[34] and 65% in A6181111[81]). Therefore, the following analyses for pNETs are based on Kaplan–Meier OS curves adjusted for crossover, using the RPSFT method (Robins and Tsiatis[128]). This approach affects only 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 of GI or lung NETs is based on RADIANT-4,[35] in which 6% of placebo patients switched to the active arm after disease progression. As no RADIANT-4 OS data were identified in which treatment switching in the placebo arm was adjusted for, the following analyses are based on the most recent ITT OS curves reported for RADIANT-4[35] (cut-off date 20 November 2015). As for the PFS Kaplan–Meier curves used in our analysis, switching to new active antineoplastic therapy before disease progression occurred in (confidential information has been removed) of patients in the everolimus arm and (confidential information has been removed) in the placebo arm (central radiological review), and these cases were censored from the analysis at the time of switch [RADIANT-4[35] final clinical study report (CSR), p. 71].

The statistical analysis used to select parametric survival functions for modelling PFS and OS outcomes and to extrapolate beyond the trial follow-up periods is presented next.

Pancreatic neuroendocrine tumours

In general, accelerated failure time models had a better fit than other models to the observed PFS data from the RADIANT-3[34] treatment arms, but their advantage was not significant (i.e. BIC difference of < 5 points between the Weibull and the log-logistic functions) in the everolimus arm (*Table 18*). The fact that the best model for the placebo arm of RADIANT-3[34] was the restricted cubic spline function (with six segments) suggests that the other models may not be valid representations of the trial data for that arm. The exponential function was the model with the best (i.e. lowest) goodness of fit statistic for sunitinib in A6181111[81] (see *Table 18*), although no significant differences were found between models. On the basis of this and the available evidence discussed in the following section, and for consistency across arms, in the base-case analysis the model adopted the Weibull function for the everolimus plus BSC and BSC-only arms and the exponential function (i.e. Weibull with the shape parameter set to the value of 1) for the sunitinib plus BSC arm.

In contrast, proportional hazard models had a better fit to the OS data, with the exception of OS in the placebo arm of RADIANT-3,[34] which was best represented by the log-normal function according to the BIC statistic (see *Table 18*). The model adopted the Weibull function for the everolimus plus BSC arm and exponential functions for the sunitinib plus BSC and BSC-only arms in the base-case analysis.

TABLE 18 Akaike's and Bayesian information criteria of parametric models of PFS and OS in pNETs

	Everolimus plus BSC[a] (*n* = 207)			Sunitinib plus BSC[b] (*n* = 86)			Placebo plus BSC[a] (*n* = 203)		
Model	Number of parameters	AIC	BIC	Number of parameters	AIC	BIC	Number of parameters	AIC	BIC
PFS									
Weibull	2	416	422	2	178	183	2	465	472
Exponential	1	424	428	1	176	**179**	1	488	492
Gompertz	2	422	429	2	177	182	2	485	491
Log-normal	2	413	420	2	174	179	2	440	447
Log-logistic	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**
OS									
Weibull	2	554	561	86	237	242	203	396	403
Exponential	1	555	558	86	235	**238**	203	399	402
Gompertz	2	555	561	86	237	242	203	401	407
Log-normal	2	560	567	86	**233**	238	203	387	**394**
Log-logistic	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

a Source: recreated data from ITT PFS (central review) Kaplan–Meier curves in RADIANT-3[34] and RPSFT model-adjusted OS Kaplan–Meier curves in RADIANT-3.[33,34]

b Source: recreated data from ITT PFS Kaplan–Meier curves in A6181111[81] and PFSFT model-adjusted OS Kaplan–Meier curves in A6181111[81] (Raymond *et al.*,[88] Pfizer submission to NICE).[32]

Note

Bold text indicates best-fit result.

Progression-free survival

Our base-case analysis adopted the Weibull function for PFS outcomes for the everolimus plus BSC and BSC-only arms and the exponential function for the sunitinib plus BSC arm. In scenario analyses we adopted the log-logistic, exponential and log-normal functions for the everolimus plus BSC, sunitinib plus BSC and BSC-only arms respectively.

Everolimus plus best supportive care

The log-logistic model has the most favourable goodness-of-fit results (i.e. lowest value of information criteria) for the data from the everolimus arm of RADIANT-3,[34] although its advantage over the log-normal and Weibull models is not statistically significant (see *Appendix 12*, *Figure 38*). The log-logistic model also follows the shape of the instantaneous risk (hazard) of progression or death (see *Appendix 12*, *Figure 38*).

The log-logistic and log-normal models perform similarly to each other in fitting the Kaplan–Meier PFS curve, with the Weibull model fitting the data almost as well as the log-logistic and log-normal models. However, by the end of the observed follow-up period, the risk of progression or death with the Weibull model is increasing, whereas the risk of progression or death with the log-normal and log-logistic models is declining (see *Appendix 12*, *Figure 38*).

By the end of the observation period, almost 2 years after randomisation, 20% of patients in the everolimus arm are alive and their disease has not progressed (*Figure 12*). 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) model, whereas according to the Weibull model all patients would have progressed or died by 6 years after randomisation (*Figure 13*).

Best supportive care alone

The BSC-only arm was modelled from data from the placebo arm in RADIANT-3.[34] The information criteria favour the log-normal, log-logistic and generalised gamma models over the rest (see *Table 21*). The AIC and BIC statistics, however, do not discriminate between the favoured models (their magnitudes differ by < 5 points).

The hazard function is non-constant and non-monotonic, which suggests that the Weibull and exponential models are inappropriate models for these data (see *Appendix 12*, *Figure 39*). The information criteria statistics are consistent with this observation and suggest that the log-normal or gamma model fit the data best.

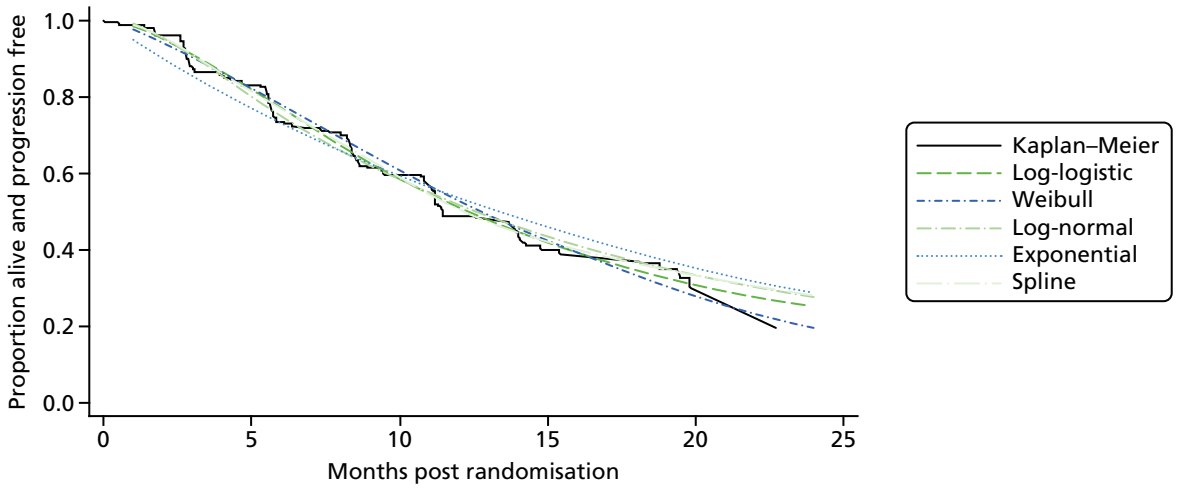


FIGURE 12 Everolimus arm in RADIANT-3:[34] Kaplan–Meier and best-fitting parametric PFS curves.

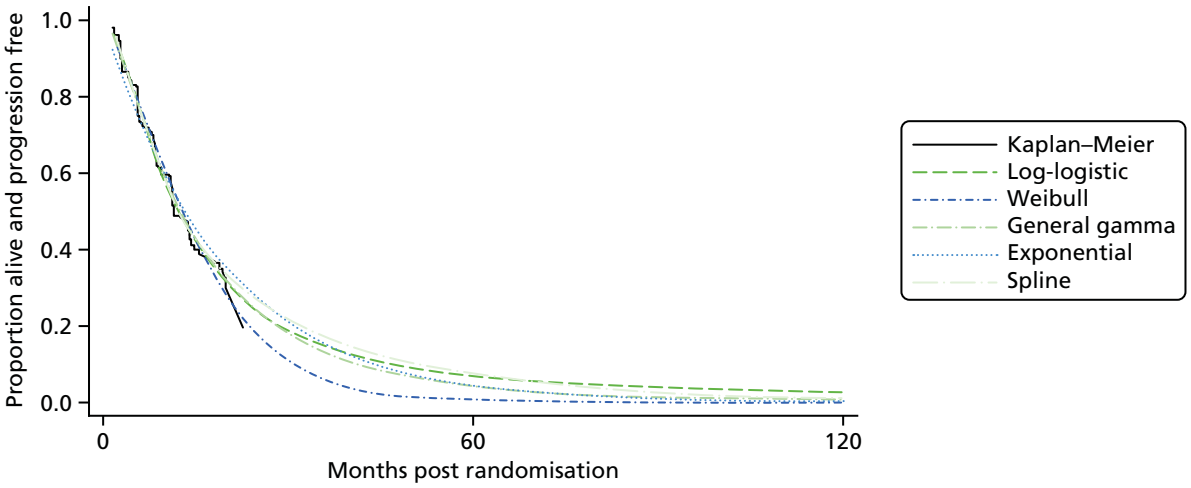


FIGURE 13 Progression-free survival in the everolimus arm in RADIANT-3:[34] extrapolation to 10 years.

Consistent with the model diagnostics of *Table 21*, the generalised gamma model is a closer match to the hazard function (see *Appendix 12*, *Figure 39*). The log-normal model approximates the smoothed hazard in *Figure 39* (see *Appendix 12*), except for the drop between week 20 and week 40.

As illustrated in *Figure 14*, the Weibull model underestimates PFS early on, overestimates it in the medium term and underestimates it in the final part of the analytical horizon. The log-normal and generalised gamma models differ only in the final part; the log-normal model appears to fit better the final part of the Kaplan–Meier curve. Nevertheless, the choice of curve has little impact on mean PFS in this case.

Sunitinib plus best supportive care

As presented in *Figure 15*, for the PFS data from the sunitinib arm of A6181111,[81] the generalised gamma function provides the best diagnostic results, although the differences between the generalised gamma model and the exponential and log-normal models are not significant.

As depicted in *Figure 40* (see *Appendix 12*), the generalised gamma model consistently underestimates the risk of progression, whereas the exponential model, with its constant risk, fits the pattern of risk up to approximately week 30 and underestimates it thereafter. The log-logistic model seems to follow the shape of the hazard function for longer periods than the other models.

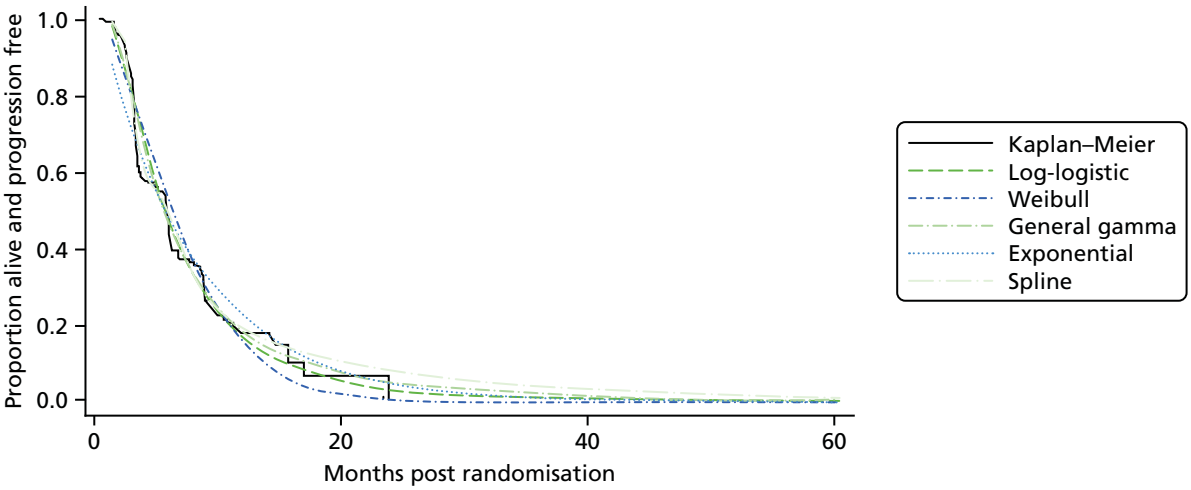


FIGURE 14 Placebo arm in RADIANT-3:[34] Kaplan–Meier and best-fitting parametric PFS curves.

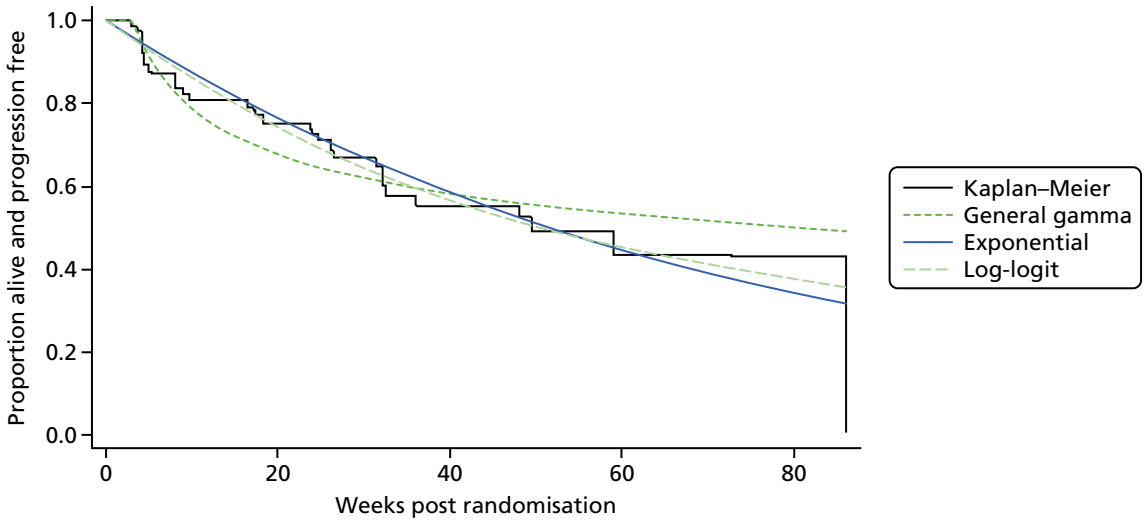


FIGURE 15 Sunitinib arm in A6181111:[81] Kaplan–Meier and best-fitting parametric PFS curves.

The implications of adopting one of these curves to extrapolate outcomes for cost-effectiveness analysis is illustrated in *Figure 16*. The generalised gamma model's parametric flexibility appears to produce an overly optimistic forecast of approximately 35% of patients still alive and not 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 predictions of the generalised gamma model and the exponential model, but much closer to the exponential forecast than the generalised gamma forecast.

The apparent contradiction between the diagnostic results, which suggest that the generalised gamma function fits the data best, and the hazard and survival function fits, which suggest that the log-logistic 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

To derive estimates of PFS time for the sunitinib arm that were comparable to the PFS estimates in RADIANT-3,[34] the sunitinib parametric PFS distribution was adjusted by the ratio of the area under

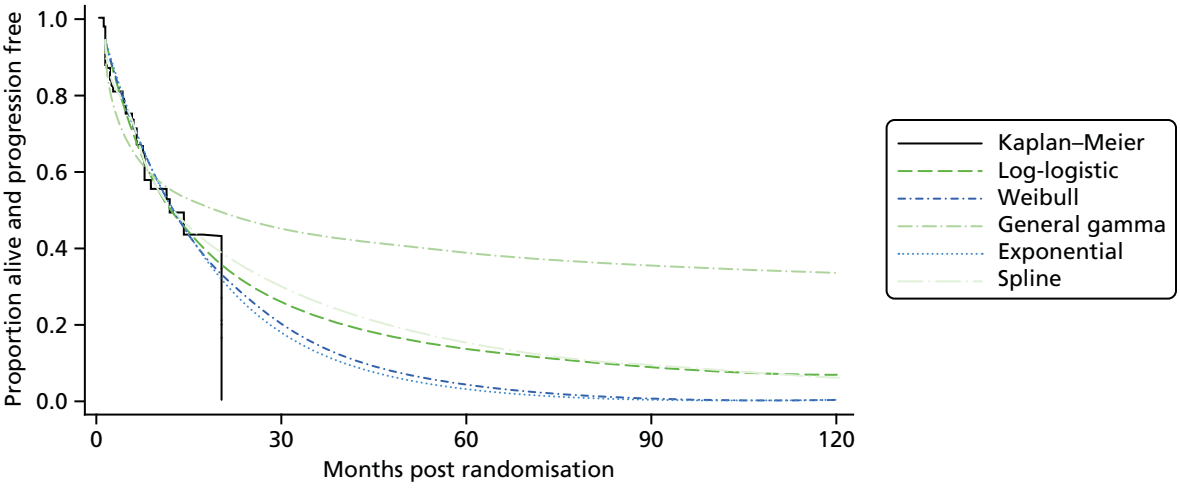


FIGURE 16 Progression-free survival in the sunitinib arm: extrapolation to 10 years.

the non-parametric Kaplan–Meier curve of the placebo arm in A6181111[81] to the area under the non-parametric Kaplan–Meier curve of the placebo arm in RADIANT-3[34] 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 being determined solely by the observed data, as in our 'restricted means' approach. Thus, in the base case, in which the sunitinib PFS parametric distribution was the exponential, the sunitinib PFS parametric distribution function was adjusted according to the equation:

$$\widehat{\lambda_s} = \left\{ \frac{1}{\lambda_s} * \frac{AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Ap}}{AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Rp}} \right\}^{-1} = \left(\frac{1}{0.01345} * \frac{28.85}{25.68} \right)^{-1} \quad (1)$$

where $\widehat{\lambda_s}$ is the adjusted hazard function of the exponential time-to-disease progression or death distribution, λ_s is the hazard function of the exponential distribution estimated from the sunitinib arm of A6181111[81] and the $AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Ap}$ and $AUC\left(t_{\min\{T_{Ap},T_{Rp}\}}\right)_{Rp}$ functions are the area under the Kaplan–Meier curve of the placebo arms of A6181111[81] and RADIANT-3,[34] respectively, evaluated at the shortest of the maximum observation times in the placebo arms of the two trials (i.e. 65 weeks). This is illustrated in *Figure 17*, where the vertical discontinuous line denotes the 65th-week time point. At this point, the mean PFS in the placebo arm is 25.69 weeks in A6181111[81] and 28.85 weeks in RADIANT-3.[34] 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 used for OS.

Individual patient data provided by Pfizer to the AG for this assessment allowed us to investigate the robustness of indirect comparisons of PFS outcomes between the sunitinib arm in A6181111[81] and the everolimus and placebo arms in RADIANT-3.[34] We conducted a MAIC following the methods described in a previous study by Signorovitch *et al.*[129] We obtained similar results (which are academic-in-confidence) to those reported here.

Overall survival

Using similar criteria to those described for the analysis of PFS, the diagnostics information in *Table 18* and visual fit in *Figures 41–43* (see *Appendix 12*), and extrapolated survival rates in *Figures 18–20*, 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.[34] The resulting equation for sunitinib was then matched to the RADIANT-3[34] arms using the same scaling method as described for the PFS time-to-event analysis. For scenario analyses, the OS function for the BSC-only arm was changed to the log-normal function while keeping the exponential function for the active treatment arms.

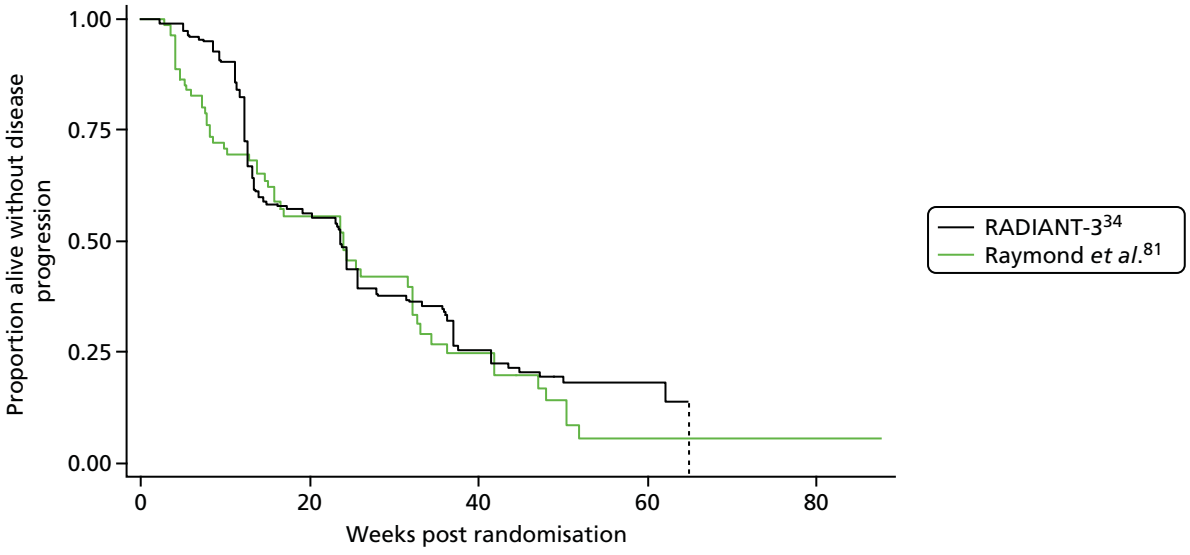


FIGURE 17 Progression-free survival in the placebo + BSC arms of pNETs trials.

Everolimus plus best supportive care

As illustrated in *Figure 18*, according to the exponential function, by 15 years (180 months) 4% of patients initially treated with everolimus remain alive, whereas according to the log-normal survival curve, 10% of patients would be alive at that time point. In its submission, Novartis[33] cites an estimated 15-year survival rate of 6% for patients with advanced pNETs from the Surveillance, Epidemiology, and End Results Program (SEER) database, and considers as plausible extrapolating only those curves 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. (Confidential information has been removed.) 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.*
>
> *Novartis submission, p. 93*[33]

[In English life tables, the 15-year survival rate in the general population aged 60 years increased from 56% in males and 74% in females in 1980–2, to 75% and 83%, respectively, in 2006–8 (Office for National Statistics[130])]. 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[34] trial would not be substantially less than that for patients with advanced pNETs in the SEER registry' (Novartis submission, p. 93[33]).

Best supportive care alone

The log-normal function had the best fit to the data of the placebo plus BSC arm in RADIANT-3.[34] The generalised gamma function had a good visual fit to the risk of death observed in the trial period (see *Appendix 12*, *Figure 42*) but an overly optimistic 20-year OS rate of 20% (*Figure 19*). The exponential function underestimated the hazard risk throughout the trial period (see *Appendix 12*, *Figure 42*), but had a 20-year PFS in the middle of those depicted in *Figure 19*.

Sunitinib plus best supportive care

The log-normal and exponential functions had the best fit to the OS data for the sunitinib arm in A6181111[88] (*Table 21*), although the log-normal function tracked the risk of death (hazard) observed in the trial better than the exponential function (see *Appendix 12*, *Figure 43*). The projected 15-year survival rate with the log-normal function is > 10%, whereas with the exponential function it is 4.7% (see *Figure 20*). However, the 15-year OS rate used in the model was higher than that seen with the exponential function as, after adjusting the exponential function for the difference in the placebo arms of the A6181111[81] and RADIANT-3[34] trials (see the following section), the OS rate was 9.7%.

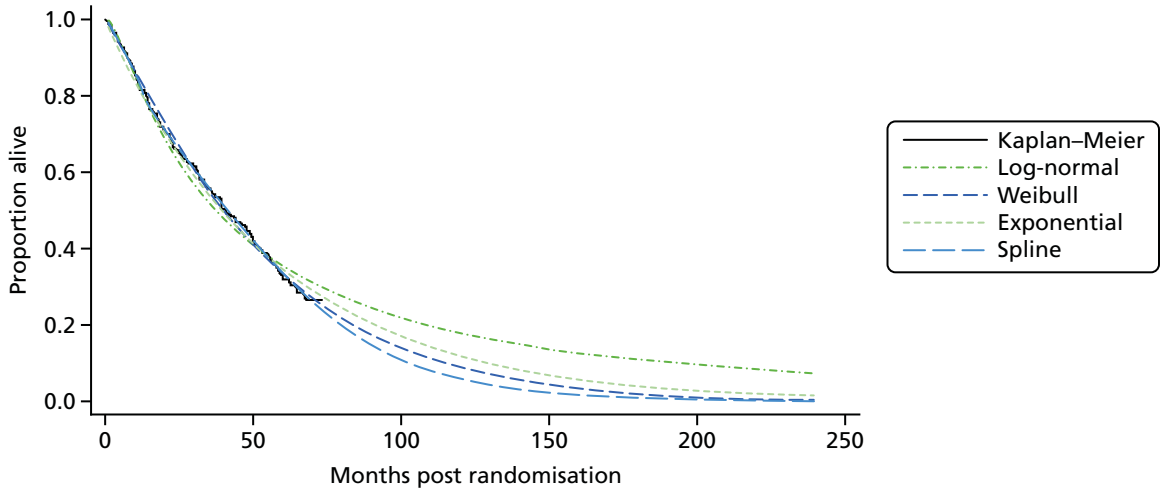


FIGURE 18 Overall survival in the everolimus arm of RADIANT-3:[34] extrapolation to 20 years.

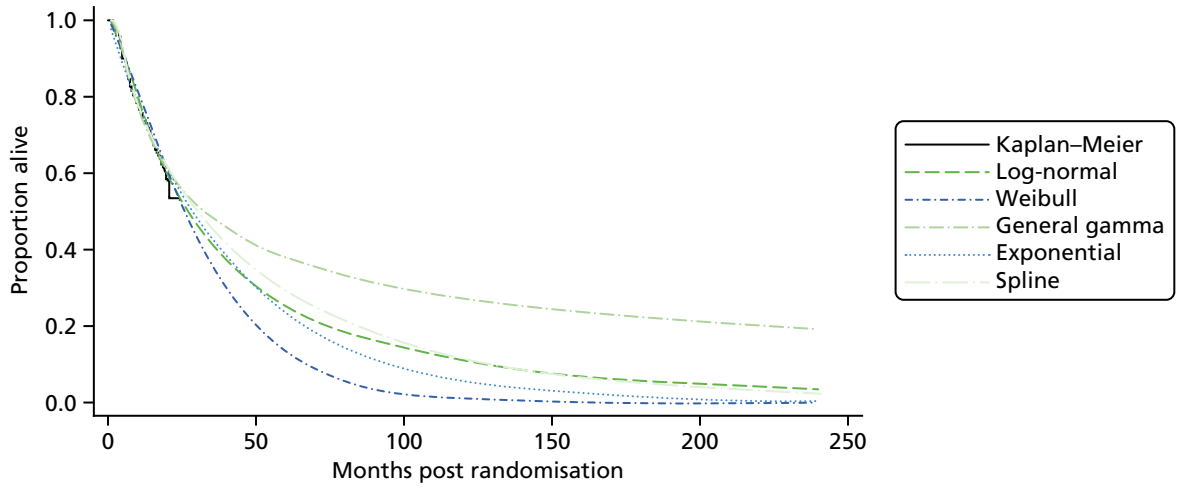


FIGURE 19 Rank-preserving structural failure time (RPSFT)-adjusted OS in the placebo arm of RADIANT-3:[34] extrapolation to 20 years.

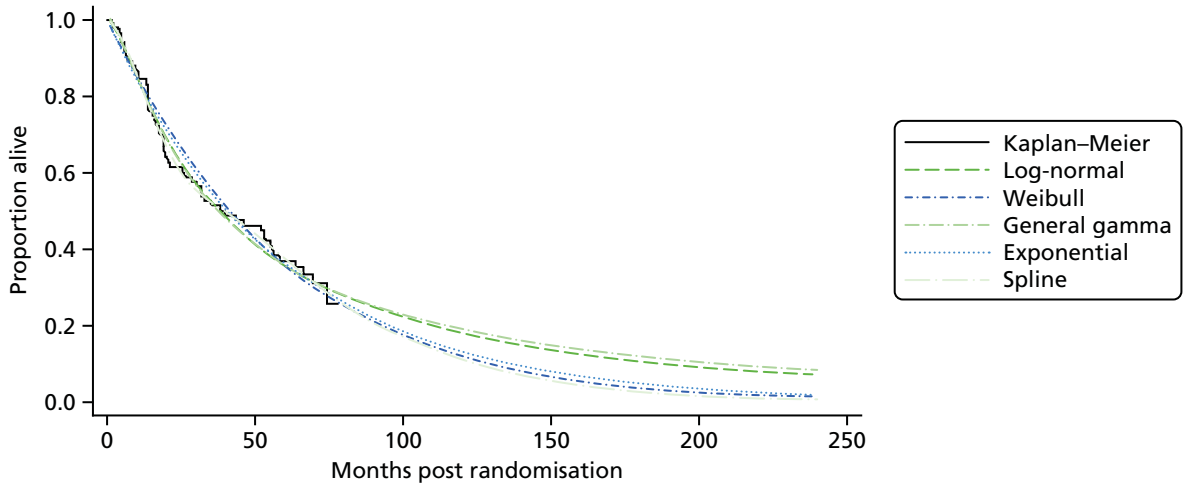


FIGURE 20 Overall survival in the sunitinib arm of A6181111:[81] extrapolation to 20 years.

Adjustment for indirect comparison

As before, to derive comparable OS estimates for the treatments in RADIANT-3,[34] the OS exponential curve for sunitinib was adjusted to reflect the difference in RPSFT-adjusted OS between the placebo arm of A6181111[81] and the placebo arm of RADIANT-3.[34] *Figure 21* illustrates the difference, and the vertical discontinuous line marks the point at which the area under the curve calculation was restricted for both arms (24 months).

Gastrointestinal and lung neuroendocrine tumours

In gastrointestinal 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,[35] whereas the two-parameter models were inferior to the three-parameter gamma or six-parameter spline model were the best fit to the PFS data in the placebo arm of RADIANT-4[35] (*Table 19*). In contrast, the exponential, Gompertz and Weibull models fitted the OS data as well as or better than other models.

Progression-free survival

In the base-case analysis, the Weibull function was chosen for the everolimus plus BSC arm and the BSC-only arm based on data from RADIANT-4.[35] In scenario analyses, the generalised gamma function was used instead for both model arms. See *Appendix 13* for details.

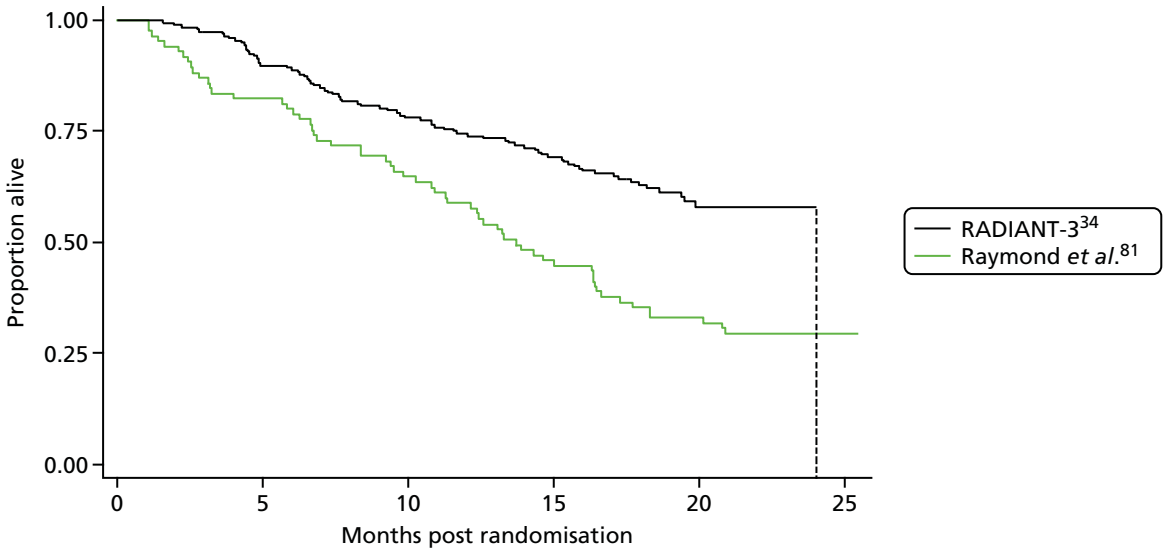


FIGURE 21 Kaplan–Meier RPSFT-adjusted OS in the placebo + BSC arms of the pNETs trials.

TABLE 19 Akaike's and Bayesian information criteria of parametric models of PFS and OS in GI/lung NETs

	Everolimus + BSC[a] ($n = 205$)			Placebo + BSC[a] ($n = 97$)		
Model	**Number of parameters**	**AIC**	**BIC**	**Number of parameters**	**AIC**	**BIC**
PFS						
Weibull	2	456	463	2	258	263
Exponential	1	461	465	1	256	259
Gompertz	2	462	469	2	253	258
Log-normal	2	**446**	**453**	2	237	242
Log-logistic	2	450	456	2	240	246
Gamma	3	447	457	3	211	218
Spline	6	449	469	6	**198**	**213**
OS						
Weibull	2	340	347	2	194	199
Exponential	1	346	350	1	**192**	**195**
Gompertz	2	**338**	**345**	2	194	199
Log-normal	2	348	355	2	193	198
Log-logistic	2	342	349	2	193	198
Gamma	3	341	351	3	195	202
Spline	6	344	364	5	198	210

a Source: recreated data from ITT PFS (central review; Yao *et al.*[35]) and ITT OS Kaplan–Meier curves in RADIANT-4[35] (CSR and Novartis submission[33]).

Note

Bold text indicates best-fit result.

Overall survival

The base-case analysis adopted exponential distributions separately fitted to OS data in the everolimus arm and the placebo arm of RADIANT-4.[35] The Gompertz and Weibull distributions had the best goodness of fit statistics and seemed to provide the best fit to the everolimus hazard rates (see *Appendix 12*, *Figure 46*) and Kaplan–Meier curves (*Figure 22*), whereas the exponential function seemed to be the best fit to the placebo data (see *Figures 23* and *47*). However, only the extrapolations of the exponential and log-logistic distributions seemed plausible, as discussed in the following two sections. In scenario analyses, log-logistic distributions separately estimated for the two trial arms were adopted.

Everolimus plus best supportive care

To reflect the uncertainty resulting from immature data, *Figure 22* presents the OS extrapolations for all available parametric curves. The exponential function appears to overestimate the risk of death (see *Appendix 12*, *Figure 46*) and underestimate the Kaplan–Meier OS curve (see *Figure 22*) in the early part of the trial observation period[35] (data cut-off 30 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 once in the late extrapolation (beyond-trial) period. In its submission to NICE, Novartis[33] turns to external data to inform its 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)*[33]

In appendix 9 of the Novartis submission, Novartis[33] reports the data and methods used to obtain its 10% survival benchmark at 15 years; Kaplan–Meier survival curves by location from SEER were weighted according to the distribution of patients by location in RADIANT-4.[35] Novartis also acknowledges the limitations of these SEER data, as discussed earlier for pNETs.

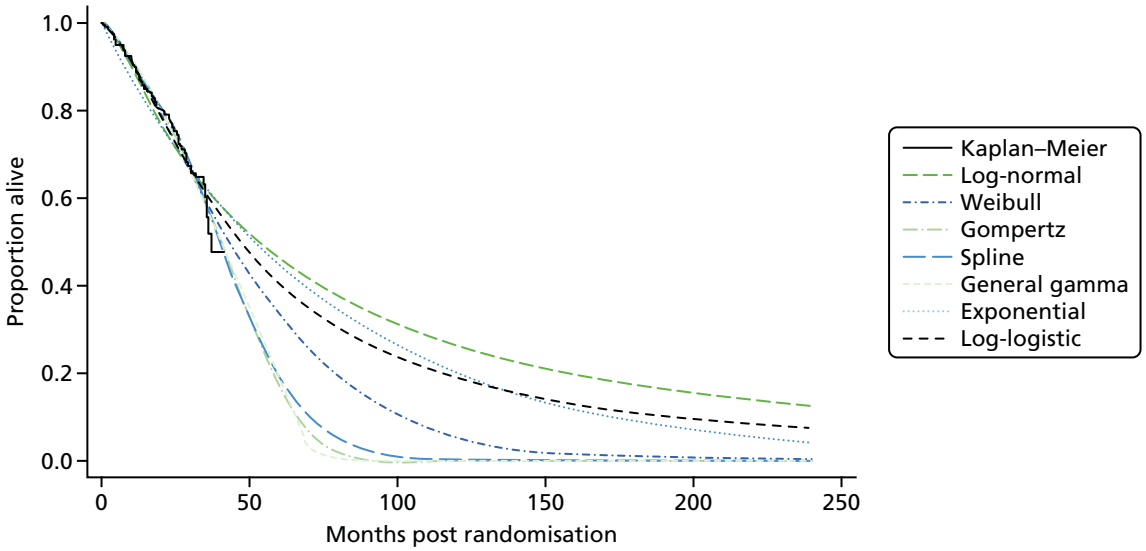


FIGURE 22 Overall survival in the everolimus arm of RADIANT-4:[35] extrapolation to 20 years.

Best supportive care alone

High degrees of uncertainty are similarly present in the later parts of the follow-up period for patients in the placebo arm of RADIANT-4,[35] as evidenced by the large steps observed after approximately 2 years of follow-up (*Figure 20*).

Gastrointestinal (midgut) neuroendocrine tumours

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 in RADIANT-4[35] for the GI (midgut) population subgroup[73] (*Table 20*).

Progression-free survival

In the base-case analysis the exponential distribution was adopted to model PFS outcomes in the everolimus arm and the placebo arm of RADIANT-4.[73] PFS in the 177Lu-DOTATATE arm of NETTER-1[102] was also modelled with an exponential distribution (see *Appendix 11* for scenario analyses).

Everolimus plus best supportive care

The exponential function, which was the function with the best statistical fit (*Figure 24*), appeared to have a poor fit to the hazard rates for everolimus in RADIANT-4[73] (see *Appendix 12*, *Figure 48*). However, this is caused by the small sample available in the latter part of the RADIANT-4[73] follow-up period. Of the candidate functions, the log-normal function has the longest PFS duration, followed by the exponential and the Weibull functions (see *Figure 24*).

Best supportive care alone

The diagnostic statistics (see *Table 20*) did not discriminate between the [accelerated failure time (AFT) or proportional hazards] models available to represent the PFS data in the placebo arm of RADIANT-4,[73] although the generalised gamma and log-normal functions displayed PFS hazard rates that were similar to those observed during the trial (see *Appendix 12*, *Figure 49*). When turning to the extrapolation of PFS, the generalised gamma function seems to result in overly optimistic disease PFS rates (see *Figure 25*). In scenario analyses, the log-normal distribution was used instead of the exponential to model the PFS experience of patients in the placebo arm.

Overall survival

In the absence of data, the base-case analysis currently assumes that the OS curve for everolimus in the GI (midgut)-only location is the exponential OS curve estimated in the GI or lung patient population in the everolimus arm of RADIANT-4,[35] discussed earlier, adjusted by the proportional difference in mean PFS in the everolimus arm of RADIANT-4[35] 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[35] in the GI (midgut)-only

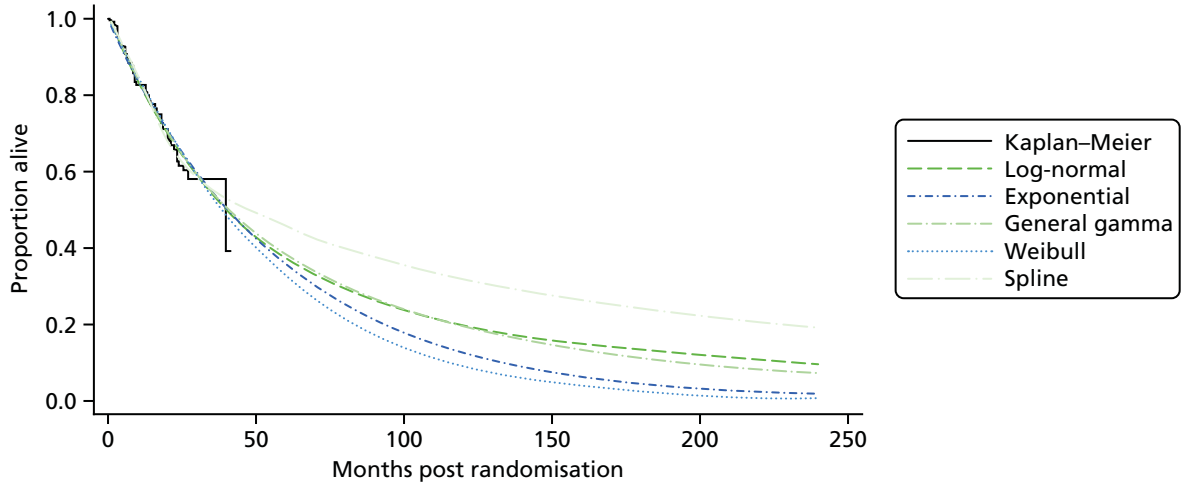


FIGURE 23 Overall survival in the placebo arm of RADIANT-4:[35] extrapolation to 20 years.

TABLE 20 Akaike's and Bayesian information criteria of parametric models of PFS and OS in GI (midgut) NETs

Model	Everolimus plus BSC[a] ($n = 80$)			177Lu-DOTATATE plus BSC[b] ($n = 116$)			Placebo plus BSC[a] ($n = 35$)		
	Number of parameters	AIC	BIC	Number of parameters	AIC	BIC	Number of parameters	AIC	BIC
PFS									
Weibull	2	149	154	2	139	145	2	87	90
Exponential	1	151	**153**	1	140	**143**	1	85	87
Gompertz	2	150	155	2	141	146	2	87	90
Log-normal	2	**149**	154	2	**138**	143	2	83	**86**
Log-logistic	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
OS									
Weibull	2	NA	NA	2	99	105	2	NA	NA
Exponential	1	NA	NA	1	**98**	**101**	1	NA	NA
Gompertz	2	NA	NA	2	99	105	2	NA	NA
Log-normal	2	NA	NA	2	99	105	2	NA	NA
Log-logistic	2	NA	NA	2	99	105	2	NA	NA
Gamma	3	NA	NA	3	101	109	3	NA	NA
Spline	6	NA	NA	6	102	119	6	NA	NA

NA, not applicable.
a RADIANT-4.[73]
b AAA submission to NICE.[31]
Note
Bold text indicates best-fit result.

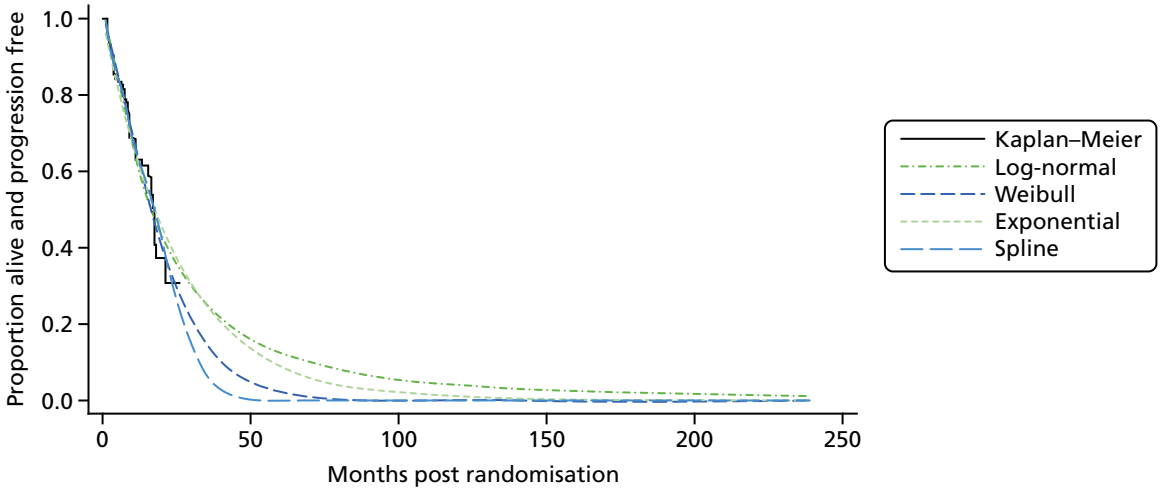


FIGURE 24 Progression-free survival in the everolimus arm of RADIANT-4[35] [GI (midgut)]: extrapolation to 20 years.

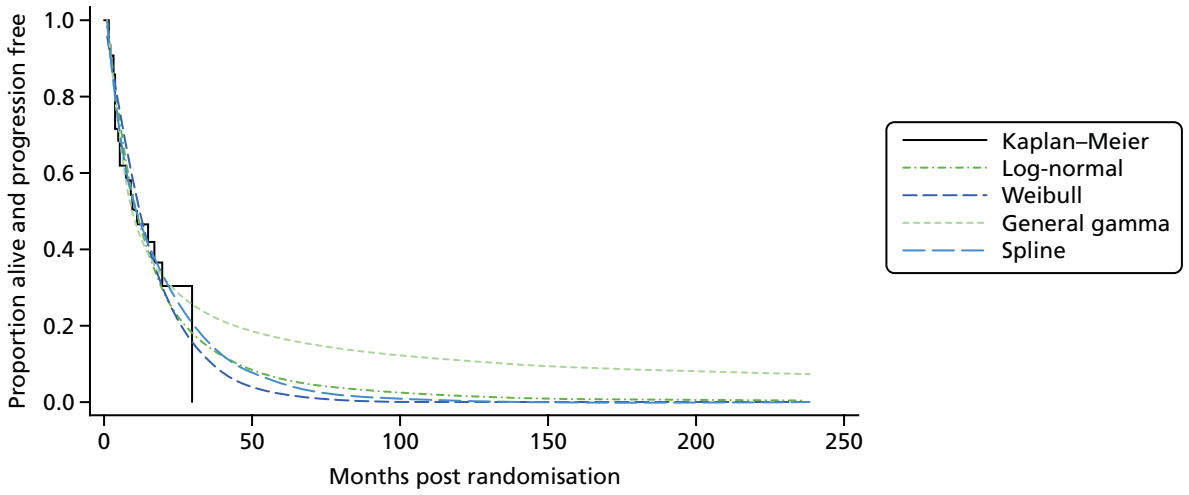


FIGURE 25 Progression-free survival in the placebo arm of RADIANT-4[35] [GI (midgut)]: extrapolation to 20 years.

population is derived from adjusting the exponential function fitted to the OS data from the everolimus arm of RADIANT-4[35] in the GI/lung population considered above by the proportional difference in mean PFS between the overall GI/lung and the GI (midgut) patient groups. These derivations follow the same steps as in *Equation 1*. We requested OS data for the GI (midgut)-only location from Novartis, but the company did not provide them to us.

Adverse events

The probabilities of AEs were used to estimate costs in the stable disease state. For the economic evaluation of treatments for pNETs, probabilities of AEs 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 *Chapter 4*, *Indirect treatment comparison: pancreatic neuroendocrine tumours*; *Appendix 21*, *Table 136* and *Appendix 9*). We updated these analyses with data provided in the Pfizer submission to NICE.[32] For the GI/lung analysis, the AG model adopted the probabilities in the Novartis model submitted to NICE,[33] as these were calculated with individual patient data not available to the AG. For everolimus plus BSC and BSC only in the GI (midgut) evaluation, we adopted the grade 3/4 AE rates for the everolimus and placebo arms reported in a recent conference poster by RADIANT-4 investigators;[73] for 177Lu-DOTATATE we used the grade 3/4 AE rates reported in the AAA submission to NICE.[31]

The AE probabilities for the pNETs model were obtained by assuming that patients had no multiple instances of the same AE type and that AEs lasted for only one cycle. This seems a reasonable assumption in the light of the evidence in the CSR for A6181111,[81] which reports the actual duration of the grade 3/4 AEs recorded in the trial (tables 5, 24, 26 and 29 in the full CSR of A618111[81]). For GI/lung and GI (midgut) NETs the same assumption was adopted.

Based on calculations by the AG the measured differences in grade 3/4 AEs between everolimus and sunitinib in patients with pNETs considered by Novartis in its submission,[33] and for which disutility values are available (see *Utility values for the Peninsula Technology Assessment Group model* for details), are associated with negligible differences in utility, equal to a 0.002 quality-adjusted months, and were therefore not used in calculating utility values for stable disease in the pNETs model. For GI/lung and GI (midgut) analyses, the available utility values, which were derived from patient-reported outcomes in RADIANT-4[35] and evidence from the ERASMUS study[31] submitted to NICE by AAA, were assumed to capture the impact of AEs.

Modelling post progression

Based on data from RADIANT-3[34] for pNETs and RADIANT-4[35] for GI and lung NETs, which we assumed applied to GI (midgut) NETs, in the base-case analysis we assumed that all patients have BSC after progression on initial treatment. This consists of palliative care and 30 mg of octreotide for symptomatic treatment, with no active drug treatment.

Subsequent treatments were allowed in the post-progression phase and were applied as a fixed cost in the first cycle after disease progression. The frequency of subsequent treatment use was assumed to be zero in the base-case analysis; scenario analyses considered applying the same costs of subsequent treatments as in the pNETs and GI and lung models from Novartis.[33] This choice of base case reflected the fact that (1) the A6181111[81] 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 (2) the way that Novartis implemented subsequent treatment costs in its models is unreliable (see *Chapter 5*, *Critical appraisal of the company submissions*). 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, which used detailed information on differences between trial arms in the frequency of treatment use post progression in RADIANT-4.[35] As we had no information for 177Lu-DOTATATE, we assumed that it had the same subsequent treatment costs as applied to everolimus.

The costs of disease monitoring in our model were obtained from the pNETs and GI and lung models from Novartis.[33] Based on the opinion of our clinical experts, we adopted a smaller number of visits for the GI and lung evaluation than were used by Novartis in its model of the same location (see *Costs of medical management and disease monitoring*).

Systematic review of utilities

The methods used to identify utility parameter values for the model are reported in *Appendix 15*.

Utility values for the Peninsula Technology Assessment Group 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 because of the differences in the treatments being evaluated and the discrepancies between the definitions 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 by tumour location, in accordance with the NICE scope. No utility values for HRQoL outcomes measured in pNET patients under treatment with everolimus were found (*Table 21*). The only available estimates for everolimus in pNETs were those reported by the preference elicitation study of Swinburn *et al.*,[131] who asked approximately 100 members of the general public to assess descriptors (vignettes) of pre-progression and post-progression health states of patients with GI NETs and pNETs, using the time trade-off method. This study also elicited utility decrements resulting from the occurrence of some of the most common AEs associated with treatment therapies (see *Appendix 10*, *Pancreatic studies*, for details; AEs considered include neutropenia, hypertension, palmar–plantar erythrodysaesthesia syndrome, leukopenia, diarrhoea, stomatitis, thrombocytopenia, anaemia, hyperglycaemia, fatigue, infections, pneumonitis and nausea). In the base-case analysis submitted to NICE, Novartis[33] 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 RADIANT-3.[34] As these values do not meet the NICE reference case[37] we considered them only in scenario analyses.

In the absence of HRQoL outcomes measured in pNET patients treated with everolimus, the base-case value was assumed to be the same as for sunitinib (see *Table 21* and its description). This assumption was adopted after calculating the net difference in disutility from grade 3/4 AEs between everolimus and sunitinib according to the disutility values reported by Swinburn *et al.*,[131] which was equal to 0.002 quality-adjusted months. Giving the uncertainty associated with other parameters in the model, including the limited quality of AE data available for economic evaluation purposes, we considered such a difference insignificant.

Estimates of the utility of pNET patients undergoing treatment with sunitinib in both the pre-progression and the post-progression health states (see *Table 21*) were obtained by mapping individual patient data onto responses to the EORTC QLQ-C30 from A6181111[81] provided by the manufacturer (Pfizer, data request through NICE) using the algorithm of McKenzie and van der Pol.[132] Using these data the utility values that the company used in the model-based cost-effectiveness evidence submitted to NICE were

TABLE 21 Utilities in pancreatic NETs: interventions – everolimus, sunitinib; comparator – BSC only

	Pre progression			Post progression		
	Everolimus + BSC	Sunitinib + BSC	Placebo	Everolimus	Sunitinib	Placebo
n	NA	86	85	NA	86	85
Mean utility	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
SE	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Source	Assumed to be equal to that for sunitinib + BSC	Analysis by the AG of individual patient data from A6181111[81] provided by the manufacturer	Analysis by the AG of individual patient data from A6181111[81] provided by manufacturer	Assumed to be equal to that for sunitinib + BSC	Analysis by the AG of individual patient data from A6181111[81] provided by manufacturer	Analysis by the AG of individual patient data from A6181111[81] provided by manufacturer
Alternative values	0.749	0.749	0.771	0.612	0.612	0.612
Source	Value from Swinburn *et al.*[131] times the ratio between the value for sunitinib and that for BSC in A6181111[81]	Assumed to be the same as that for everolimus	Value from Swinburn *et al.*[131] – AE adjusted	Value from Swinburn *et al.*[131]	Assumed to be the same as that for everolimus	Value from Swinburn *et al.*[131]

NA, not available; SE, standard error.

validated. Although the methods used by the company were not properly described in the submission itself,[32] the values used and the methods had been reported in the study by Mucino Ortega *et al.*[121] The validation exercise therefore sought to replicate the utility values submitted to NICE by following the methods described by Mucino Ortega *et al.*[121] This consisted of fitting a linear mixed-model equation to the EORTC QLQ-C30 data mapped to the EuroQol-5 Dimensions (EQ-5D) using the algorithm developed by McKenzie and van der Pol[132] 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). Confidential information has been removed. 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 > 90% of patients in the placebo arm had progressed by the end of the study.

Confidential information has been removed. This difference is the result of the incorrect use of the data in the analysis conducted by the manufacturer of sunitinib (Pfizer) in its submission to the Scottish Medicines Consortium (SMC)[133] and used by Novartis in its sensitivity analysis of the economic evaluation submitted to NICE.[33] 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 *et al.*'s[121] study led us to the following estimated linear mixed-model equation for stable disease:

$$EQ5Dm_{it} = 0.089 - 0.019\ sunitinib\ arm_i + 0.822 * EQ5Dm\ baseline_i - 0.0048 * cycle_{it} - 0.0016 * cycle * sunitinib\ arm_{it}. \quad (2)$$

where EQ-5Dm is the mapped utility score from the EORTC QOLQ-C30 in A6181111,[81] using the algorithm from McKenzie and van der Pol.[132] To estimate utilities for the two trial arms in the stable disease state, this model was fitted to data excluding the last follow-up, that is, the end-of-treatment follow-up observations, when some patients may have experienced disease progression, resulting in their withdrawal from treatment.

For GI and lung NETs patients under treatment with everolimus (*Table 22*), 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 its economic evaluation. These data were preferred to published estimates from pooled analysis[74] (i.e. utilities by health state regardless of treatment arm) used by the company in its base-case economic model submission, as they incorporate the impact of treatment-specific AEs and comorbidities on HRQoL. The treatment-specific utilities in the company's submission were based on unpublished individual patient data from RADIANT-4[35] that were not available to us for review. To validate such estimates, we mapped mean FACT-G scores in RADIANT-4,[35] reported by Singh *et al.*[74] in a poster also reporting pooled utilities by health state, using a linearised version of the algorithm from Longworth *et al.*[134] (see *Appendix 15*). The values that we obtained were approximately equal to those produced by the company from individual patient data in the pooled analysis with the original, non-linear mapping algorithm (see *Appendix 22*).

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[35] population.

No data on HRQoL for patients treated with 177Lu-DOTATATE were identified through the systematic review. For this reason, we had to rely on unpublished data submitted by AAA.[31] The utility values in the PenTAG base-case model are based on a Dutch single-arm, uncontrolled study that has not been published at the time of writing. Utility values for pre-progression GI NET patients (see *Table 22*) 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 the pre- and post-progression health states in 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 were 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.

TABLE 22 Utilities in GI and lung NETs: interventions – everolimus and 177Lu-DOTATATE

	Pre progression			Post progression		
	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[35] (Novartis[33])		ERASMUS study (AAA[31])	Pooled analysis of individual patient data from RADIANT-4[35] (Novartis[33])		Assumed to be the same as for everolimus
Alternative values	0.779		0.79	0.714	0.747	0.740
Source	Pooled analysis (Novartis[33])		Guy's and St Thomas' (UK) hospital registry (AAA[31])	Treatment arm-specific analysis (Novartis[33])		ERASMUS study (AAA[31])

SE, standard error.

The utilities adopted for the de novo model by the AG, presented in *Tables 21* and *22*, 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 Health Surgery for England 2012[135] following the approach of Ara and Brazier:[136]

$$\text{health state (HS) utility in cycle \#} = \text{HS utility in cycle 0} \times (1 - 0{:}0018 \times \text{cycle \#} - 2 \times 0{:}00001 \times \text{square of cycle \#}). \quad (3)$$

This adjustment was applied to all utilities irrespective of health state or treatment arm.

Summary

There is a lack of published evidence on HRQoL, especially for progressive disease 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,[81] provided by Pfizer through a NICE request.

The AG was able to validate the utilities derived by Novartis for the progressive disease and stable disease states in the GI location from RADIANT-4[35] data, without having access to the individual patient data but only aggregate HRQoL domain scores, by a linear approximation to the best-fitting algorithm from Longworth *et al.*,[134] used by Novartis to map individual FACT-G scores onto the EQ-5D. Linearising the best-fitting non-linear algorithm using first-order approximations enabled 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[35] population.

The analyses of individual patient data 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.

Resources and costs

Cost parameters and assumptions

The unit costs of treatments and resources were sourced according to the NICE *Guide to the Methods of Technology Appraisal 2013*.[37] Only costs that relate to the included interventions for the treatment of NETs, and to resources under the control of the NHS and PSS, were included. Value-added tax was excluded. Costs that were common and equal in all treatment strategies over the time horizon of the analysis were excluded. The cost-effectiveness results reflect the present value of costs and benefits accruing over the time horizon of the analysis.

We modelled the following costs, which were inflated to the cost year 2016, and used an annual discount rate of 3.5%:

- drug acquisition
- drug administration
- medical management and disease monitoring
- SAE management
- end-of-life care.

Costs of drug acquisition

Comparator treatments *Table 23* presents the unit costs of comparator treatments. The unit costs of everolimus and sunitinib were sourced from the *British National Formulary* (BNF) in September 2016.[36] The cost per unit of 177Lu-DOTATATE was provided by AAA as commercial-in-confidence information.

The base-case analyses used list prices. The results were also run using PAS prices, which can be found in the confidential appendix. This appendix is not included here as it contained commercial information provided by a company in confidence, as part of the NICE assessment process.

The recommended dosing for everolimus and sunitinib was sourced from their Summary of Product Characteristics (10 mg daily and 37.5 mg daily, respectively). The dose and administration schedule for 177Lu-DOTATATE (four administrations at intervals of 8 ± 1 week) was provided by AAA.

The base case used recommended dosing, adjusted for treatment interruptions and dose modifications as observed during the clinical trials. These RDIs were 85.9%[34] and 91.3%[81] for everolimus and sunitinib, respectively, in pNETs and 79.4%[35] for everolimus in GI and lung NETs. 177Lu-DOTATATE in GI (midgut) NETs had a RDI of 86.4%.

Table 24 presents the median unadjusted durations of treatment observed in the trials. 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[33] in its pNETs and GI/lung economic evaluations. Had we used exponential extrapolations fitted to the median treatment durations, the mean values for everolimus would have been 12.68 and 13.40 months for pNETs and GI/lung NETs, respectively, instead of the base case values of 9.41 and 11.54 months respectively. Time on treatment in the AG model was then assumed to follow an exponential distribution using the mean values in *Table 124*.

Table 25 presents the acquisition costs of the comparator treatments per 28-day Markov cycle. These are calculated by multiplying the unit cost for 28 days of treatment by the RDI.

The unit cost of SSAs, drugs administered as an adjunct to 177Lu-DOTATATE, chemotherapies and supportive treatments are also presented in the table.

TABLE 23 Unit cost of comparator treatments by unit size

Comparator	Unit size	Unit cost (list price) (£)[a]	PAS agreement[a]
Everolimus	5-mg tablets, 30-tablet pack	2250.00	Confidential information has been removed
	10-mg tablets, 30-tablet pack	2673.00	
Sunitinib	12.5-mg capsules, 28-capsule pack	784.70	Confidential information has been removed
	25-mg capsules, 28-capsule pack	1569.40	
	50-mg capsules, 28-capsule pack	3138.80	
177Lu-DOTATATE	7.4-GBq single cycle	Confidential information has been removed	NA

NA, not applicable.
a See information provided in the text.

TABLE 24 Median durations of treatment observed in the trials and mean values in the AG model

Comparator	Trial	Evaluation	Median treatment duration in the trial	Mean treatment duration in the AG model
Everolimus	RADIANT-3[34]	pNETs	Confidential information has been removed	(Confidential information has been removed) months[a]
	RADIANT-4[35]	GI and lung NETs	9.29 months	11.54 months[b]
	RADIANT-4[35]	GI (midgut)	Not available	13.99 months[c]
Sunitinib	A6181111[81]	pNETs	4.64 months	7.51 months[d]
177Lu-DOTATATE	NETTER-1[102]	GI (midgut) NETs	NA[e]	

NA, not applicable.
a Provided in the Novartis submission (p. 101).[33]
b Calculated by the AG from the time-on-treatment Kaplan-Meier curve provided in the Novartis submission (Figure 7.14).[33]
c Calculated by the AG from mean everolimus treatment duration in GI and lung in AG model (see footnote b) divided by the ratio of mean PFS in everolimus arm of RADIANT-4[35] to mean PFS of GI midgut subgroup in everolimus arm of RADIANT-4 (Singh *et al.*, 2016).[73]
d Calculated by the AG from the exponential extrapolation fitted to the median duration of sunitinib treatment in A6181111[81] and using a Bucher-type adjustment using the ratio of PFS between the placebo arm of A6181111[81] and the placebo arm of RADIANT-3.[34]
e 177Lu-DOTATATE is administered over a fixed number of cycles.

Use of somatostatin analogues in pancreatic neuroendocrine tumours The proportions of patients using SSAs for tumour suppression in stable disease were based on the proportions reported in clinical trials, adjusted in an ITC conducted by Novartis (section 4.7.2 of the Novartis submission[33]). The adjusted rates are presented in *Table 26*. We assumed that the SSA usage was equally split between octreotide and lanreotide and that SSA usage following sunitinib would be the same as that for everolimus.

The proportions of patients using SSAs for tumour suppression post progression were based on targeted treatment utilisation (proportions) following progression in the RADIANT-3[34] 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 of the proportion of patients using targeted treatments following progression after sunitinib. In the BSC arm of RADIANT-3,[34] 19.2% of patients were treated with targeted treatments following progression. In both the active and the BSC strategies, target treatments were assumed to be 20 mg of 50% octreotide and 90 mg of 50% lanreotide.

Somatostatin analogues were not used in stable disease for symptom control; however, we did include this resource in progressive disease. The proportion of patients using SSAs for symptom control was the same across the active treatment and BSC strategies; these were sourced from the unpublished UK utilisation survey presented in the Novartis submission.[33] The average number of SSA administrations at 500 µg was 1.9 per patient per cycle.

Use of somatostatin analogues in gastrointestinal and lung neuroendocrine tumours and gastrointestinal (midgut) neuroendocrine tumours The proportions of patients using SSAs for tumour suppression were based on octreotide utilisation in RADIANT-4.[35] The estimates used are unpublished but are reported in the CSR.[138] The estimates used in the model are presented in *Table 27*. We made the assumption that SSA utilisation concurrent and following sunitinib treatment would be the same as observed for everolimus.

Use of drugs as an adjunct to 177Lu-DOTATATE Advice from expert clinicians is that use of antiemetics 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 RDI) was accompanied by a 5-day course of an antiemetic {2 mg of granisetron [Granisetron hydrochloride, Alliance Healthcare (Distribution) Ltd]; unit cost £50.38) and an amino acid supplement

TABLE 25 Base-case costs of treatments

Treatment	Unit size	Unit cost (£)	Cost per 28 days (£)	Source
Everolimus (pNETs)	10 mg		2143.03	BNF[36]
Everolimus (GI and lung NETs)	10 mg		1980.87	BNF[36]
Sunitinib	37.5 mg		2148.93	BNF[36]
177Lu-DOTATATE [GI (midgut) NETs]	Four administrations, one per 8 ± 1-week interval	Confidential information has been removed	Confidential information has been removed	Price provided by the company to NICE for this evaluation
Octreotide	20-mg depot preparation	632.40	632.40	eMIT[137]
	30-mg depot preparation	806.42	806.42	eMIT[137]
	500-mc SC PFS	5.02	140.56	eMIT[137]
Lanreotide	90-mg prefilled syringe	736.00	736.00	BNF[36]
Granisetron	1-mg tablets, 10-tablet pack	50.38	50.38	BNF[36]
Vamin 18	1 l premixed	26.70	26.70	BNF[36]
5-fluorouracil[a]	250-mg vial	4.00	52.00	BNF[36]
	500-mg vial	6.40		
Capecitabine[b]	500-mg tablets, 120-tablet pack	225.72	158.00	BNF[36]
Doxorubicin[c]	50-mg vial	100.12	200.24	BNF[36]
Streptozocin	NA	Nil[d]	Nil	
Interferon alpha[e]	5 million IU	28.37	397.32	BNF[36]
Temozolomide[f]	180-mg capsules, 5-capsule pack	296.48	762.38	BNF[36]
Lidocaine[g] (Ralvo, Grunenthal Ltd)	50 mg/g plasters, 30	72.40	67.57	BNF[36]
Dexamethasone (Aspen Pharma Trading Ltd)[h]	2-mg tablets, 100-tablet pack	78.00	131.04	BNF[36]
Prednisone (Lodotra; Napp Pharmaceuticals Ltd)[i]	5-mg tablets, 100-tablet pack	89.00	74.76	BNF[36]
Prochlorperazine (Actavis UK Ltd)[i]	5-mg tablets, 84-tablet pack	2.09	2.09	BNF[36]

eMIT, electronic market information tool; NA, not applicable; PFS, pre-filled syringes; SC, subcutaneously.
a One treatment cycle of 716 mg requires one 500-mg vial and one 250-mg vial.
b 750 mg/m^2 twice daily; at an average body surface area of 1.79 m^2, this is equal to 2685 mg per day for 14 days, equivalent to six 500-mg tablets per day and 84 tablets per treatment cycle.
c 40 mg/m^2 per treatment cycle; at an average body surface area of 1.79 m^2, this approximates to 100 mg, equivalent to two 50-mg vials.
d Assumed to be a cost to the CDF, budgeted separately from direct NHS resources.
e 5 million IU every other day, effectively 5 million IU 14 times per 28-days.
f 200 mg/m^2 every day for 4 days; at an average body surface area of 1.79 m^2, this equates to two 180-mg capsules per day.
g One 50-mg plaster per day.
h 12 mg per day for 28 days, which equates to six 2-mg tablets per day or 168 tablets per 28-day cycle.
i 5 mg three times a day or 84 tablets per 28-days.

TABLE 26 Proportion of patients using SSAs prior to progression in clinical trials

Comparator	Trial	Arm	Proportion using SSAs (%)[a]
Everolimus	RADIANT-3[34]	Active	37.7
		Placebo	39.9
Sunitinib	A6181111[81]	Active	36.8[b]

a This proportion was split equally between octreotide and lanreotide.
b OR 1.04 (95% CI: 0.48 to 2.26).

TABLE 27 Proportions of patients using SSAs in the evaluations of GI and lung NETs and GI (midgut) NETs

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

[an intravenous infusion of Vamin 18 (Amino-Acid electrolyte-free, Fresenius Kabi Ltd, Runcorn, UK); unit cost £26.70].

Chemotherapy utilisation post progression For the pNETs evaluation we adopted unpublished chemotherapy utilisation rates from RADIANT-3,[34] provided by Novartis[33] and presented in *Appendix 15*, *Table 111*. Slightly different data were also provided in table 3.7 of appendix 3 of the Novartis evidence submission to NICE on the rate of subsequent treatments in RADIANT-3[33,34] for patients who progress following active treatment (29.4%) and BSC (29.1%)]. In the absence of post-progression treatment information for patients in A618111,[81] we assumed the same chemotherapy utilisation rates for people who progressed following sunitinib as was observed for everolimus.

For the GI and lung NETs evaluation and the GI (midgut) evaluation, we adopted unpublished chemotherapy utilisation rates from RADIANT-4[35] (supplied in the Novartis evidence submission[33]), presented in *Appendix 16*, *Table 113*.

Other supportive drug therapies Other therapies are used to support patients with NETs in addition to the use of SSAs, including analgesics, antiemetics, and antidiarrhoeals. We included the cost of these therapies in the GI and lung NETs evaluation and the GI (midgut) NETs evaluation using the unpublished utilisation rates supplied in the Novartis submission,[33] which are based on data from RADIANT-4.[35] These are presented in *Table 114* (see *Appendix 16*). No equivalent utilisation estimates were identified for other supportive therapies for patients with pNETs and so no costs of this type were included.

Costs 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.[139,140] The cost of hospital pharmacy dispensing, applied at each outpatient clinic visit, was included in our costing for the oral preparations. This required 12 minutes of hospital pharmacist time, equating to £14.40.

In contrast, the administration of 177Lu-DOTATATE is resource intensive. As a radiolabelled and intravenously delivered drug, it requires specialist oversight and a hospital setting. AAA[31] concurs in its data submission (section 2, p. 25) by stating that its 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 28 presents the cost of drug administration for 177Lu-DOTATATE. The estimated quantity of resource required is the average elicited from two NHS consultants in nuclear medicine. Unit costs were obtained from standard sources.[141,142]

The costs associated with administering supportive treatments are presented in *Table 29*. Unit costs were obtained from standard sources.[141,142] Supportive treatments in *Tables 25* and *114* but not listed here did not attract an administration cost; the cost of dispensing was not included for any supportive treatment.

Costs 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.

TABLE 28 Resource requirement for the administration of 177Lu-DOTATATE

Resource	Quantity[a]	Unit cost (£)	Cost of resource type (£)
Hospital admission	90%	586.93[b]	528.24
Day case	10%	720.78[b]	72.08
Nuclear medicine consultant	2.5 hours	137.00[c]	342.50
General medicine consultant	0.25 hours	137.00[c]	34.25
Radiographer	1.5 hours	40.00[c]	60.00
Physicist (band 7)	0.5 hours	52.00[c]	26.00
Total			1063.07

a This is the average of two estimates.
b *NHS Reference Costs 2014 to 2015*[141] for hospital services, non-elective inpatient stays (short stays), national average.
c *Unit costs of Health and Social Care 2015*.[142]

TABLE 29 Unit cost of administering supportive treatments

Administration	Visit	Treatments	Unit cost (£)
Intravenous/intramuscular injection	First[a]	5-fluorouracil, doxorubicin, streptozocin, lanreotide	239.12
	Subsequent[b]		326.46
Subcutaneous injection	Any	Octreotide	22.00[c]

a Healthcare Resource Group currency code SB12Z: deliver simple parenteral chemotherapy at first attendance.
b Healthcare Resource Group currency code SB15Z: deliver subsequent elements of chemotherapy cycle.
c 15 minutes of hospital nurse time (band 5) at £88 per hour.[142]

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 are. 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 resource that a patient with NETs requires during the course of the disease and estimate the number of times that a patient would see each physician each month. The resource use for the given NETs 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[34] and GI NETs and lung NETs in RADIANT-4,[35] to determine resource use for the overall trial populations.

For the BSC strategy in the pNETs evaluation, which was not modelled by Novartis, the resource utilisation of patients with stable disease was assumed to be the same as that presented for patients on active treatment. For patients with pNETs who progressed on BSC, resource utilisation was assumed to be equal to that for those who progressed on active treatment.

In some instances we modified the raw survey findings for our modelling:

- The frequency of resource use for people who progressed following active treatment was adjusted downwards 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 frequencies of consultations and procedures and tests for people with stable pNETs receiving BSC were reduced to below the estimates for active treatment. The reductions were proportionate to the differences 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 downwards to the average of estimates from our expert clinicians. Utilisation survey estimates gathered by Novartis appeared high in absolute terms but also compared with frequencies in people with pNETs.

We used standard sources for the unit costing of disease management and monitoring.[141] These unit costs are presented in *Table 30*.

Rates of hospital resource use are presented in *Table 31* for the pNETs evaluation and *Table 32* for the GI and lung NETs and GI (midgut) NETs evaluations.

Other supportive procedures following progression Additional supportive procedures were included in the pNETs evaluation based on patient-level data from RADIANT-3[34] supplied by Novartis in its evidence submission.[33]

Similarly, supportive treatments were included in the costing for the GI and lung NETs and GI (midgut) NETs evaluations. These rates of utilisation were based on patient-level data from RADIANT-4[35] supplied by Novartis in its evidence submission.[33]

Costs of adverse event management

Adverse events experienced by patients on treatment attract additional health-care resources. To approximate the cost of managing those treatment-related AEs that could influence the cost-effectiveness of included treatments, we included only grade 3 and 4 AEs (SAEs) occurring in $\geq 2\%$ of patients in either arm of the trials (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03[111]).

TABLE 30 Unit costs of admissions, consultations, procedures and tests

Resource	Unit	Unit cost (£)
Hospitalisation	Per admission	
General admission		586.93
Emergency admission		147.30
Outpatient clinic consultations	Per consultation	
Medical oncologist		158.54
Surgeon		132.95
Palliative care		185.92
Respirologist		156.29
Nurse specialist		37.26
Dietitian		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 radiography		42.12
Octreoscan/SRS		806.32
I-131 mIBG scan		348.54
FDG PET		492.51
Pro-BNP		20.37
Standard blood test: biomarkers		1.19
Special blood test: other		3.01

BNP, B-type natriuretic peptide; FDG, fluorodeoxyglucose; I-131 mIBG, iodine-131 meta-iodobenzylguanidine; SRS, somatostatin receptor scintigraphy.

In the evaluation of pNETs this included SAEs reported in RADIANT-3[34] and A6181111.[81] In the evaluation of GI and lung NETs, as well as GI (midgut) NETs, this included SAEs reported in RADIANT-4[35] and NETTER-1.[102]

In pNETs, an ITC was conducted to match the trial populations of A6181111[81] and NETTER-1[102] to the trial populations of the respective RADIANT trials (see *Table 135*). For each active treatment in the three evaluations, an OR was applied to the weighted average rate to give a relative rate by strategy for each

TABLE 31 Base-case frequency of resource use for pNETs per 28 days

Resource	Stable disease	Progressive disease	Stable disease	Progressive disease
	Active treatment	BSC	Active treatment	BSC
Hospitalisation				
General admission	0	0	0.0577	0.0577
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 radiography	0	0	0.0128	0.0128
Standard blood test: biomarkers	0.2254	0.0660	0.3333	0.3333
Special blood test: other	0.5715	0.4280	0.7051	0.7051

SRS, somatostatin receptor scintigraphy.

event type (see *Table 115*). In GI and lung NETs (see *Table 116*), and GI (midgut) NETs (see *Table 117*), the unadjusted proportions of patients experiencing a SAE as reported in RADIANT-4[35] and NETTER-1[102] were used.

Based on the assumption that no patient would report more than one SAE of any specific type during their time on treatment, we applied the costs of SAE management only to the initial Markov cycle in the progression-free health state.

Cost of end-of-life care

On the basis that the average cost of health resource use in the final weeks of the life of a cancer patient is a reasonable surrogate for patients with a NET, we used an estimate from the literature for cancer patients in England and Wales (£4346.19). This includes elective and non-elective inpatient admissions, outpatient appointments, accident and emergency visits and district nurse and general practitioner (GP) visits from the point at which a strong opioid is first used.[143]

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 be equal to total mean QALYs when all utilities are set to 1.

TABLE 32 Base-case frequency of resource use for GI and lung NETs and GI (midgut) NETs per 28 days

Resource	Stable disease	Progressive disease	Stable disease	Progressive disease
	Active treatment	BSC	Active treatment	BSC
Hospitalisation				
General admission	0.0357	0.0357	0.0005	0.0052
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
Dietitian	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 radiography	0.0065	0.0067	0.0052	0.0053
Octreoscan/SRS	0.0771	0.0780	0.0375	0.0372
I-131 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

BNP, B-type natriuretic peptide; FDG, fluorodeoxyglucose; I-131 mIBG, iodine-131 meta-iodobenzylguanidine; SRS, somatostatin receptor scintigraphy.

Cost-effectiveness results

Base-case results

In this section, we report the outputs of our base-case analysis on a per-tumour location basis assuming list prices for everolimus and sunitinib.

Pancreatic neuroendocrine tumours

According to the model predictions, the highest mean survival time is expected in patients with pNETs treated with sunitinib (6.39 years); an 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 produced in patients treated with sunitinib followed by patients treated with everolimus and BSC only. The highest costs are predicted in patients in the sunitinib arm, followed by patients in the everolimus and BSC-only arms, with the costs of drug acquisition being the major driver of the total costs.

The resulting mean ICER for everolimus compared with BSC is £45,493 per QALY. As this figure is higher than the ICER for sunitinib compared with everolimus, sunitinib and BSC extendedly dominate everolimus, so that, ultimately, the relevant comparison is sunitinib compared with BSC, for which the ICER is £20,717.

The breakdown of life-year, QALY and cost outcomes is presented in *Table 33*. It may be noted that, although sunitinib incurs higher incremental per-patient drug acquisition costs compared with BSC than everolimus does (£27,431 vs. £26,885), sunitinib more than compensates for the excess in costs through the larger corresponding incremental gain in QALYs compared with BSC (1.32 years vs. 0.59 years). The majority of the difference in QALY outcomes originates from survival time in the post-progression health state (1.89 years vs. 0.52 years), which has the same associated HRQoL under both treatment options.

Gastrointestinal and lung neuroendocrine tumours

The comparison between treatment with everolimus and treatment with BSC for the GI and lung NETs patient subpopulation yielded an ICER of £44,557 per QALY, exceeding the upper bound of NICE's threshold range. Treatment of these patients with everolimus results in better survival (6.21 years vs. 4.82 years for BSC). Likewise, the treatment costs in the everolimus arm are higher, driven by the drug acquisition costs in the pre- and post-progression health states (*Table 34*).

Gastrointestinal (midgut) neuroendocrine tumours

In our analysis, treatment of patients from the GI (midgut) NETs subpopulation with everolimus and BSC results in survival times of 7.5 years and 7.05 years respectively. Predicted QALYs are slightly higher in patients treated with everolimus than in patients treated with BSC (4.37 vs. 4.12).

A mean cost of £55,842 per patient was incurred in the everolimus arm, whereas the mean cost in the BSC arm was £21,119 per patient. Drug acquisition was the major cost component in this analysis (*Table 35*). The resulting ICER for everolimus compared with BSC was £199,233 per QALY.

In *Table 36* we present the results for the treatment of GI (midgut) NETs with 177Lu-DOTATATE. This analysis incorporates background mortality as explained in *Background mortality*.

Sensitivity analyses are presented in *Appendix 18*. Subgroup analyses and scenario analyses are presented in *Appendix 11*.

Discussion

In patients with NETs of pancreatic origin, sunitinib plus BSC was estimated to incur a cost per QALY gained compared with BSC alone of £17,890. Everolimus was found to be an inefficient treatment option

TABLE 33 Peninsula Technology Assessment Group detailed base-case results for pancreatic NETs

Outcome or cost measure/health state	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	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	0.18	0.43	0.62
Post progression	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	0.55	0.16	0.71
Total	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	0.73	0.59	1.32
Costs (mean, discounted) (£)						
Pre progression						
Drug acquisition	22,216	25,547	2003	–3331	23,544	20,213
Drug administration	1308	1104	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	2712	–2994	24,847	21,853
Post progression						
Drug acquisition	8120	6113	4660	2006	1453	3460
Drug administration	1949	1468	1106	482	361	843
Medical management	4993	3759	3394	1234	365	1599
End-of-life care	3565	3747	3889	–182	–142	–324
Total (post progression)	18,627	15,087	13,049	3540	2038	5578
Total	43,192	42,646	15,761	546	26,885	27,431
ICER (cost/QALY) (£)				745	45,493	20,717

as it achieves QALY gains compared with 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 per QALY.

As discussed in *Chapter 7*, sunitinib also meets the end-of-life criteria from NICE in the patient population of A6181111,[81] as it extends mean OS in patients with pNETs by > 3 months relative to placebo plus BSC, for which life expectancy is not significantly different from 24 months at conventional levels of statistical significance (i.e. $p < 0.05$).

TABLE 34 Peninsula Technology Assessment Group detailed base-case results for GI and lung NETs

Outcome or cost measure/health state	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	4141	2038	2102
AEs	171	34	137
Total (pre progression)	30,513	2450	28,063
Post progression			
Drug acquisition	4331	2511	1820
Drug administration	21	10	11
Medical management	8886	7822	1064
End-of-life care	3583	3732	–149
Total (post progression)	16,822	14,076	2746
Total	47,334	16,526	30,809
ICER (cost/QALY) (£)			44,557

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 was substantial treatment crossover from the placebo arms to the active arms in these trials. The companies sponsoring the two treatments have conducted statistical analyses that seek to adjust for such crossover. The AG asked the companies to provide the codes and data to be able to replicate their crossover-adjusted analyses of OS and understand whether the methods are likely to be comparable. The sponsor of everolimus provided such information too close to the end of the reviewing period to allow the AG to review and incorporate the evidence in this report. The sponsor of sunitinib provided the trial data but not the code to replicate the results of its crossover-adjusted analysis of OS. This leaves a crucial source of uncertainty unaddressed, as the available crossover-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[34]) is 30% higher than life expectancy in the placebo arm of the sunitinib trial (A6181111;[81] 18 vs. 14 months).

TABLE 35 Peninsula Technology Assessment Group detailed base-case results for everolimus in GI NETs

Outcome or cost measure/health state	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	5945	3449	2495
AEs	287	105	182
Total (pre progression)	38,215	4194	34,021
Post progression			
Drug acquisition	4637	3260	1377
Drug administration	23	13	10
Medical management	9515	10,155	–640
End-of-life care	3452	3497	–45
Total (post progression)	17,627	16,925	702
Total	55,842	21,119	34,723
ICER (cost/QALY) (£)			199,233

Our analyses extend the evaluation of pNETs submitted by the companies to include the BSC-only arm, in line with the NICE scope for this assessment. There is no clear justification for excluding this treatment option from the analysis, especially as the RCTs in this patient population have themselves included this 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 NETs patient population, the available head-to-head trial evidence from the Phase III RADIANT-4[35] trial suggests that everolimus is not cost-effective at the upper NICE threshold of £30,000 per QALY, even after adjusting for the negotiated PAS discount. Contrary to the analysis submitted to NICE by the company sponsoring everolimus, we adopted different utility values in stable disease to acknowledge the effect of treatment on patient HRQoL. Whereas the company found that everolimus is (confidential information has been removed) after applying the PAS discount, we found that the ICER was £39,323 per QALY. Our analysis reveals that the company's results were not robust to limited variations in the

TABLE 36 Peninsula Technology Assessment Group detailed base-case results for 177Lu-DOTATATE in GI (midgut) NETs

Outcome or cost measure/health state	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	Confidential information has been removed	633	31,152	Confidential information has been removed	Confidential information has been removed
Drug administration	178	Confidential information has been removed	4	174	Confidential information has been removed	Confidential information has been removed
Medical management	5904	Confidential information has been removed	3437	2466	Confidential information has been removed	Confidential information has been removed
AEs	287	Confidential information has been removed	105	182	Confidential information has been removed	Confidential information has been removed
Total (pre progression)	38,155	Confidential information has been removed	4180	33,975	Confidential information has been removed	Confidential information has been removed
Post progression						
Drug acquisition	3349	1093	2117	1232	–2256	–1024
Drug administration	16	5	8	8	–11	–3
Medical management	6871	2242	6595	276	–4629	–4353
End-of-life care	3627	3522	3728	–101	–105	–206
Total (post progression)	13,863	6862	12,448	1415	–7001	–5586
Total	52,018	83,667	16,628	35,390	31,649	67,039
ICER (cost/QALY) (£)				78,330	50,499	62,158

interpretation of the same available data (derived from the RADIANT-4[35] trial and the company's resource use survey) used to populate model parameter values and specify the survival time structure in the model. We provide a detailed comparison of the analyses produced by the AG and those submitted to NICE by the companies in *Appendix 23*.

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 compared with BSC. This analysis is subject to high levels of uncertainty because of the 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,[35] 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 in which evidence from the NETTER-1[102] trial for the 177Lu-DOTATATE arm was matched to the midgut population of RADIANT-4[35] by assuming that the control arm in NETTER-1[102] represents the same treatment as that given in the placebo plus BSC arm in RADIANT-4.[35] As this assumption has been questioned by our clinical experts, we consider this analysis with reservation. Subject to these caveats, 177Lu-DOTATATE is associated with higher QALY benefits compared with BSC than everolimus compared with BSC, 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.

Chapter 7 End of life

For each of the 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, which was used as the source of data in the AG model. For pNETs the curve used in these analyses was the placebo Kaplan–Meier curve adjusted using the RPSFT method,[48,69,122] whereas for GI/lung only, for which only unadjusted Kaplan–Meier data were available (crossover in the placebo arm was 6%[35,88]), the ITT placebo Kaplan–Meier curve was used. The results are presented in *Table 37*.

Mean survival estimates from head-to-head trials show that the null hypothesis that the pNETs population in A6181111[81] meets the life expectancy end-of-life criterion is not rejected by the data as the 95% CI of the extrapolated (to a maximum age of 100 years) mean survival in the placebo arm (95% CI 16 to 27 months) crosses the 24-month threshold. In other words, the data support the view that life expectancy with BSC only in A6181111[81] may be ≤ 2 years. In contrast, the pNETs population in RADIANT-3[34] has an extrapolated mean survival estimate in the placebo arm that is statistically significantly higher than 24 months (95% CI 34 to 54 months). The same result is obtained for GI/lung NETs, for which the data reject the null hypothesis that the life expectancy of the population is < 24 months (95% CI 44 to 86 months) at the 5% significance level.

Sunitinib is estimated to have a mean treatment effect of 5.9 months, using observed data from A6181111[81], or 38.5 months, using a parametric (exponential) survival curve 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[34] is 1.6 months using observed data and 14.7 months according to the extrapolated survival curve. The respective estimates for everolimus in GI or lung NETs are 2.6 and 16.6 months.

In conclusion, the end-of-life criteria may be met only by sunitinib in the pNETs population of A6181111.[81] In GI or lung NETs, life expectancy does not meet the end-of-life criteria set by NICE.[37]

TABLE 37 Life expectancy and extension to life observed in each trial

	pNETs		GI/lung NETs
Treatment	**[a]RADIANT-3[34]**	**A6181111[81]**	**RADIANT-4[35]**
Restricted mean (95% CI) at the end of follow-up (area under the Kaplan–Meier curve) (months)			
Placebo + BSC	18.3 (17.2 to 19.4)	14.5 (12.6 to 16.3)	29.1 (26.1 to 32.1)
Everolimus + BSC	19.9 (19.0 to 20.9)		
Sunitinib + BSC		20.4 (18.9 to 22.0)	31.7 (29.9 to 33.5)
Treatment effect (active treatment arm – placebo arm)	1.6	5.9	2.6
Extrapolated mean (95% CI) using the exponential survival function[b] (months)			
Placebo + BSC	41.6 (33.9 to 53.6)	20.5 (16.4 to 27.4)	57.9 (43.5 to 86.2)
Everolimus + BSC	56.3 (48.2 to 67.7)		74.5 (60.0 to 97.8)
Sunitinib + BSC		59.0 (55.8 to 80.0)	
Treatment effect (active treatment arm – placebo arm)	14.7	38.5	16.6

a Restricted to the maximum observed time (24 months) in the arm (placebo + BSC) with the shortest length of follow-up.
b Restricted at 40 years after the start of treatment (≈100 years of age).

Chapter 8 Discussion

Aim

The key objectives of this technology assessment report, in keeping with the final NICE scope, were twofold: first, to estimate the clinical effectiveness of three interventions (everolimus, 177Lu-DOTATATE and sunitinib) for treating unresectable or metastatic NETs with disease progression and, second, to establish the cost-effectiveness of these interventions. The comparator treatments were chemotherapy, interferon alpha and BSC.

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 18 August 2016,[30] lanreotide and octreotide were dropped.

Clinical effectiveness evidence

The interventions of interest were everolimus (NETs of pancreatic, GI or lung origin), 177Lu-DOTATATE (NETs of pancreatic or GI origin) and sunitinib (pNETs).

Three trials, RADIANT-3,[34] A6181111[81] and RADIANT-4,[35] met the inclusion criteria for the clinical effectiveness systematic review.

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

Clinical effectiveness results: pancreatic neuroendocrine tumours

Key results only are given here. A fuller summary of the results is provided in *Chapter 4*, *Summary*.

Two trials provided evidence on the effectiveness of everolimus (RADIANT-3[34]) and sunitinib (A6181111[81]) for the treatment of pNETs. Both interventions were compared with placebo. In both trials, BSC was also given in both the intervention arm and the placebo arm.

Evidence consistently suggested a treatment effect in favour of both everolimus plus BSC and sunitinib plus BSC compared with 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 to 0.44, by central review). Similarly, treatment with sunitinib was associated with a 68% reduction in the risk of progression or death (HR 0.32, 95% CI 0.18 to 0.55).

Treatment switching from the placebo arm to the treatment arm occurred in 73% of participants in RADIANT-3[34] and 69% of participants in A6181111.[81] The treatment switching significantly compromised the OS results. The HR for unadjusted OS was reported to be 0.94 (95% CI 0.73 to 1.20; $p = 0.30$) in RADIANT-3[34] and 0.73 (95% CI 0.50 to 1.06; $p = 0.094$) in A6181111.[81] Using the RPSFT model, the HR for OS was reported to be 0.60 (95% CI 0.09 to 3.95) in RADIANT-3[34] and 0.34 (95% CI 0.14 to 1.28; $p = 0.094$) in A6181111.[81]

Overall, AEs were more commonly reported following treatment with everolimus and sunitinib than following treatment with placebo.

We compared everolimus with sunitinib in a simple ITC using the Bucher method.

Clinical effectiveness results: gastrointestinal/lung neuroendocrine tumours

One trial (RADIANT-4[35]) provided evidence for the effectiveness of everolimus plus BSC in GI and lung NETs.

Evidence consistently suggested a treatment effect in favour of the use of everolimus plus BSC compared with 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 to 0.54). For OS, treatment with everolimus plus BSC was associated initially with a 36% improvement for individuals with lung and GI NETs compared with placebo (HR 0.64, 95% CI 0.40 to 1.05). However, in follow-up data from the company submission,[33] a 27% improvement in OS following treatment with everolimus was reported (HR 0.73, 95% CI 0.48 to 1.11); however, this was unadjusted for crossover.

Overall, AEs were more commonly reported following treatment with everolimus than following treatment with placebo.

Clinical effectiveness results: gastrointestinal neuroendocrine tumours

Following a data request from us to Novartis, results from RADIANT-4[35] were provided for people recruited with only GI NETs.

Median PFS for those with GI NETs from RADIANT-4[35] was 13.1 months for treatment with everolimus and 5.4 months for placebo (HR 0.56, 95% CI 0.37 to 0.84). OS estimated from a Kaplan–Meier curve at the 25th percentile was (confidential information has been removed) in the everolimus arm compared with (confidential information has been removed) in the placebo arm.

Overall, AEs were more commonly reported following treatment with everolimus than following treatment with placebo for people with GI NETs.

Clinical effectiveness results: lung neuroendocrine tumours

Following a data request from us to Novartis, results from RADIANT-4[35] were provided for people recruited with only lung NETs.

Everolimus was associated with a 50% reduction in the risk of disease progression compared with placebo. Survival was improved by 44% following everolimus treatment compared with treatment with placebo.

Overall, AEs were more commonly reported following treatment with everolimus than following treatment with placebo.

Strengths and limitations of the clinical effectiveness review

Strengths of the clinical effectiveness review

A strength of this study is that a systematic review of RCTs of everolimus, 177Lu-DOTATATE and sunitinib in people with unresectable or metastatic NETs with disease progression was conducted to evaluate relative efficacy. In the absence of head-to-head RCTs, an ITC was conducted to assess the relative efficacy of everolimus and sunitinib for pNETs and everolimus and 177Lu-DOTATATE for GI NETs for the outcomes of PFS, OS, RRs and AEs. The strength of our review was the systematic nature of our search and review of published and unpublished data from the few available RCTs in this field, especially information held by sponsoring companies, which were willing to provide commercial-in-confidence information through the NICE process.

Limitations of the clinical effectiveness review

- We were unable to compare 177Lu-DOTATATE with everolimus and sunitinib in individuals with pNETs, as the NETTER-1 RCT[102] 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 assumptions in the ITC comparing everolimus and 177Lu-DOTATATE in GI NETs, primarily that 30 mg of octreotide is equivalent to placebo plus BSC; therefore, these analyses should be treated with caution.

Cost-effectiveness

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 the inclusion of costing studies relevant to the UK, economic evaluations 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 (the USA,[120] Mexico[121] and Poland[123,144]). 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 USA and sponsored by Novartis found that everolimus was cost-effective compared with sunitinib, based on an ICER for everolimus equivalent to £30,524 per QALY gained relative to sunitinib at 2015 UK prices. This study was based on an ITC of relative outcomes compared with placebo for RADIANT-3[34] and A6181111.[81] A strength of the study was its use of matching methods that acknowledge the heterogeneity in patient populations across trials.[129] A weakness was its omission of BSC alone as a comparator in its own right, especially as both RADIANT-3[34] and A6181111[81] included this treatment option as a control arm.

A second study, conducted in Mexico and sponsored by Pfizer, found that sunitinib was cost-effective based on an ICER equivalent to £32,842 per QALY gained compared with BSC alone at 2015 UK prices. The study was based on trial data from A6181111.[81] A strength of the study was its assessment of quality of life using patient-reported outcomes in the trial. A weakness of the study was its omission of an 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 crossover from placebo to sunitinib in the open-label phase of A6181111,[81] which results in an underestimation of health benefits and likely overestimation of the ICER of initial treatment with sunitinib.

A third study, conducted in Poland and also sponsored by Pfizer, found that sunitinib was cost-effective based on an ICER equivalent to £33,866 per QALY gained relative to BSC alone at 2015 UK prices. The study was based on trial data from A6181111.[81] A strength of the study was its adjustment for the effect of crossover from placebo to sunitinib in the open-label phase of A6181111.[81] One limitation was the lack of an active treatment comparator in the evaluation. Another limitation was 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 of a study conducted in this clinical area in Europe.

A fourth study, the only one identified that was conducted in the UK,[122] which was 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 per QALY gained relative to placebo at 2015 UK prices. The strength of the study was its adjustment for the effect of treatment crossover from placebo to sunitinib on OS. The main limitation was the lack of adequate methodological detail available from the report.

Critique of the company model submissions

Of the three companies that submitted evidence to NICE, two included economic evaluations in their submission. Novartis[33] evaluated treatments in pNETs and GI and lung NETs. AAA[31] evaluated treatments in pNETs and GI NETs. Pfizer did not submit an economic evaluation.

The economic evaluation by Novartis used a partitioned survival model of sunitinib compared with everolimus in pNETs, based on an ITC of placebo-controlled outcomes in A6181111[81] and RADIANT-3.[34] The company found that sunitinib dominated everolimus as it had lower costs and produced more QALYs. This result was derived by assuming equal PFS and OS outcomes between treatments, which in turn was based on the CIs found in the ITC, that is, a PFS HR of 1.08 (95% CI 0.59 to 1.99) and a RPFST-adjusted OS HR of 1.39 (95% CI 0.17 to 11.72). As a result, the only health benefit on which treatments were compared was HRQoL (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,[34] the company imputed treatment differences according to the incidence of AEs 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 do not meet the NICE requirement that HRQoL data be derived from actual patient outcomes, hamper the value of this evidence for NICE decision-making. Furthermore, the data used in this evaluation by Novartis[33] from A6181111[81] appear to be outdated.

A second evaluation by Novartis assessed everolimus plus BSC relative to BSC alone in the non-functional GI and lung NETs population using data from RADIANT-4.[35] Novartis found that everolimus had an ICER of £43,642 per QALY gained relative to BSC alone or an ICER of (confidential information has been removed) when a PAS discount of (confidential information has been removed) was applied to the list price. The main strength of this assessment was its use of data from RADIANT-4[35] to populate the model parameters. The main limitations were the immaturity of the OS data in the trial, the lack of adjustment for treatment crossover to targeted treatments and the lack of adjustment for treatment switching before disease progression (13% and 14% in the everolimus and placebo arms respectively), which was dealt with by censoring data for switching cases at the time of the switch. Finally, the study adopted a high frequency of oncologist visits.[33]

Advanced Accelerator Applications submitted an evaluation in pNETs of 177Lu-DOTATATE compared with everolimus and sunitinib but the value of the resulting evidence is questionable as it was based on trial data from NETTER-1,[102] which included only midgut NETs patients. Furthermore, the AAA evaluation lacked BSC as a relevant comparator. The company also submitted an assessment of 177-Lu-DOTATATE compared with everolimus in the GI NETs subpopulation of SSTR+ patients, which produced a base-case ICER of (confidential information has been removed). This evidence is also of limited quality as it involved an ITC of NETTER-1 outcome data with data from RADIANT-4,[35] which included non-midgut GI and lung NETs. This analysis by AAA in the GI NET population also omitted BSC alone, a relevant comparator. There is also a limitation in that costs did not include resource use for disease monitoring, for example oncologist visits and the costs of 177Lu-DOTATATE administration were underestimated.[31]

Strengths and limitations of the evidence from company model submissions

The company submissions benefit from having individual patients from the few trials available to inform their assessments. The main limitation with the 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 from RADIANT-4,[35] in particular the use of the same utility values in stable disease 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[35] are uniquely available from this source. On the other hand, the evidence on treatment regimens used and the frequency of contacts with health professionals was 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 are limited, particularly for A6181111,[81] with, for example, information on treatments used after disease progression not collected for this trial.

Given the limitations of the evidence from industry submissions and the literature, the AG requested from Novartis individual patient data from RADIANT-3 to replicate some of the ITCs (MAICs) and adjustment for treatment crossover in pNETs. The company declined to provide the MAIC analysis data, noting that the analyses in question did not inform its economic evaluation. However, the company did agree to provide data on its adjustment of OS outcomes for crossover in RADIANT-3[48,69] which the AG could use to replicate the company's findings submitted to NICE. Pfizer also agreed to provide its individual patient data and code for its own crossover-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 ITC, matching the A6181111[81] sample of individual patient data to the RADIANT-4[35] baseline characteristics. This highlighted the limitations associated with simple standard Bucher-type comparisons underpinning the Novartis submission,[33] originating from the small sample size of A6181111[81] and the consequent imbalance in key baseline characteristics between trial arms, that is, PS, 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.

Independent economic assessment

The AG built a three-health-state partitioned survival model in two NET patient populations. One was in 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 RADIANT-3[34] and A6181111.[81] The second evaluation compared everolimus plus BSC with BSC alone in patients with non-functional GI and lung NETs, based on RADIANT-4[35] data. In addition, we conducted a subgroup analysis of everolimus plus BSC, BSC alone and 177Lu-DOTATATE plus 30 mg of octreotide in the GI (midgut) population using PFS data for this subgroup from RADIANT-4[35] 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 digitised from the latest OS and PFS Kaplan–Meier curves from published sources and industry submissions. Resource use model parameters were populated with data from the Novartis submission,[33] with modifications to reflect our clinical experts' opinions of resource use intensity associated with disease monitoring. Prices and other details adhered to the NICE reference case recommendations.

In the pNETs population, we found that sunitinib had an ICER of £20,717 per QALY gained relative to BSC alone, at the current list price. The corresponding figure for everolimus was £45,493 per QALY gained. These figures imply that sunitinib is superior to everolimus as it may achieve the same amount of benefit at a lower cost to the NHS. In the GI and lung population, everolimus had an ICER of £44,557 per QALY gained relative to BSC alone. In the GI (midgut) subgroup, the ICER for everolimus relative to BSC alone was £199,233 per QALY gained. It must be noted that the results in the GI (midgut) subgroup are affected by a high level of uncertainty because of PFS-based imputation of OS outcomes in the model, as we did not have available actual OS data on this subgroup of RADIANT-4[35] 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 gained relative to BSC alone, at the current list price; the respective figure for 177Lu-DOTATATE plus 30 mg of octreotide was £62,158 per QALY gained. Both these results and the 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 treatment relies critically on adjusting for the effects of crossover from placebo to sunitinib on OS. At current list prices, the ICERs for initial treatment with sunitinib and everolimus relative to BSC were £37,217 and £136,455 per QALY gained, respectively, without adjustment for crossover, 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 NETs and from NETTER-1 data.[102] In particular, there is evidence that the cost-effectiveness of everolimus in GI and lung NETs depends on benefits that arise in the later years of life, and it is thus sensitive to the discount rate.

The above figures appear to suggest that the data for sunitinib are more robust than those for everolimus in both pNETs and GI and lung NETs, which are more sensitive to adjustment for treatment crossover and the effects of the time horizon and discounting. In addition, 177Lu-DOTATATE was found to produce the largest health benefits of all treatment strategies investigated for GI (midgut) NETs, that is, 1.76 and 0.91 more years of life than the BSC alone and everolimus strategies, respectively. These figures are remarkable, especially because the fact that 60 mg of octreotide was given in the control arm would suggest that the health benefits of 177Lu-DOTATATE relative to other treatments are underestimated in our analysis.

On request from the NICE appraisal committee, we performed further analyses for lung NETs (see addendum in *Appendix 17*) and, separately, the overall GI location (see addendum in *Appendix 19*) using RADIANT-4 data on these populations extracted from survival curves provided in analyses performed by Novartis in response to our assessment herein. We found that in these two locations and at current list prices, everolimus has ICERs of > £20,000 per QALY relative to BSC (base case: overall GI location £26,383; lung £31,016).

Strengths and limitations of the independent economic assessment

Our analysis of pNETs was based on the most up-to-date effectiveness data from the RCT informing the ITC of the targeted treatments sunitinib and everolimus. (For the comparison of our results with the company results see *Appendix 23*.) However, the ITC 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 suggests that the diseases of the two patient groups have different propensities to progress and, given the theoretical and empirical evidence linking PFS and OS outcomes, different associated death risks. In such a 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. Confidential information has been removed.

Nevertheless, caveats are due with respect to the small size of the A6181111[81] trial, which resulted in an imbalance in key baseline characteristics. A Bucher-type analysis does not adequately deal with bias arising from such an imbalance in baseline characteristics across arms within the same trial. Confidential information has been removed. Our findings on 177LU-DOTATATE are based on a limited quantity and quality of data available for the ITC with everolimus. The immaturity of the available effectiveness data from NETTER-1, and the fact that the control arm received 60 mg of octreotide and therefore was of a different nature to BSC in the RADIANT-4[35] GI (midgut) subgroup, suggests that these results need to be considered with caution. It is not clear, in particular, whether or not the GI (midgut) subgroup of RADIANT-4[35] represents a patient population with a similar prognosis to 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, the availability of individual patient data from RADIANT-3[34] would allow the robustness of the findings to be tested and would be better suited for that task than the individual patient data from A6181111[81] made available to us by Pfizer. This is because RADIANT-3[34] was a larger trial and therefore is less subject to instability than A6181111[81] as a result of small effective sample sizes remaining after matching, Similar analyses will be required to assess the robustness of indirect comparisons with 177Lu-DOTATATE outcomes in the NETTER-1 trial[102] using Bucher-type compared with more elaborate methods of indirect comparison, while adjusting for treatment crossover. Information on the quality-of-life outcomes measured in NETs patients receiving targeted treatments is also required, as such information is available only for patients in stable disease who are subject to high rates of missing data.

The analyses presented as addenda to this report, for the lung (see *Appendix 17*) and separately for the overall GI population (see *Appendix 19*) in RADIANT-4,[35] are subject to the limitations already discussed for RADIANT-4[35] data. In addition, we could not verify the quality of the OS data for the overall GI group as the only information available was a single Kaplan–Meier curve provided by the company in response to our assessment. Further research is needed to confirm our findings in the overall GI location.

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 whether targeted treatments may be given initially or after disease progression in patients who have progressive disease. The 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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Contributions of authors

Ruben Mujica-Mota (Senior Lecturer, Economic Evaluation) 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. He 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.

Jo Varley-Campbell (Research Fellow, Systematic Review) led the clinical effectiveness systematic review from August 2016, screened abstracts and papers, extracted the data and second-checked the data extraction. She wrote the results for the clinical effectiveness review, the background and the critique of the company submissions, contributed to the corresponding sections within the executive summary, discussion and appendices and contributed to the editing of the report and collation of the final report.

Irina Tikhonova (Associate Research Fellow, Economic Evaluation) contributed to the design and parameterisation of the PenTAG economic model, implemented the model in Microsoft Excel and wrote the sections on the design and the results of the model. She contributed to the cost-effectiveness systematic review by screening titles, abstracts and papers of published cost-effectiveness studies and contributed to the editing of the report.

Chris Cooper (Senior Research Fellow, Systematic Review and Information Specialist) provided guidance on the review of clinical effectiveness. He screened titles, abstracts and papers for inclusion in the systematic review, extracted data and second-checked the data extraction, led on contacting ongoing trial and study authors and checked and extracted studies from relevant systematic reviews. He 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 and the editing of the report. He supported the clinical data extraction and carried out literature searches for clinical effectiveness, cost-effectiveness and HRQoL studies. He undertook separate searches to inform a network meta-analysis. He also advised on citation and supplementary searches and critiqued the company literature searches. He wrote the sections on literature searching and the appendices on the systematic searches of clinical effectiveness and cost-effectiveness and utilities and wrote the section on literature searching for the network meta-analysis. Finally, he undertook document retrieval.

Ed Griffin (Associate Research Fellow, Economic Evaluation) provided a critique of the submission by AAA and contributed to the development of the PenTAG independent economic assessment, including the analysis of costs and their methodological description.

Marcela Haasova (Research Fellow, Systematic Review) 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 (Senior Research Fellow, Statistician) carried out the ITC, wrote the critique of the company submissions of effectiveness evidence and contributed to the writing and editing of the report.

Stefano Lucherini (Student Intern, Economic Evaluation) reviewed the utility literature to populate the de novo economic model and wrote the corresponding section.

Juan Talens-Bou (Graduate Trainee, Systematic Review) was the third reviewer from August 2016 to the project completion. He screened the abstracts and papers and extracted data and undertook update searching, searching for background information and supplementary searching. He checked all data tables and calculations, contributed to the editing of the clinical effectiveness review and executive summary and contributed to the editing of the report.

Linda Long (Research Fellow, Systematic Review) contributed to the systematic review of clinical effectiveness, assessed and wrote the summary of non-RCTs and contributed to the writing of the background section.

David Sherriff (Consultant Oncologist) provided clinical advice and contributed to the editing of the report.

Mark Napier (Consultant Oncologist) provided clinical advice and contributed to the editing of the report.

John Ramage (Professor and Consultant Physician in Gastroenterology and Hepatology) provided clinical advice and contributed to the editing of the report.

Martin Hoyle (Associate Professor) was the 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. He was the director and guarantor of the report.

Data-sharing statement

Access to the executable economic model developed within this study can be requested and is subject to appropriate agreements being in place. All queries should be submitted to the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Literature search strategies

Literature searching was undertaken in May 2016, with update searches carried out in September 2016.

Searching of bibliographic and ongoing trials databases

The following search strategies were run on 19 May 2016 and rerun on 29 September 2016.

MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to present.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 1334.

#	Searches	Results
1	exp Neuroendocrine Tumors/	146,579
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.	46,552
4	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	52,214
5	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	70,454
6	1 or 2 or 3 or 4 or 5	292,693
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

EMBASE

Host: Ovid.

Data parameters: 1946 to present.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 4863.

#	Searches	Results
1	exp neuroendocrine tumor/	60,694
2	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	62,025
3	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	68,495
4	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	109,421
5	1 or 2 or 3 or 4	273,156
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.	10,357
7	everolimus/	18,280
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/	16,334
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	37,159
15	5 and 14	4863

The Cochrane Library

Host: Wiley Online Library.

Data parameters: 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 (NHS EED), Issue 2 of 4, April 2015.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 247.

#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 (12,098)

#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)

Web of Science

Host: Thomson Reuters.

Data parameters: Science Citation Index Expanded (SCIE),1900 to present; Social Sciences Citation Index (SSCI), 1956 to present; Conference Proceedings Citation Index – Science (CPCI-S), 1990 to present; Conference Proceedings Citation Index – Social Science & Humanities (CPCI-SSH), 1990 to present.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 1875.

#10	1875	#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	6271	**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	2331	**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	1080	**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	7488	**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			

Current Controlled Trials

Date searched: 25 May 2016.

Searched via 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
Text Search	Lanreotide	1	1

Field searched	Search terms	*n* identified	*n* for screening
Text Search	Somatuline	0	0
Text Search	ITM-014	0	0
Text Search	108736-35-2	0	0
Text Search	Lutetium-177	0	0
Text Search	Lutetium	0	0
Text Search	Lutathera	0	0
Text Search	Sunitinib	9	9
Text Search	Sutent	4	1
Text Search	SU 011248	0	0
Text Search	557795-19-4	0	0

ClinicalTrials.gov

Date searched: 26 May 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 VOTUBIA	0	0
Text Search	Conditions: Neuroendocrine Intervention: Zortress	85	3
Text Search	Conditions: NETs Intervention: Zortress	12	0

APPENDIX 1

Field searched	Search terms	*n* identified	*n* for screening
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
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
Text Search	Lutetium	21	21
Text Search	Lutathera	1	1
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

Field searched	Search terms	*n* identified	*n* for screening
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

US Food and Drug Administration website

Searched via www.fda.gov/Drugs/

Date searched: 6 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

Drugs@FDA

Searched via www.accessdata.fda.gov/scripts/cder/drugsatfda/

Date searched: 6 July 2016.

Search term	Hits	Included
Everolimus/ Zortess	2	2
Lanreotide	0	0
Lutetium-177	0	0
Lutetium	6	1
Sunitinib	2	2

European Medicines Agency

Searched via www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp

Date sarched: 6 July 2016.

Search term	Hits	Included
Everolimus	2	2
Lanreotide	0	0
Lutetium-177	0	0
Lutetium	6	1
Sunitinib	2	2

Economic study searches

Database	Hits
MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations	299
EMBASE	716
NHS EED	3
Web of Science	123
EconLit	1
Total	1143
Duplicates	247
Unique records to screen	896

MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to present.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 299.

#	Searches	Results
1	exp Neuroendocrine Tumors/	146,579
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.	46,552
4	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	52,214
5	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	70,454
6	1 or 2 or 3 or 4 or 5	292,693

#	Searches	Results
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 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	exp Economics/	526,611
13	ec.fs.	363,988
14	economics, medical/	8869
15	Economics, Nursing/	3937
16	Economics, Pharmaceutical/	2619
17	Economics, Hospital/	10,680
18	(economic* or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration* or expenditure or expenditures or budget* or afford* or pharmacoeconomic or pharmaco-economic*).tw.	502,094
19	(cba or cea or cua).ti,ab.	29,189
20	exp "Fees and Charges"/	28,197
21	(fee or fees or charge* or preference*).tw.	304,749
22	(fiscal or funding or financial or finance).tw.	102,276
23	exp "Costs and Cost Analysis"/	197,689
24	exp Health Care Costs/	52,041
25	cost*.tw.	433,649
26	exp decision support techniques/	66,124
27	exp Models, Economic/	11,688
28	exp Statistical Model/	314,512
29	markov*.tw.	17,327
30	markov chains/	11,224
31	monte carlo.tw.	36,521
32	monte carlo method/	22,617
33	(decision adj2 (tree* or analy* or model*)).tw.	15,053
34	(survival adj3 analys*).tw.	34,011
35	"Deductibles and Coinsurance"/	1525
36	exp Health expenditures/	17,233
37	uncertain*.tw.	118,654
38	uncertainty/	8052
39	(quality adj3 life).tw.	191,145
40	quality of life/	137,192
41	value of life/	5500
42	Quality-adjusted life years/	8422

#	Searches	Results
43	(qol* or qoly or qolys or hrqol* or qaly or qalys or qale or qales).tw.	41,092
44	(sensitivity analys* or discrete event or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc*).tw.	28,468
45	utilit*.tw.	147,802
46	valu*.tw.	1,601,201
47	exp hospitalization/	181,928
48	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	3,893,099
49	6 and 11 and 48	299

EMBASE

Host: Ovid.

Data parameters: 1946 to present.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 716.

#	Searches	Results
1	exp neuroendocrine tumor/	60,694
2	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	62,025
3	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	68,495
4	((((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	109,421
5	1 or 2 or 3 or 4	273,156
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.	10,357
7	everolimus/	18,280
8	(Lanreotide or Somatuline or ITM-014 or 108736-35-2).ti,ab,kw.	1072
9	angiopeptin/	2770
10	(Lutetium-177 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/	16,334
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	37,159
15	exp Economics/	233,417
16	exp health-economics/	690,449
17	exp economic-evaluation/	242,008

#	Searches	Results
18	exp pharmacoeconomics/	178,599
19	(economic* or price or prices or pricing or priced or discount or discounts or discounted or discounting or ration* or expenditure or expenditures or budget* or afford* or pharmacoeconomic or pharmaco-economic*).tw.	663,479
20	Cost benefit analysis/	71,608
21	Cost effectiveness analysis/	114,041
22	Cost minimization analysis/	2798
23	(cba or cea or cua).ti,ab.	38,314
24	"cost of illness"/	16,348
25	exp "health care cost"/	233,023
26	cost*.tw.	561,500
27	(fee or fees or charge* or preference*).tw.	317,066
28	(fiscal or funding or financial or finance).tw.	127,595
29	markov*.tw.	20,044
30	monte carlo.tw.	32,840
31	(decision adj2 (tree* or analy* or model*)).tw.	20,035
32	(survival adj3 analys*).tw.	50,880
33	(quality adj3 life).tw.	283,909
34	(sensitivity analys* or discrete event or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc* or uncertain*).tw.	182,839
35	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	2,444,303
36	5 and 14 and 35	716

NHS Economic Evaluation Database

Host: Wiley Online Library.

Data parameters: Issue 2 of 4, April 2015.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 3.

#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 (12,098)

#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 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)

Web of Science

Host: Thomson Reuters.

Data parameters: Science Citation Index Expanded (SCIE),1900 to present; Social Sciences Citation Index (SSCI), 1956 to present; Conference Proceedings Citation Index – Science (CPCI-S), 1990 to present; Conference Proceedings Citation Index – Social Science & Humanities (CPCI-SSH), 1990 to present.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 123.

#13	123	#12 AND #9 AND #4 Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan = All years	Edit	Select to combine sets. ☐	Select to delete this set. ☐
#12	3,777,475	#11 OR #10 Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan = All years	Edit	Select to combine sets. ☐	Select to delete this set. ☐
#11	52,810	**TOPIC:** ((decision near/1 (model* or tree* or analy*))) Indexes = SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan = All years	Edit	Select to combine sets. ☐	Select to delete this set. ☐
#10	3,745,638	**TOPIC:** ((pharmacoeconomic* or pharmaco-economic* or economic* or price* or pricing* or discount or discounted or discounts or discounting or ration* or cost* or budget* or fiscal or funding or financial or finance* or expenditure* or afford* or cba or cea or cua or "health utilit*" or "value for money" or cba or cea or cua or fee or fees or charge* or preference* or fiscal or funding or financial or finance or monte carlo or markov or "resource* alloca*" or "resource* use")) 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	6271	**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	2331	**TOPIC:** (((Lutetium-177 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	1080	**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	7488	**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			

Ovid EconLit

Host: EBSCO*host*.

Data parameters: 1886 to present.

Date searched: 19 May 2016.

Searcher: CC.

Hits: 1.

#	Query	Limiters/expanders	Last run via	Results
S4	TI ((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)) OR AB ((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))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S3	TI ((Lutetium-177 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).) OR AB ((Lutetium-177 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).)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S2	TI ((Lanreotide or Somatuline or ITM-014 or 108736-35-2)) OR AB ((Lanreotide or Somatuline or ITM-014 or 108736-35-2))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S1	TI ((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)) OR AB ((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))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1

Appendix 2 Review of effectiveness for non-randomised controlled trial evidence for 177Lu-DOTATATE

Methods

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

Identification of studies

Study identification was undertaken in May 2016, with update searches carried out in September 2016. Our literature searches were not limited by study design and so the same searches were used to identify randomised and non-randomised studies.

The searches are reported in *Chapter 4* and *Appendix 1*.

Inclusion and exclusion criteria

Non-randomised studies of individuals with pNETs or GI NETs receiving 177Lu-DOTATATE and reporting outcomes of interest were included in the review. Non-randomised evidence included prospective observational cohort studies, both comparative and single-arm studies. Case studies were excluded.

Screening

Titles and abstracts were independently double-screened by two reviewers. Full texts of studies meeting the inclusion criteria at title and abstract stage were double-screened by three reviewers.

Data extraction and management

A standardised data specification form was used and the data extracted were independently checked. When 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, percentage of male participants, tumour functionality, tumour differentiation and ECOG or WHO PS) and whether or not any previous treatments had been given. Outcomes extracted included follow-up duration, PFS, OS, RR, AEs and HRQoL.

Critical appraisal strategy

Included studies were not critically appraised.

Methods of data synthesis

Data are presented in summary tables. The following outcomes have been narratively synthesised in the following section: PFS, OS, RR, AEs and HRQoL.

Results for non-randomised controlled trial evidence

Quantity and quality of research available

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is presented in *Figure 26*. Studies were coded separately in the first round of screening so that they could be reintroduced if (and in this case) necessary.

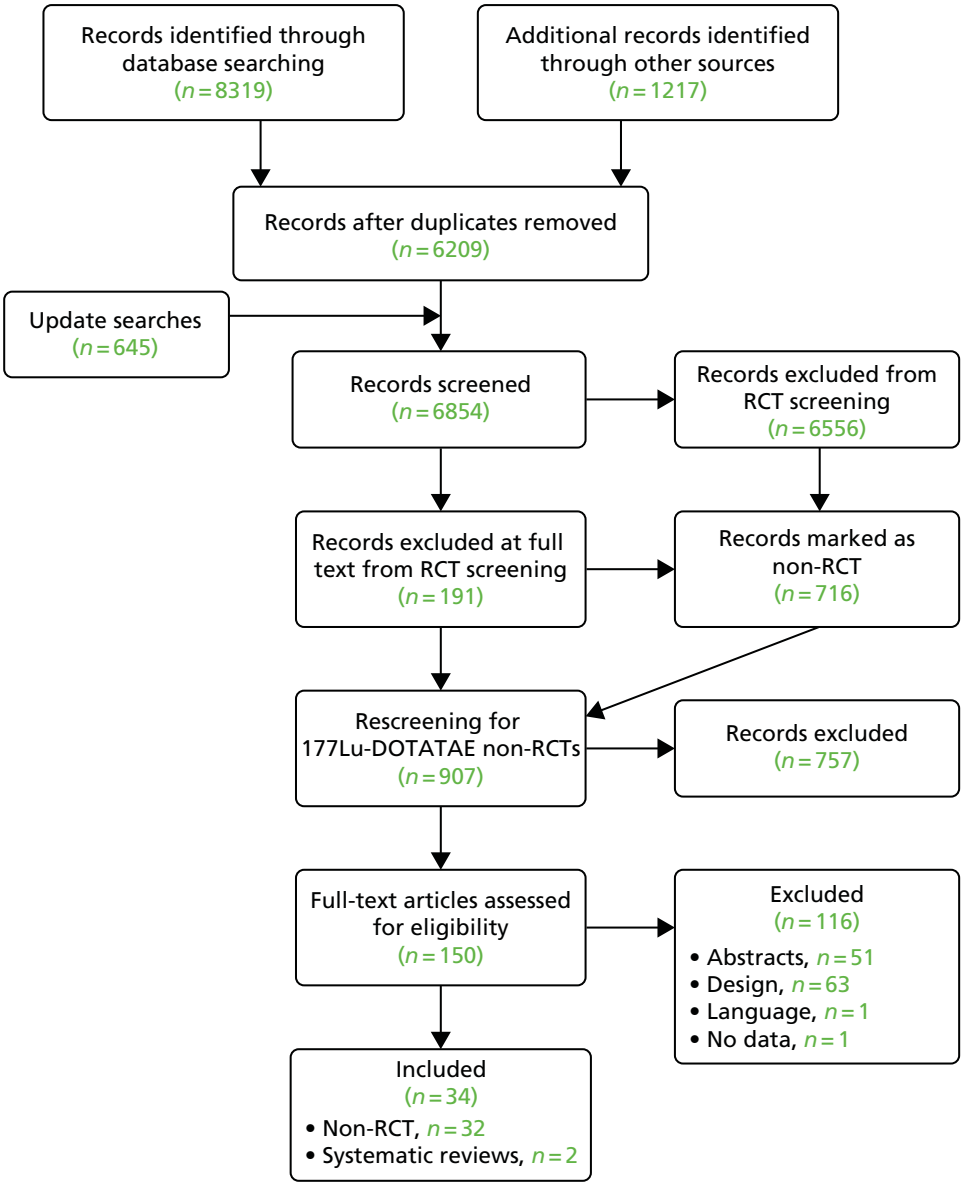

FIGURE 26 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for non-randomised studies of 177Lu-DOTATATE.

Overview of results

All 32 included studies[103,104,145–174] were case series with no internal controls. There was a wide variation in the number of study participants ($n = 5$–310), with only four[103,104,163,164] out of the 32 studies having > 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 to 40 months and OS ranged from 34.2 to 105 months. In terms of RRs, complete response ranged from 2% to 27% and partial response ranged from 12% to 100% [with a standard deviation (SD) range from 12% to 100%].

This wide variation in outcome measures is likely to be because of factors inherent in study design and compounded by wide variations in participant characteristics, for example tumour sites, with outcomes often reported for mixed tumour locations, for example data gut, pancreas and lung NETs grouped together.

Twenty-three[143,145–152,155,158–168,170,171] of the 32 studies reported on AEs, whereas seven[143,146,148,152,154,159,161] of the 32 studies reported on HRQoL outcomes.

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

Non-randomised controlled trials of 177Lu-DOTATATE

No non-RCT comparative trials were identified; all 32 studies identified were single-arm trials. The baseline characteristics of these 32 trials are provided in *Table 38* and the outcomes in the trials are provided in *Table 39*.

TABLE 38 Baseline characteristics in the non-randomised studies of 177Lu-DOTATATE

Study	Country	*n*	Location of NETs	Lutetium dose	Other drugs	Age (years)	Male, *n/N* (%)	Tumour functioning, *n/N* (%)	Tumour differentiation, *n/N* (%)	Previous treatments, *n/N*
Balter 2016[146]	Uruguay	5	Pancreas, $n=2$; ileum, $n=2$; bronchial, $n=1$	Cumulative dose of 4.44–22.2 GBq	NR	Range 51–79	4/5 (80)	NR	NR	NR
Barber 2012[147]	Australia[a]	5	Pancreas, $n=4$; duodenum, $n=1$	7.0–10.0 GBq (mean 8.6 GBq)	Premedication: granisetron (3 mg), dexamethasone (8 mg), amino acid solution. Concurrent: 5-FU chemotherapy (200 mg/m^2/24 hours)	Range 55–72, mean 68	5/5 (100)	Non-functioning 5/5 (100)	5/5 (100) well differentiated	Pancreatic 2/5; SSA 1/5; chemotherapy 1/5; incomplete resection duodenum 1/5
Basu 2016[148]	India[a]	5	Lung, $n=1$; bronchial carcinoid, $n=2$; unknown, $n=1$; duodenum, $n=1$	Cumulative dose of 16.1–25.6 GBq	NR	Range 26–62	3/5 (60)	NR	3/5 (60) Well differentiated ($n=3$ thoracic NETs)	NR
Bodei 2011[149]	Italy	51	Bronchial, $n=5$; appendix, $n=1$; pancreatic, $n=14$; duodenal, $n=3$; ileum, $n=19$; sigma-rectal, $n=2$; unknown, $n=3$; paraganglioma, $n=3$; meningioma, $n=1$	Group 1: 3.7–5.18 GBq/cycle, median in six cycles 26.4 GBq; group 2: 5.18–7.4 GBq/cycle, median in four cycles 25.2 GBq	100 ml of physiological saline, 25 g of lysine diluted in 1 l of normal saline, 12.5 g of lysine diluted in 500 ml of normal saline	Range 30–79, median 57	26/51 (51)	NR	35/37 (94.6) well differentiated	SSA 43/51
Bodei 2016[150]	Italy	54	Bronchial, $n=13$; GEP-NETs, $n=35$; unknown, $n=6$	PRRT-naive patients (risk factors and no risk factors): 18.5 or 27.8 GBq in four cycles; PRRT pretreated: 14.8 in four cycles	NR	Range 43–83, median 66	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; PRRT 16/54; radiotherapy 6/54; TACE 4/54

Study	Country	*n*	Location of NETs	Lutetium dose	Other drugs	Age (years)	Male, *n/N* (%)	Tumour functioning, *n/N* (%)	Tumour differentiation, *n/N* (%)	Previous treatments, *n/N*
Claringbold 2011[151]	Italy	33	Pancreas, $n = 10$; small bowel, $n = 13$; large bowel, $n = 2$; lung, $n = 2$; unknown, $n = 6$	7.8 GBq	Amino acids (Synthamin; Baxter Healthcare Australia, Old Toongabbie, NSW, Australia): 11.6 g/l of lysine and 23 g/l of arginine at 250 ml/hour for 4 hours; 5 mg of tropisetron (Navoban; Novartis Pharmaceuticals Australia, Macquarie Park, NSW) and 2 mg of lorzaepam (Ativan; Sigma Pharmaceuticals, Watford, UK); 1650 mg/m^2 of capecitabine. Of the 19 patients with carcinoid, 18 were receiving regular octreotide analogue therapy for symptom control	Range 32–82, median 60	21/33 (63)	Functioning 21/33 (64)	33/33 (100) well or moderately well differentiated	Surgery 20/33; octreotide 18/33; chemotherapy 5/33
Claringbold 2012[152]	Australia	34	Bowel, $n = 15$; GEP NETs, $n = 17$; lung, $n = 2$	7.8 GBq	1500 mg/m^2 of capecitabine and 200 mg/m^2 of temozolomide. Amino acids: 11.6 g/l of lysine and 23 g/l of arginine at 240 ml/hour	Range 33–81, median 63	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 2015[154]	Australia	16	Pancreas, $n = 5$; small bowel, $n = 11$	7.8 GBq	5, 7.5 and 10 mg daily of everolimus. Amino acids: 11.6 g/litre of lysine and 23 g/litre of arginine at 240 ml/hour. Intravenous tropisetron and dexamethasone and oral aprepitant	Range 43–72, median 63	9/16 (56)	NR	NR	Surgery 8/16; SSA 11/16; chemotherapy 6/16; PRRT 5/16; sunitinib 1/16;[67] Y-microspheres 2/16
Claringbold 2016[153]	Australia	30	Pancreas	7.9 GBq	1500 mg/m^2 of capecitabine and 200 mg/m^2 of temozolomide. Amino acids: 11.6 g/l of lysine and 23 g/l of arginine at 240 ml/hour. Tropisetron and lorazepam	Range 38–78, median 60	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

continued

TABLE 38 Baseline characteristics in the non-randomised studies of 177Lu-DOTATATE (*continued*)

Study	Country	*n*	Location of NETs	Lutetium dose	Other drugs	Age (years)	Male, *n/N* (%)	Tumour functioning, *n/N* (%)	Tumour differentiation, *n/N* (%)	Previous treatments, *n/N*
Delpassand 2014[145]	USA	37	Pancreas, *n* = 14; small bowel, *n* = 12; rectal, *n* = 3; large bowel, *n* = 1; unknown, *n* = 7	200 mCi (7.4 GBq ± 10%) administered up to cumulative dose of 800 mCi (29.6 GBq ± 10%)	Kidney-protecting agents, 15% Clinisol (1000 ml), mixture composed of positively charged amino acids	Range 43–86, median 64	16/37 (43)	NR	NR	Sandostatin 28/37
Ezziddin 2011[155]	Australia	81	Pancreas, *n* = 37; GEP NET, *n* = 44 (foregut, *n* = 5; midgut, *n* = 19; hindgut, *n* = 2; undetermined primary, *n* = 18)	Mean activity 7.9 GBq per cycle	NR	Range 33–83, mean 61	46/81 (57)	Non-functioning 63/81; functioning18/81	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 2011[156]	Germany	42	Pancreas, *n* = 12; non-pancreatic GEP NETs, *n* = 30	Mean activity 8.1 ± 0.98 GBq per cycle	NR	Range 44–88, mean 62	26/42 (70)	NR	42/42 (100) well differentiated	Surgery 22/42; biotherapy 17/42; chemotherapy 11/42; locoregional treatment 2/42
Ezziddin 2014[157]	Germany[a]	74	Pancreas, *n* = 33; non-pancreatic GEP NETs, *n* = 41	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 250 ml/hour)	Range 34–83, mean 62.5	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 2014[158]	Germany[a]	68	Pancreas	Mean activity 8.0 GBq (216 mCi) per cycle	Nephroprotective: 2.5% lysine and 2.5% arginine in 1 l of 0.9% NaCl; infusion of 250 ml/hour	Range 37–82, mean 62	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 2015[159]	Sweden	24	Pancreas	Range 4.0–7.9 GBq per cycle	Kidney protection: 2 l of mixed amino acids solution (Vamin, 14 g/l, without added electrolytes; Fresenius Kabi Ltd)	Range 43–78	13/24 (54)	NR	NR	NR
Kong 2014[160]	Australia	68	Pancreas, *n* = 33; non-pancreatic NETs, *n* = 35	Median cumulative dose 31 GBq (21–45.3 FBq)	Granisetron and dexamethasone with amino acid infusion (25 g of lysine and 25 g of arginine in 1 l of normal saline). 5-FU chemotherapy (200 mg/m^2/24 hours)	Range 17–76, median 56	39/68 (57)	NR	NR	NR

Study	Country	*n*	Location of NETs	Lutetium dose	Other drugs	Age (years)	Male, *n/N* (%)	Tumour functioning, *n/N* (%)	Tumour differentiation, *n/N* (%)	Previous treatments, *n/N*
Kunikowska 2013[161]	Poland[a]	28	Foregut, $n = 14$; midgut, $n = 9$; hindgut, $n = 1$; unknown primary, $n = 2$; other, $n = 2$	Total maximum dose of 7.4 GBq/m^2, for an injected activity per course of 2.2–3.7 GBq, of 90Y/177Lu-DOTATATE	Total maximum dose of 7.4 GBq/m^2, for an injected activity per course of 2.2–3.7 GBq, of 90Y/177Lu-DOTATATE Amino acid infusion, consisting of 11.3 g of arginine and 9.0 g of lysine (1000 ml of Vamin 18) and Ringer's solution (500 ml). Ondansetron (8 mg) (Zofran; Glaxo Wellcome, Atossa, Anpharm S.A.)	Range 39–78, mean 55 ± 10.9	10/28 (36)	NR	NR	Chemotherapy 9/28
Kwekkeboom 2003[162]	Netherlands	35	Pancreas, $n = 12$; carcinoid, $n = 12$; unknown origin, $n = 8$; gastrinoma, $n = 3$	100, 150 or 200 mCi to a final cumulative dose of 600–800 mCi (27.8–29.6 GBq)	3 mg of granisetron and amino acids (2.5% lysine and 2.5% arginine in 1 l of 0.9% NaCl infusion 250 ml/hour). Eight patients used sandostatin	Range 19–78, mean 54	14/35 (40)	NR	NR	Surgery 12/35; radiotherapy 1/35; chemotherapy 3/25; octreotide (Sandostatin; Novartis) 14/35
Kwekkeboom 2005[163]	Netherlands	131	Gastrinoma, $n = 8$; insulinoma, $n = 2$; non-functioning endocrine pancreatic tumours, $n = 33$; endocrine tumours of unknown origin, $n = 18$; carcinoid tumours, $n = 70$	600–800 mCi (22.2–29.6 GBq). Cycle dosages were 100 mCi (3.7 GBq), 150 mCi (5.6 GBq) and 200 mCi (7.4 GBq)	3 mg of granisetron and amino acids (2.5% lysine and 2.5% arginine in 1 l of 0.9% NaCl infusion 250 ml/hour)	Range 19–83, mean 56	65/129 (50)	NR	NR	Surgery 63/129; external beam radiation 6/129; chemotherapy 20/129; SSA 66/129
Kwekkeboom 2008[164]	Netherlands	310	Carcinoid, $n = 188$; non-functioning pNETs, $n = 72$; unknown, $n = 31$; gastrinoma, $n = 12$; insulinoma, $n = 5$; VIPoma, $n = 2$	750–800 mCi (27.8–29.6 GBq). Cycle dosages were 100 mCi (3.7 GBq), 150 mCi (3.6 GBq) and 200 mCi (7.4 GBq)	3 mg of granisetron or 8 mg of ondasentron and amino acids (2.5% lysine and 2.5% arginine in 1 l of 0.9% NaCl infusion 250 ml/hour)	Range 21–85, mean 59	164/310 (53)	NR	NR	Surgery 153/310; radiotherapy 16/310; chemotherapy 52/310; SSA168/310

continued

TABLE 38 Baseline characteristics in the non-randomised studies of 177Lu-DOTATATE (*continued*)

Study	Country	*n*	Location of NETs	Lutetium dose	Other drugs	Age (years)	Male, *n/N* (%)	Tumour functioning, *n/N* (%)	Tumour differentiation, *n/N* (%)	Previous treatments, *n/N*
Paganelli 2014[165]	Italy	43	Stomach, $n=2$; appendix, $n=1$; small intestine (midgut), $n=34$; colon, $n=5$; rectum, $n=1$	Cumulative dose 18.5 or 27.8 GBq, (cycle dosages of 3.7 or 5.5 GBq); 25 patients (58%) treated with a 'standard' Lu-PRRT full dose of 25.7 GBq (range 22.2–27.8 GBq), with a reduced dosage of 18.4 GBq for patients at risk. Some patients were treated with reduced dosage of 3.7 GBq per cycle	Amino acids [70 mEq of lysine in 500 ml of saline (250 ml in 30 minutes immediately before therapy, 250 ml during therapy), 70 mEq of lysine in 500 ml of saline in the first 3 hours after therapy and 60 mEq of lysine in 500 ml of saline over 1 hour twice the following day]	Range 44–82, median 65	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 2013[166]	Germany	68	Pancreas, $n=23$; non-pancreatic GEP NETs, $n=45$	8.1 ± 0.76GBq	NR	Range 40–88, mean 63	39/68 (57)	NR	68/68 (100) well differentiated	Surgery 35/68; biotherapy 30/68; chemotherapy 18/68; locoregional treatment 2/68
Sabet 2013[167]	Germany[a]	6	Pancreas, $n=2$; non-pancreatic NETs, $n=4$	Mean cumulative dose 48.7 GBq (range 29.6–96.7 GBq)	2.6–3.3 GBq of Re-HEDP, cumulative dose 5.9 GBq	Range 43–70	5/6 (83)	NR	NR	Radiation 1/6; chemotherapy 5/6; locoregional treatment 3/6; biotherapy 4/6; surgery 2/6
Sabet 2014[168]	Germany	11	Pancreas, $n=3$; non-pancreatic GEP NETs, $n=8$	Mean dose of 6.95 GBq per cycle; aimed for four courses and standard intervals of 3 months	Amino acids were co-administered to reduce the absorbed dose to the kidneys	Range 40–78, mean 62	7/11 (64)	NR	11/11 (100) well differentiated	Surgery 6/11; SSAs 6/11; chemotherapy 8/11; locoregional treatment 2/11; PRRT 4/11
Sabet 2015[169]	Germany	61	Advanced small intestinal NETs	Mean activity 7.9 GBq (214 mCi) per cycle (four cycles); mean cumulative activity per patient was 27.2 ± 5.9 GBq	Amino acids (2.5% lysine and 2.5% arginine in 110.9% NACI; infusion of 250 ml/hour)	Range 34–83, mean 62	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 2013[170]	Italy	52	Advanced pNETs	$n=26$ received full dose of 25.5 GBq (range 20.7–27.8 GBq); $n=26$ received reduced dose of 17.8 GBq (range 11.1–19.9 GBq)	Amino acids (70 mEq of lysine in saline)	Range 26–82, mean 61	30/52 (58)	NR	NR	Surgery 22/52; chemotherapy 14/52; SSA 34/52; Y-PRRT 14/52; other treatments 8/52

Study	Country	*n*	Location of NETs	Lutetium dose	Other drugs	Age (years)	Male, *n/N* (%)	Tumour functioning, *n/N* (%)	Tumour differentiation, *n/N* (%)	Previous treatments, *n/N*
Severi 2015[171]	Italy	26	Pancreas $n = 17$; ileum, $n = 5$; appendix, $n = 1$; colon, $n = 1$; rectum, $n = 1$; unknown, $n = 1$	Total activity 14.8–18.5 GBq in four or five cycles (median dose 16.5 GBq). Primary treatment: median dose 10.8 GBq in five cycles. Retreatment: median dose 16.5 GBq in five cycles	Amino acids [70 mEq of lysine in 500 ml of saline (250 ml over 30 minutes immediately before therapy, 250 ml during therapy), 70 mEq of lysine in 500 ml of saline during the first 3 hours after therapy and 60 mEq of lysine in 500 ml of saline over 1 hour twice the following day	Range 37–79, median 54	15/26 (58)	NR	NR	Surgery 13/26; chemotherapy 13/26; locoregional treatments 3/26; SSA 24/26
Soydal 2016[172]	Turkey	29	Pancreas, $n = 9$; unknown, $n = 5$; colon, $n = 1$; stomach, $n = 2$; lung, $n = 2$; retroperitoneum, $n = 2$; ovary, $n = 2$; thyroid, $n = 2$; ileum, $n = 3$; appendix, $n = 1$	7400 MBq each cycle	100 MBq of Ga-68 DOTATATE, 50-g cocktail of 25 g of lysine and 25 g of arginine diluted in 2 l of normal saline	Range 19–76, mean 50.7 ± 14.6	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 2007[173]	Netherlands	16	Bronchial, $n = 9$; gastric, $n = 5$; thymic carcinoids, $n = 2$	Cumulative dose 22.2–29.6 GBq;. cycle doses were 7.4 GBq. Cumulative dose could be reduced to 22.2–27.8 GBq. Dose of the last cycle adjusted to 3.7 or 5.55 GBq	3 mg of granisetron, amino acids (2.5% lysine, 2.5% arginine)	Range 37–76, median 57	10/16 (62)	NR	NR	Surgery 11/16; chemotherapy 4/16; radiotherapy 3/16
van Essen 2010[174]	Netherlands	33	Pancreas $n = 8$; unknown, $n = 5$; carcinoid, $n = 20$ (bronchial, $n = 3$; gastric, $n = 1$; rectal, $n = 1$; midgut, $n = 15$)	Intended cumulative dose of 14.8 GBq in two cycles; cycle dose of 7.4 GBq or occasionally 3.7 GBq	3 mg of granisetron, amino acids (1 l of 2.5% arginine and 2.5% lysine)	Range 35–75, median 57	NR	NR	NR	NR

continued

TABLE 38 Baseline characteristics in the non-randomised studies of 177Lu-DOTATATE (*continued*)

Study	Country	*n*	Location of NETs	Lutetium dose	Other drugs	Age (years)	Male, *n*/*N* (%)	Tumour functioning, *n*/*N* (%)	Tumour differentiation, *n*/*N* (%)	Previous treatments, *n*/*N*
van Vliet 2013[103]	Netherlands	268	Pancreas, *n* = 72; GI or thoracic NETs, *n* = 178 (foregut, *n* = 22; midgut, *n* = 145; hindgut, *n* = 11); unknown, *n* = 18	Cycle dose of 3.7 or 7.4 GBq, cumulative intended dose of 22.2–29.6 GBq. 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	3 mg of granisetron (Kytril; Roche), amino acids (1 l of 2.5% arginine and 2.5% lysine)	Range 23–83, mean 59	138/268 (52)	Non-functioning 61 (85); functioning 11 (15)	NR	Octreotide 142/268; surgery 118/268; chemotherapy 26/268; radiotherapy 10/268
van Vliet 2015[104]	Netherlands	119	Pancreas: G1 (*n* = 15): borderline or unresectable pNETs; G2 (*n* = 14): borderline or unresectable pNETs and oligometastatic disease (three or fewer liver metastases); G3 (*n* = 90): pNETS and more than three liver metastases or other distant metastases	Cycle dose of 7.4 GBq, cumulative dose of 22.2–29.6 GBq	3 mg of granisetron, amino acids (1 l of 2.5% arginine and 2.5% lysine)	Range 23–85, mean 55	54/119 (45)	Non-functioning 119/119 (100)	NR	NR

5-FU, fluorouracil; IFN, interferon; NaCl, sodium chloride; NR, not reported; PRRT, peptide receptor radionuclide therapy; Re-HEDP, Rhenium-186–1-hydroxyethylidene-1,1-diphosphonate; TACE, transcatheter arterial chemoembolisation.

a Likely study location based on author institute locations.

Note

Baseline data extracted for all patients.

TABLE 39 Outcomes from non-randomised studies of 177Lu-DOTATATE

Study	Follow-up (months)	PFS (months)	OS (months)	RR, *n*/*N* (%)	AEs, *n*/*N* (%)	HRQoL
Balter 2016[146]	3	NR	NR	pNETs: PR 1/2; SD 1/2; ileal NETs: PR 2/2; bronchial NETs: PR 1/1	NR	NR
Barber 2012[147]	12–48	NR	*n* = 5/5 (100)	Radiological response: pNETs: PR 4/4; duodenal NETs: SD 1/1	NR	NR
Basu 2016[148]	10–27	Duodenum 27; unknown 10	NR	Duodenum and unknown: PR 2/2	PRRT well tolerated; no haematological toxicity	Improved symptomatic palliation/quality of life
Bodei 2011[149]	4–66	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 2016[150]	Median 16, range 1–33	Median PFS was not achieved	NR	Responders (SD + PR + CR): 71% GI and 93% pancreas	No serous side effects with PRRT	NR
Claringbold 2011[151]	16, range 5–33	Outcome not reported by tumour location; however, for the 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 2012[152]	Median 18, range 12–33	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 NETs: 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 2015[154]	Median 34, range 18–42	Outcome 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	Outcome not reported by tumour location	NR
Claringbold 2016[153]	Median 33, range 13–58	Median 48	Not reached after 33 months' follow-up	ORR 80% (95% CI 66% to 93%); CR 4/30; PR 20/30; SD 6/30	Thrombocytopenia (grade 3 severity) 3/30; myelodysplastic syndrome 1/30	NR

continued

TABLE 39 Outcomes from non-randomised studies of 177Lu-DOTATATE (*continued*)

Study	Follow-up (months)	PFS (months)	OS (months)	RR, *n*/*N* (%)	AEs, *n*/*N* (%)	HRQoL
Delpassand 2014[145]	Average 14.26, median 16.11, range 0.3–26.87	Median PFS not reached. GI: Kaplan–Meier survival estimate at 12 months 72.7% (95% CI 49.1% to 86.7%) and at 24 months 72.7% (95%CI 49.1% to 86.7%). Pancreas: Kaplan–Meier survival estimate at 12 months 79.5% (95% CI 39.3% to 94.5%) and at 24 months 63.6% (95% CI 22.2% to 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 2011[155]	NR	NR	NR	pNETs: PR 57%, MR 13.5%, SD 16%, PD 13.5%; GEP NETs: PR 23%, MR 13.5%, SD 45.5%, PD 18%	NR	NR
Ezziddin 2011[156]	Median 32 (95% CI 29 to 35)	pNETS: median 29 (95% CI 18 to 40); other GEPNETs: median 35 (95% CI 16 to 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 2014[157]	Median 47 (95% CI 44.5 to 49.5)	Outcome not reported by tumour location	pNETs: median 57 (95% CI 48 to 66); other GEP NETs: median 43 (95% CI 31 to 55)	pNETs: PR 54.5%, MR 18.2%, SD 18.2%, PD 9.1%; other GEP NETs: PR 22%, MR 17.1%, SD 48.8%, PD 12.2%	Outcome not reported by tumour location	NR
Ezziddin 2014[158]	Median 58, range 4–112	Median PFS 34 (95% CI 26 to 42)	Median 53 (95% CI 46 to 60)	PR 41/68, MR 8/68, SD 9/68, PD 10/68	Reversible haematotoxicity (grade 3 or above) 4/68; no significant nephrotoxicity (grade 3 or above)	NR
[a]Ilan 2015[159]	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

Study	Follow-up (months)	PFS (months)	OS (months)	RR, *n*/*N* (%)	AEs, *n*/*N* (%)	HRQoL
Kong 2014[160]	Median 60, range 5–86	NR	Outcomes not reported by tumour location	Partial and minor responses: pNETs: 55%; non-pancreatic NETs: 81% (OR 0.28; 95% CI 0.08 to 0.94)	NR	NR
[b]Kunikowska 2013[161]	NR – other measures taken at 48 months	Event-free survival 24.3; TTP 24.3	Median 49.8	NR	Grade 1 + 2 nephrotoxicity 3/28; mild nausea in both groups (38% of entire population)	NR
Kwekkeboom 2003[162]	Average 9	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 reported by tumour location	Outcome not reported by tumour location
Kwekkeboom 2005[163]	Median 16, range 7–44	Outcome not reported 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 reported by tumour location	NR
Kwekkeboom 2008[164]	NR	Outcome not reported by tumour location	Outcome not reported 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 reported by tumour location	Outcome not reported by tumour location
Paganelli 2014[165]	Median 38, range 11–59	Median PFS 36 (95% CI 24 to NR)	Mean OS not yet reached	Median duration objective response 25 (95% CI 7 to 50) months. CR 3/43; SD 33/43; PD 7/43. Disease control rate 84% (95% CI 73% to 95%)	No cases of major toxicity; most common side effects were nausea (maximum grade 2), asthenia and mild alopecia	NR

continued

TABLE 39 Outcomes from non-randomised studies of 177Lu-DOTATATE (*continued*)

Study	Follow-up (months)	PFS (months)	OS (months)	RR, *n*/*N* (%)	AEs, *n*/*N* (%)	HRQoL
Sabet 2013[166]	Median 48 (95% CI 39 to 54)	NR	pNETs: median 48 (95% CI 29 to 67); other GEP NETs: median 57 (95% CI 36 to 78)	Regression (CR, PR or MR): pNETs 14/23; other GEP NETs 19/45	Outcome not reported by tumour location	NR
Sabet 2013[167]	NR	NR	pNETs 5; GI NETs range 2–9	Remission response for pNETs: SD 1/2, PD 1/2; Remission response for GI NETs: SD 1/4, PD 3/4	Outcome not reported by tumour location	NR
Sabet 2014[168]	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 2015[169]	Median 62 (95% CI 57 to 67), range 4–102	Median PFS 33 (95% CI 25 to 41)	Median 61 (95% CI NA)	PR 8/61, MR 19/61, SD 29/61, PD 5/61. Objective response was associated with longer survival (median OS not reached vs. 49 months)	Reversible haematotoxicity (grade 3 or above) 5/61; relevant haematotoxicity (grade 3/4) 5/61. No other relevant toxicities (including nephrotoxicity) or treatment-related deaths were observed	NR
Sansovini 2013[170]	Median 25, range 9–39	Median PFS for whole group 29 (95% CI 19 to 39); median PFS not reached in the full-dose group and was 20 months in the reduced-dose 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% to 89%)	No major acute or delayed haematological toxicity. The most common minor side effects were nausea (maximum grade 2), asthenia and mild alopecia. One patient developed grade 3 renal toxicity	NR
Severi 2015[171]	Median 36, range 4–58	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

Study	Follow-up (months)	PFS (months)	OS (months)	RR, *n*/*N* (%)	AEs, *n*/*N* (%)	HRQoL
Soydal 2016[172]	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 2007[173]	18 and 21	Gastric carcinoids: estimated median TTP 16	NR	Gastric carcinoids: CR 1/5, MR 1/5, SD 2/5, PD 1/5	Outcome not reported by tumour location	NR
van Essen 2010[174]	Median 16, range 1–40	Median TTP: pNETS ($n = 8$) 17; carcinoid NETs ($n = 27$) 20	Outcome not reported by tumour location	pNETs: PD 5/8; carcinoid NETs: PD 12/27	Treatment effects in patients with pNETs were similar to those in patients with other GEP NETs	NR
van Vliet 2013[103]	NR	Outcome not reported by tumour location	Outcome not reported by tumour location	pNETS: Objective response (CR + PR + MR) 20/61, SD 22/61, PD 19/61; midgut: Objective response 31/138, SD 80/138, PD 27/138	NR	NR
van Vliet 2015[104]	NR	Median PFS (in 29 patients in groups 1 and 2) was 55 (95% CI 37 to 73) months; 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 > 105 months. Median OS was > 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): Objective response (CR + PR + MR) in 72/119 (61%) patients; stable disease in 24/119 (20%) and progressive disease in 21/119 (18%)	NR	NR

CR, complete response; MR, minor response; NA, not available; NR, not reported; ORR, objective response rate; PD, progressive disease; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease; TTP, time to progression.

a Paper focuses on dose–response, i.e. dose absorption and tumour size.

b Non-randomised comparative study of 90Y-DOTATATE.

Note

Outcome data extracted for pNETs and GEPNETs where possible.

Appendix 3 Table of excluded studies with rationale

Number	Reference	Reason for exclusion
1	Adlbrecht C, Wild C. Targeted Radionuclide Therapy with 90Y- and 177-Lu-DOTATOC in Patients with Neuroendocrine Tumors (Structured Abstract). 2007. URL: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32008000054/frame.html	Design
2	Anonymous. Everolimus 10 mg and pancreatic neuroendocrine tumours: many adverse effects and uncertain benefit. *Prescrire International* 2012;**21**:234	Design
3	Anonymous. Sunitinib and pancreatic neuroendocrine tumours. More assessment needed. *Prescrire International* 2012;**21**:123–5	Design
4	Anonymous. Lanreotide slows growth of neuroendocrine cancer. *Cancer Discovery* 2014;**4**:OF3	Design
5	Anonymous. 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* 2016;**14**:11–13	Design
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Appendix 4 Included citations

Reference	Type
RADIANT-3[34]	
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). *Regul Pept* 2010;**164**:6–7[52]	Abstract
Hobday T, Pommier R, Van Cutsem E, Panneerselvam A, Saletan S, Winkler RE, Yao JC. 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**:345[53]	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. *J Clin Oncol* 2011;**29**(15 Suppl. 1):e21091[54]	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. *Endocr Rev* 2011;**32**:OR25–2(3 Meeting Abstracts)[55]	Abstract
Ito T. Current status of mTOR inhibitor as a new therapeutic strategy for advanced pancreatic endocrine tumors. *Ann Oncol* 2011;**22**:ix30[56]	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. *Jpn J Clin Oncol* 2012;**42**:903–11[49]	Full text
Ito T, Okusaka T, Ikeda M, Tajima T, Kasuga A, Fujita Y, Furuse J. Everolimus versus placebo in Japanese patients with advanced pancreatic neuroendocrine tumors (pNET): Japanese subgroup analysis of RADIANT-3. *J Clin Oncol* 2011;**29**(4 Suppl. 1):289[57]	Abstract
Lombard-Bohas C, Van Cutsem E, Capdevila J, De 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). *Eur J Cancer* 2011;**47**:S459[58]	Abstract
Lombard-Bohas C, 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. *J Clin Oncol* 2013;**31**:224[51]	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[50]	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. *Ann Oncol* 2012;**23**:xi15[59]	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[60]	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. *Eur J Cancer* 2013;**49**:S619[61]	Abstract
Pavel ME, Lombard-Bohas C, Van 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. *J Clin Oncol* 2015;**33**(15 Suppl. 1):4091[62]	Abstract
Pommier R, Yao J, Hobday T, Van Cutsem 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[63]	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. *J Clin Oncol* 2011;**29**:4103[64]	Abstract

Reference	Type
Shah MH, Ito T, Lombard-Bohas C, Wolin EM, Van 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). *J Clin Oncol* 2011;**29**(4 Suppl. 1):158[65]	Abstract
Shah MH, Öberg 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**:331–2[66]	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). *J Clin Oncol* 2011;**29**(15 Suppl. 1):4009[67]	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). *Am J Gastroenterol* 2011;**106**:S59[68]	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). *Ann Oncol* 2014;**25**:iv394[70]	Abstract
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**:134[69]	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[71]	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. *J Clin Oncol* 2016;**34**:3906–13[48]	Full text
Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, *et al.* Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;**364**:514–23[34]	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). *Ann Oncol* 2010;**21**:viii4–5[72]	Abstract
RADIANT-4[35]	
Anonymous. From ECC 2015 – neuroendocrine cancer: RADIANT-4[35] trial – NET improvement with everolimus? *Nat Rev Clin Oncol* 2015;**12**:684[79]	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. *J Clin Oncol* 2016;**34**(Suppl. 15):e15657[78]	Abstract
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. *J Clin Oncol* 2016;**34**:315[73]	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. *J Clin Oncol* 2016;**34**:4093[74]	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. *Eur J Cancer* 2015;**51**:S709–10[75]	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[35]	Full text
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[76]	Abstract

Reference	Type
Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin EM, *et al.* Everolimus (EVE) in advanced, nonfunctional, well-differentiated neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin: second interim overall survival (OS) results from the RADIANT-4 study. *J Clin Oncol* 2016;**34**(Suppl. 15):4090[80]	Abstract
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. *Ann Oncol* 2015;**26**:ix40[77]	Abstract
A6181111[81]	
Anonymous. From ECC 2015 – neuroendocrine cancer: SSA therapies – 177Lu-DOTATATE is a better one in NETTER-1. *Nat Rev Clin Oncol* 2015;**12**:684[181]	Abstract
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). *Ann Oncol* 2012;**23**:ix376[82]	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**:327[83]	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[84]	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). *J Clin Oncol* 2010;**28**:4000[85]	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. *Eur J Cancer Supp* 2009;**7**:361[86]	Abstract
Raymond E. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors (vol 364, pg 501, 2011). *N Engl J Med* 2011;**364**:1082[81]	Erratum to 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. *N Engl J Med* 2011;**364**:501–13. [Erratum published in *N Engl J Med* 2011;**364**:1082][81]	Full text
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[87]	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. *J Clin Oncol* 2016;**34**:309[88]	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). *Ann Oncol* 2010;**21**:vi13[89]	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). *J Clin Oncol* 2011;**29**:4008[90]	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). *J Clin Oncol* 2010;**28**:4031[91]	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**:54–5[92]	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 tumours: results of the phase III NETTER-1 trial. *Eur J Cancer* 2015;**51**:S710[105]	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[106]	Abstract

Reference	Type
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. *J Clin Oncol* 2016;**34**:194[191]	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). *Ann Oncol* 2010;**21**:viii264[93]	Abstract
Valle J, Niccoli P, Raoul JL, Bang YJ, Borbath I, Van 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). *Eur J Cancer* 2011;**47**:S462[94]	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, well-differentiated pancreatic neuroendocrine tumours (NET) treated with sunitinib (SU) or placebo. *Ann Oncol* 2010;**21**:viii235[95]	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. *J Clin Oncol* 2011;**29**:249[96]	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. *J Clin Oncol* 2010;**28**:4003[97]	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**:334–5[98]	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* 2012;**41**:350[99]	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). *J Clin Oncol* 2012;**30**:4118[100]	Abstract

Appendix 5 Additional literature search strategies

Search 1: randomised controlled trials of octreotide

The first search attempted to identify studies reporting RCTs of octreotide.

MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to present.

Date searched: 30 September 2016.

Searcher: CC.

Hits: 72.

#	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/	149,135	
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.	47,802	
7	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	53,142	
8	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	72,758	
9	4 or 5 or 6 or 7 or 8	299,124	
10	3 and 9	2558	
11	randomized controlled trial.pt.	428,443	
12	10 and 11	36	

EMBASE

Host: Ovid.

Data parameters: 1946 to present.

Date search: 30 September 2016.

Searcher: CC.

Hits: 121.

#	Searches	Results	Annotations
1	exp neuroendocrine tumor/	62,334	
2	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	63,805	
3	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	69,708	
4	(((low$ or intermediate) adj3 grade) or ("grade 1" or "grade 2")).ti,ab,kw.	112,582	
5	1 or 2 or 3 or 4	279,923	
6	octreotide/	18,643	
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.	10,946	
8	6 or 7	20,348	
9	5 and 8	6168	
10	randomized controlled trial/	416,370	
11	9 and 10	72	

Cochrane Central Register of Controlled Trials (CENTRAL)

Host: Ovid.

Data parameters: 1946 to present.

Date search: 16 August 2016.

Searcher: CC.

#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 (398,696)
#12 #10 and #11 (28)

Search 2: searches for dosing studies

The second search attempted to identify dosing or dose-ranging studies.

MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to present.

Date searched: 30 September 2016.

Searcher: CC.

#	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.	72,876	
5	3 and 4	112	

EMBASE

Host: Ovid.

Data parameters: 1974 to 17 August 2016.

Date searched: 30 September 2016.

Searcher: CC.

#	Searches	Results	Annotations
1	Octreotide/	18,635	
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.	10,948	
3	1 or 2	20,343	
4	(dos* adj5 stud*).ti,ab,kw.	103,372	
5	3 and 4	171	

Chemotherapy

The third search attempted to identify RCTs of chemotherapy use in NETs.

The Cochrane Library

Host: Wiley Online Library.

Data parameters: not applicable.

Date searched: 5 September 2016.

Searcher: CC.

#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*) (45,476)
#7 #5 and #6 (1132) (Trials 802)

EMBASE

Host: Ovid.

Data parameters: 1974 to 2 September 2016.

Date searched: 5 September 2016.

Searcher: CC.

#	Searches	Results	Annotations
1	exp neuroendocrine tumor/	62,582	
2	(Neuroendocrine or NETs or GEPNETs or GI NETs or pNETs or fNETs or f-NETs or NF-NETs or NFNETs).ti,ab,kw.	64,123	
3	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	69,943	
4	1 or 2 or 3	172,631	
5	chemotherapy/	119,461	
6	(chemotherapy or chemo therap$).ti,ab,kw.	443,631	
7	5 or 6	457,535	
8	randomized controlled trial/	418,791	
9	4 and 7 and 8	106	

MEDLINE Epub Ahead of Print, MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to present.

Date searched: 5 September 2016.

Searcher: CC

#	Searches	Results	Annotations
1	exp Neuroendocrine Tumors/	149,452	
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.	47,967	
4	exp Neuroendocrine Tumors/	149,452	
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.	47,967	
7	((neuro or endocrine or carcinoid$1 or carcinoma$1) adj5 (tumour$ or tumor$)).ti,ab,kw.	53,239	
8	4 or 5 or 6 or 7	229,980	
9	(chemotherapy or chemo therap$).ti,ab,kw.	291,430	
10	randomized controlled trial.pt.	429,552	
11	8 and 9 and 10	251	

Appendix 6 Additional evidence from the NETTER-1 trial

The NETTER-1 trial was identified through four published abstracts[103–106] in accordance with the original NICE scope. The NETTER-1 trial was not included in the systematic review in this assessment report as it did not meet the revised inclusion criteria in the updated scope issued by NICE on 18 August 2016.[30] As the NETTER-1 trial is the only RCT to have assessed the effectiveness of 177Lu-DOTATATE, the AG has presented the findings from the trial here.

There are currently four published abstracts[103–106] relating to the NETTER-1 trial in the public domain. Data provided on the NETTER-1 trial in this appendix are from the company submission (AAA)[31] or are data given to the AG following a request to AAA. The data presented in the company submission are from taken from the CSR for the NETTER-1 trial.[175]

Study design

The NETTER-1 trial compared treatment with 177Lu-DOTATATE plus BSC (30 mg of octreotide LAR) with treatment with high-dose octreotide LAR (60 mg). All participants had metastatic midgut NETs and were previously receiving octreotide LAR (20 or 30 mg) prior to randomisation to the trial.[31]

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 a constant dose of octreotide (≤ 6 and > 6 months).

177Lu-DOTATATE was administered in a dose of 7.4 GBq (200 mCi), over 8 ± 1-week intervals. For kidney protection, amino acid infusions (Vamin 18 in European centres and Aminosyn II 10% in the US centres) were given concomitantly with 177Lu-DOTATATE; for symptom control, 30 mg of octreotide LAR was given. For the comparator arm, 60 mg 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 was 25.6 GBq overall and 7.2 GBq per cycle.

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 trial.[31]

The primary outcome was PFS. Secondary outcomes included ORR, OS and time to progression, safety, tolerability and HRQoL. Median treatment follow-up was (confidential information has been removed) for 177Lu-DOTATATE and (confidential information has been removed) for octreotide LAR. At the time of the primary end point analysis, (confidential information has been removed) of the safety population had been exposed to (confidential information has been removed) of 177Lu-DOTATATE. The study is still ongoing.

Rationale for the choice of comparator

In the company submission, AAA reported 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 submission (p. 44)*[31]

Baseline characteristics in the NETTER-1 trial

The baseline characteristics of participants recruited to the NETTER-1 trial are presented in *Table 40*.

TABLE 40 Baseline characteristics from the NETTER-1 trial[31]

Characteristic	177Lu-DOTATATE + 30 mg of octreotide LAR (*N* = 116)	60 mg of octreotide LAR (*N* = 113)
Male, *n*/*N* (%)	63/116 (54.3)	53/113 (46.9)
Age (years), median	63.5	65
Age (years), mean ± SD	63.3 ± 9.4	64.1 ± 9.7
ENETS grade 1 (≤ 2% positive tumour cells), *n*/*N* (%)	76/116 (65.5)	81/113 (71.7)
ENETS grade 2 (3–20% positive tumour cells), *n*/*N* (%)	40/116 (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 (34.5)	32/113 (28.3)
WHO PS score	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)
Chemoembolisation	14/116 (12.1)	11/113 (9.7)
Chemotherapy	47/116 (40.5)	51/113 (30.0)
Radiotherapy	7/116 (6.0)	8/113 (4.7)
SSAs	116/116 (100)	113/113 (100)
Other	48/116 (41.4)	40/113 (23.5)

Note
Tumour differentiation was completed by the company following a data request from the AG; the ENETS grade was provided in the company submission.[31] (The numbers are the same.)
Source: AAA submission[31] and data on file from AAA.

Outcomes in the NETTER-1 trial

Progression-free survival

Progression-free survival was reported as the primary outcome in the company submission[31] 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 using RECIST version 1.1.

Confidential information has been removed.

TABLE 41 Progression-free survival, full analysis set. Confidential information has been removed.

Overall survival

Confidential information has been removed.

Response rate

Adverse events

TABLE 42 Summary of AEs reported in ≥ 10% of the patients who received 177Lu-DOTATATE (regardless of whether or not treatment related)

		177Lu-DOTATATE ($N = 111$)				Octreotide LAR ($N = 110$)			
		All grades		Grades 3–5		All grades		Grades 3–5	
SOC	Patient	*n*	%	*n*	%	*n*	%	*n*	%
All SOCs	All patients	105	94.6	46	41.4	92	83.6	36	32.4
GI 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[a]	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[b]	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[c]	32	28.8	2	1.8	22	20.0	1	0.9
Blood and lymphatic system disorder	Thrombocytopenia[d]	28	25.2	2	1.8	1	0.9	0	0.0
	Lymphopenia[e]	20	18.0	10	9.0	2	1.8	0	0.0
	Anaemia[f]	16	14.4	0	0.0	6	5.5	0	0.0
	Leukopenia[g]	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

SOC, System Organ Class.
a Includes 'abdominal discomfort', 'abdominal pain', 'abdominal pain lower', 'abdominal pain upper' and 'GI pain'.
b Includes 'asthenia' and 'fatigue'.
c Includes 'arthralgia', 'back pain', 'bone pain', 'flank pain', 'groin pain', 'musculoskeletal chest pain', 'musculoskeletal discomfort', 'musculoskeletal pain', 'myalgia', 'neck pain', 'pain in extremity' and 'spinal pain'.
d Includes 'thrombocytopenia' and 'platelet count decreased'.
e Includes 'lymphopenia' and 'lymphocyte count decreased'.
f Includes 'anaemia', 'haemoglobin decreased' and 'normochromic normocytic anaemia'.
g Includes 'leukopenia' and 'white blood cell count decreased'.

Health-related quality of life
Confidential information has been removed.

Subgroup analysis
No subgroup analysis was carried out by AAA for the NETTER-1 trial.[31]

Indirect treatment comparison

Methods: intended indirect treatment comparison
Data on the effectiveness of everolimus and 177Lu-DOTATATE in participants with GI NETs were identified from RADIANT-4[35] (everolimus + BSC vs. placebo + BSC) and NETTER-1[31] (177Lu-DOTATATE + 30 mg of octreotide vs. 60 mg of octreotide). The AG intended to indirectly compare everolimus with 177Lu-DOTATATE for GI NETs as shown in *Figure 27*.

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

Search 1: randomised controlled trials 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 & Other Non-Indexed Citations (Ovid), EMBASE (Ovid) and CENTRAL (The Cochrane Library, Wiley Interface).

Search 2: 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 & Other Non-Indexed Citations (Ovid) and EMBASE (Ovid).

The searches were not limited by language or date and both searches are fully reported in *Appendix 5*.

Results of searches
Search 1 (RCTs of octreotide) identified 83 citations for screening. Screening criteria were defined as RCTs, NETs population and octreotide given in doses of ≥ 30 mg. One study was eligible for inclusion in the review (PROMID),[176] in which 30 mg of octreotide LAR was compared with placebo ($n = 42$ vs. $n = 43$

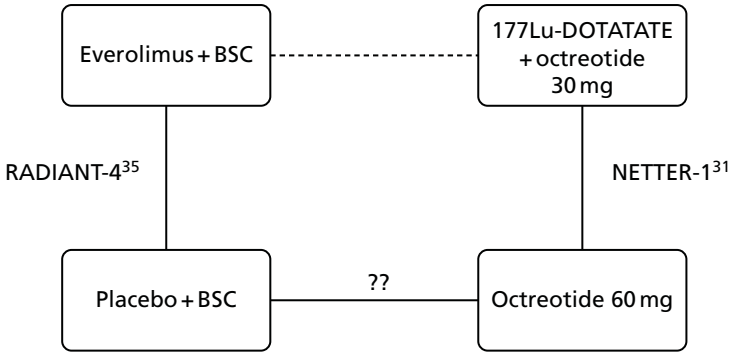

FIGURE 27 Intended ITC for 177Lu-DOTATATE and everolimus.

respectively). Individuals recruited to the PROMID study were treatment naive. Following consultation with our clinicians, it was considered by the AG that the population of treatment-naive patients was not comparable to the populations in RADIANT-4[35] and NETTER-1,[31] with a minimum of 59% of the population in RADIANT-4[35] and 100% of the population in NETTER-1[31] having had at least one previous treatment.

Search 2 (dosing studies) identified 180 citations for screening. Screening criteria were defined as RCTs, NETs population and octreotide given in doses to include at least 30 mg or 60 mg in one arm. No studies were eligible for inclusion in the review.

Methods: actual indirect treatment comparison

As additional trials comparing placebo plus BSC with 60 mg of octreotide could not be found, the intended ITC in *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 that it was appropriate to link the RADIANT-4[35] and NETTER-1[31] trials by assuming that placebo plus BSC (as used in RADIANT-4[35]) was equivalent to 60 mg of octreotide (as used in NETTER-1;[31] *Figure 28*).

However, in a sensitivity analysis, the AG has made the strong assumption that placebo and BSC can be considered equivalent to 60 mg of octreotide, although this ITC should be interpreted with caution. Moreover, the data used for this network were obtained through a request for data by the AG to the companies as the NETTER-1 trial[31] is currently unpublished and RADIANT-4[35] does not report outcomes for the subgroup of participants with GI NETs only (instead, RADIANT-4[35] 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[31] recruited only individuals with midgut NETs, whereas RADIANT-4[35] recruited those with fore-, mid- and hind-gut NETs. *Table 43* reports the tumour locations of the individuals recruited to NETTER-1[31] and RADIANT-4.[35]

The results reported for GI NETs only from RADIANT-4[35] in the clinical effectiveness section in *Chapter 4* (see *Outcomes for RCT evidence for GI NETs*) include all of the tumour locations in *Table 43* except for 'unknown' and one less participant in the everolimus group for 'other'. This resulted in a total of $n = 118$ for everolimus plus BSC (down from $n = 142$) and $n = 57$ for placebo plus BSC (down from $n = 70$). The definition of GI NETs omitting the 'unknown' location was used by Singh *et al.*[73] in their published poster. The definition of GI used by Singh *et al.*[73] is the definition of GI that the AG used in its ITC for NETTER-1.[31]

Despite the concerns raised above, the Bucher method[41] was used to indirectly compare everolimus with 177Lu-DOTATATE in individuals with GI NETs for the following outcomes: central review of PFS, OS, RR and various AEs. Because there were only two relevant trials for this synthesis we could not undertake any analyses for heterogeneity between the trials or inconsistency in the network.

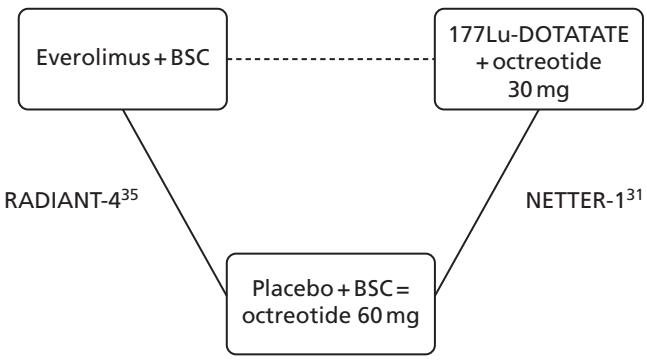

FIGURE 28 Diagram of the ITC for GI NETs.

TABLE 43 Tumour locations for GI NETs: comparison between NETTER-1[31] and RADIANT-4[35]

	NETTER-1,[31] *n/N* (%)		RADIANT-4,[35] *n/N* (%)	
Tumour location	177Lu-DOTATATE	Octreotide 60 mg	Everolimus + BSC	Placebo + BSC
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)

NA, not available.

For AEs, instead of providing data on all grades of AE and grade 3 and 4 AEs as requested by the AG, AAA provided data on all grades of AEs and grade 3–5 AEs from NETTER-1;[31] Novartis provided the requested data for all grades of AEs and for grade 3 and 4 AEs from RADIANT-4.[35] As grade 5 AEs are defined as death associated with an AE, the AG attempted to identify whether or not any deaths associated with AEs had occurred in RADIANT-4.[35] Confidential information has been removed. It was therefore assumed that data on the grade 3–5 AEs provided by AAA could be compared with data on the grade 3 and 4 AEs provided by Novartis.

Results

Two RCTs were used to compare everolimus with 177Lu-DOTATATE: RADIANT-4[35] (everolimus + BSC vs. placebo + BSC) and NETTER-1[31] (177Lu-DOTATATE + 30 mg of octreotide vs. 60 mg of octreotide) (see *Figure 28*).

For PFS, the ITC (*Table 44*) suggested that 177Lu-DOTATATE plus 30 mg of octreotide is associated with a statistically significant reduction of 63% in disease progression or death compared with everolimus plus BSC.

The results of the ITC for OS (*Table 45*) suggest that a (confidential information has been removed) in the hazard for death with 177Lu-DOTATATE plus 30 mg of octreotide compared with everolimus plus BSC; however, this result is associated with a wide 95% CI (confidential information has been removed).

From the available data on response rates (*Table 46*), the ITC results suggest that objective response and stable disease (confidential information has been removed) with everolimus plus BSC than 177Lu-DOTATATE plus 30 mg of octreotide: objective response (confidential information has been removed); stable disease (confidential information has been removed). However, the evidence suggests (confidential information has

TABLE 44 Hazard ratios (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[35] (from AG data request to Novartis)	Confidential information has been removed
177Lu-DOTATATE + octreotide 30 mg	Octreotide 60mg	NETTER-1[31] (from AG data request to AAA)	Confidential information has been removed
177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Calculated by AG	0.37 (0.19 to 0.69)

TABLE 45 Hazard ratios (95% CIs) for OS in GI NETs

Intervention	Comparator	Data source	HR (95% CI)
Everolimus + BSC	Placebo + BSC	RADIANT-4[35] (from AG data request to Novartis)	Confidential information has been removed
177Lu-DOTATATE + octreotide 30 mg	Octreotide 60 mg	NETTER-1[31] (from AG data request to AAA)	Confidential information has been removed
177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Calculated by AG	Confidential information has been removed

TABLE 46 Odds ratios (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[35] (from AG data request to Novartis)[a]	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE + octreotide 30 mg	Octreotide 60 mg	NETTER-1[31] (from AG data request to AAA)[a]	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Calculated by AG	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

a ORs calculated by the AG from the company response to a data request.

been removed) of progressive disease between 177Lu-DOTATATE plus 30 mg of octreotide and everolimus plus BSC (confidential information has been removed).

For all grades, data on nine AEs could be compared between RADIANT-4[35] and NETTER-1.[31] *Table 47* shows the ORs for the AEs from each study and the results of the ITC. The findings suggest that 177Lu-DOTATATE is generally associated with (confidential information has been removed) of experiencing AEs compared with everolimus plus BSC. This finding is statistically significant for the AEs of (confidential information has been removed) but not for (confidential information has been removed). The (confidential information has been removed) of experiencing fatigue associated with 177Lu-DOTATATE compared with everolimus plus BSC is (confidential information has been removed). For peripheral oedema, there is a (confidential information has been removed) of experiencing the AE with everolimus plus BSC than with 177Lu-DOTATATE: (confidential information has been removed).

TABLE 47 Odds ratios (95% CIs) for all grades of AEs in GI NETs

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

Data on grade 3/4 AEs were available only for the ITC for five AEs: abdominal pain, decreased appetite, diarrhoea, fatigue and nausea. The ORs from the studies and those calculated in the ITC are shown in *Table 48*. For the grade 3/4 AEs, 177Lu-DOTATATE is associated with a (confidential information has been removed) of experiencing the AE compared with everolimus plus BSC, (confidential information has been removed) between the two treatments.

TABLE 48 Odds ratios (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 to 2.57)
	177Lu-DOTATATE + octreotide 30 mg	Octreotide 60 mg	Confidential information has been removed
	177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Confidential information has been removed
Decreased appetite	Everolimus + BSC	Placebo + BSC	1.00 (0.12 to 8.57)
	177Lu-DOTATATE + octreotide 30 mg	Octreotide 60 mg	Confidential information has been removed
	177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Confidential information has been removed
Diarrhoea	Everolimus + BSC	Placebo + BSC	3.55 (0.88 to 14.35)
	177Lu-DOTATATE + octreotide 30 mg	Octreotide 60 mg	Confidential information has been removed
	177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Confidential information has been removed
Fatigue	Everolimus + BSC	Placebo + BSC	3.11 (0.50 to 19.27)
	177Lu-DOTATATE + octreotide 30 mg	Octreotide 60 mg	Confidential information has been removed
	177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Confidential information has been removed
Nausea	Everolimus + BSC	Placebo + BSC	2.04 (0.30 to 13.75)
	177Lu-DOTATATE + octreotide 30 mg	Octreotide 60 mg	Confidential information has been removed
	177Lu-DOTATATE + octreotide 30 mg	Everolimus + BSC	Confidential information has been removed

Appendix 7 Additional clinical effectiveness data

TABLE 49 Survival rates following everolimus, placebo and RPSFT-corrected placebo treatment in RADIANT-3[34]

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

NA, not assessable.
Source: Novartis submission, table 4.6 (p. 45)[33] and Yao *et al.*[34]

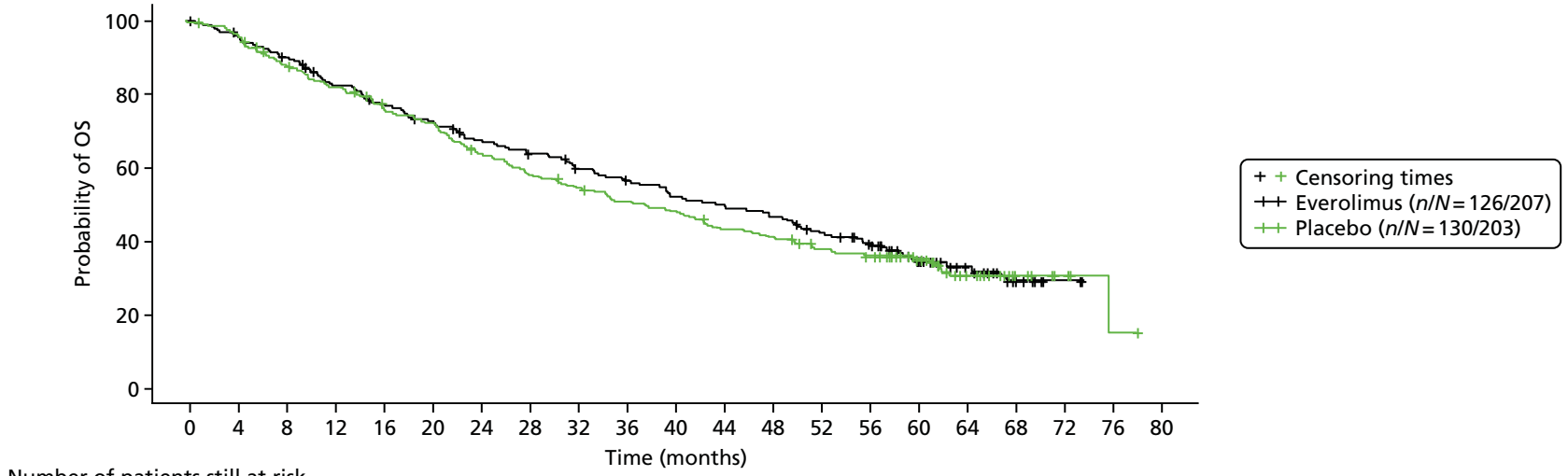

FIGURE 29 Kaplan–Meier plot for OS from RADIANT-3[34] (everolimus vs. placebo). Kaplan–Meier medians: everolimus 44.02 months; placebo 37.68 months. HR 0.94 (95% CI 0.73 to 1.20); log-rank $p = 0.300$ (significance boundary 0.0249). Source: figure 4.6 (p. 44) of the Novartis submission.[33]

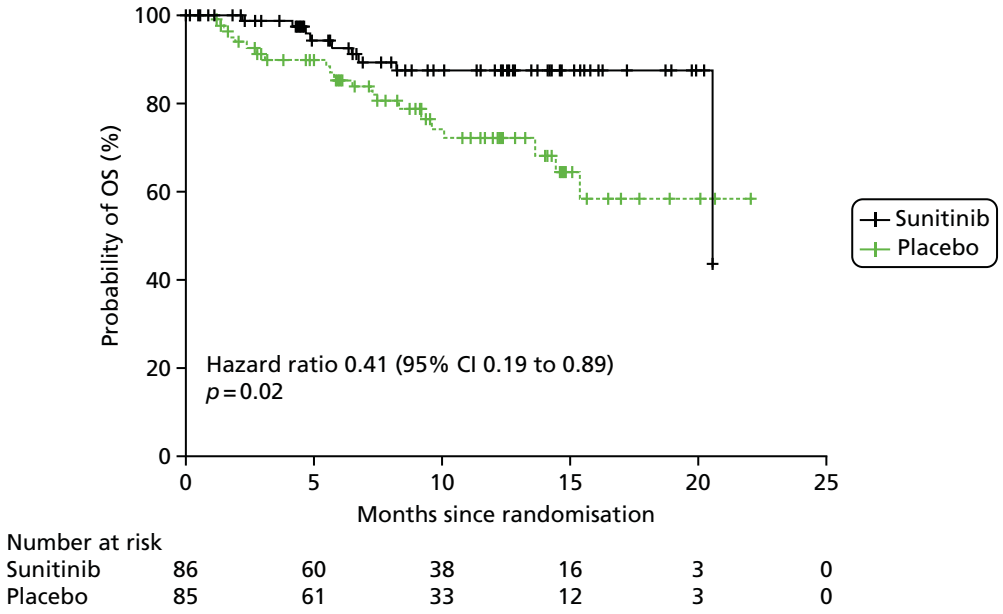

FIGURE 30 Overall survival, blinded phase, ITT population, from A6181111[81] (sunitinib vs. placebo). HR 0.41 (95% CI 0.19 to 0.89); $p = 0.02$. Source: figure 5 (p. 46) of the Pfizer submission.[32]

TABLE 50 Treatment-related AEs occurring in ≥ 20% of patients in RADIANT-3[34]

	Number of participants (%)					
	Everolimus + BSC (*N* = 204)		Placebo + BSC (*N* = 203)		Open-label everolimus (*N* = 225)	
AE	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All or any AE	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)
Peripheral oedema	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 (p. 57).[33]

TABLE 51 Adverse events reported in ≥ 10% of patients in RADIANT-4[35] regardless of study drug relationship (safety population)

	n (%)			
	Everolimus + BSC (*N* = 202)		Placebo + BSC (*N* = 98)	
AE	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All Aes	200 (99.0)	140 (69.3)	87 (88.8)	28 (28.6)
Stomatitis[a]	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)
Pruritus	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)

a Included in this category are stomatitis, aphthous stomatitis, mouth ulceration and tongue ulceration.
Source: Novartis company submission.[33]

TABLE 52 Most common (≥ 5% of sunitinib-treated subjects) treatment-related AEs in A6181111[81]

	n (%)			
	Sunitinib (*N* = 83)		Placebo (*N* = 82)	
AE	All grades	Grade 3 or 4	All grades	Grade 3 or 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)

continued

TABLE 52 Most common (≥ 5% of sunitinib-treated subjects) treatment-related AEs in A6181111[81] (*continued*)

	n (%)			
	Sunitinib (*N* = 83)		Placebo (*N* = 82)	
AE	All grades	Grade 3 or 4	All grades	Grade 3 or 4
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,[32] with its source being the CSR.[110]

TABLE 53 Overall post-baseline EORTC QLQ-C30 scores (mixed-effects model), showing differences between groups

Variable	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 (p. 53) of the Pfizer submission.[32]

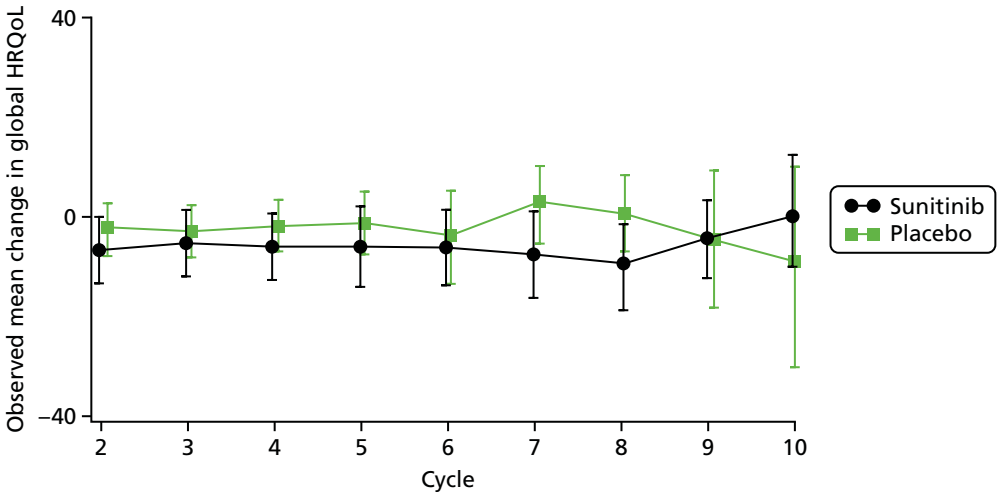

FIGURE 31 Change scores and 95% CIs for EORTC QLQ-C30 global HRQoL scores by cycle: patient-reported outcome analysis set. Source: figure 7 (p. 52) of the Pfizer submission.[32]

TABLE 54 Subgroup analysis of PFS from A6181111[81]

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

Source: Pfizer submission, figure 8 (p. 54).[32]

TABLE 55 Subgroup analysis of PFS from RADIANT-3[34]

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

Source: Novartis Submission, figure 4.4 (p. 40).[33]

TABLE 56 Subgroup analysis of OS from RADIANT-3[34]

Covariate	Subgroup	*n*	HR (95% CI); *p*-value
Previous chemotherapy	Yes	189	
	No	221	0.78 (0.61 to 1.01); 0.056
Previous long-acting SSA use	Yes	203	
	No	207	1.15 (0.89 to 1.49); 0.288

Source: appendix 3, table 3.8 (p. 55) of the Novartis submission.[33]

TABLE 57 Odds ratios (95% CIs) for AEs of all grades in pNETs

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

TABLE 57 Odds ratios (95% CIs) for AEs of all grades in pNETs (*continued*)

Outcome	Intervention	Comparator	OR (95% CI)
Headache	Everolimus	Placebo	3.45 (1.78 to 6.69)
	Sunitinib	Placebo	1.42 (0.62 to 3.29)
	Everolimus	Sunitinib	2.43 (0.84 to 7.05)
Vomiting	Everolimus	Placebo	2.62 (1.33 to 5.17)
	Sunitinib	Placebo	1.16 (0.61 to 2.22)
	Everolimus	Sunitinib	2.26 (0.88 to 5.78)
Asthenia	Everolimus	Placebo	1.60 (0.84 to 3.05)
	Sunitinib	Placebo	1.39 (0.72 to 2.70)
	Everolimus	Sunitinib	1.15 (0.46 to 2.90)

TABLE 58 Odds ratios (95% CIs) for AEs of grades 3 and 4 in pNETs

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

TABLE 59 Hazard ratio 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[34]	0.40 (0.28 to 0.57)	0.36 (0.25 to 0.51)
Sunitinib + BSC	Placebo + BSC	A6181111[81]	0.43 (0.21 to 0.89)	0.41 (0.22 to 0.75)
Everolimus + BSC	Sunitinib + BSC	Calculated by the AG	0.93 (0.42 to 2.08)	0.88 (0.43 to 1.78)

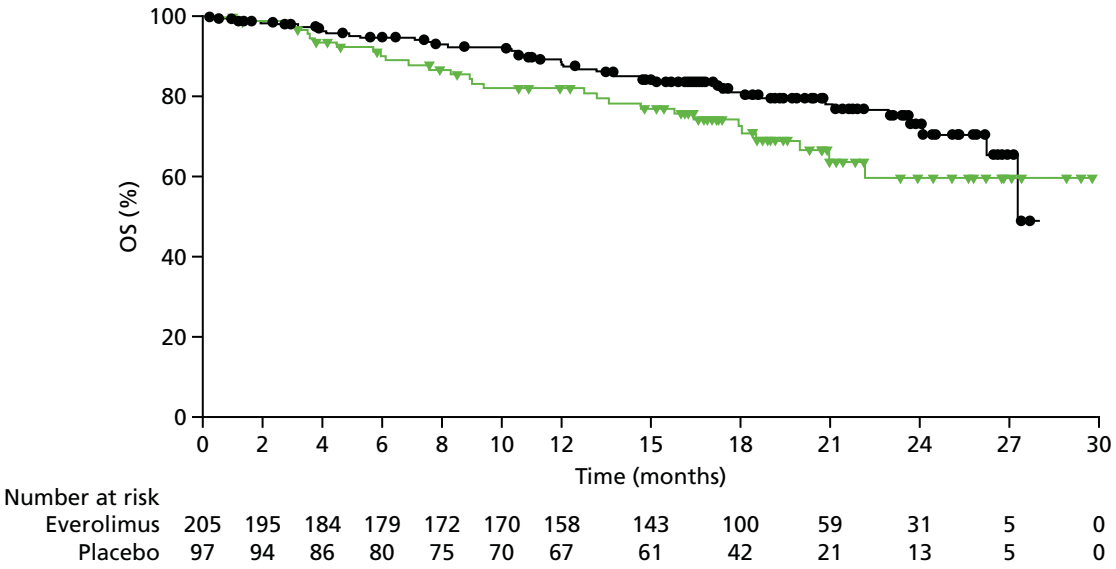

FIGURE 32 Kaplan–Meier plot for OS estimates in RADIANT-4:[35] primary data cut-off point. HR 0.64 (95% CI 0.40 to 1.05); $p = 0.037$ by stratified one-sided log-rank test. Source: figure 5.11 (p. 74) of the Novartis submission.[33]

TABLE 60 Completion rates for the FACT-G questionnaire for patients on the study at the scheduled day

Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
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TABLE 60 Completion rates for the FACT-G questionnaire for patients on the study at the scheduled day (*continued*)

	Confidential information has been removed	Confidential information has been removed
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Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

Source: Novartis company submission, table 5.6 (p. 76).[33]

FIGURE 33 Change from baseline in FACT-G total score over time (on treatment). Source: figure 5.13 (p. 77) of the Novartis company submission.[33] Confidential information has been removed.

FIGURE 34 Kaplan–Meier plot of time to deterioration in FACT-G total score by at least 7 points (full analysis set). NA, not accessible. Source: figure 5.14 (p. 78) of the Novartis submission.[33] Confidential information has been removed.

TABLE 61 Subgroup analysis of PFS from RADIANT-4[35]

Covariate	Subgroup	*n*	HR (95% CI)
Treatment naive	Yes	177	0.65 (0.39 to 1.08)
	No	185	0.51 (0.35 to 0.76)
Previous chemotherapy	Yes	77	0.35 (0.19 to 0.64)
	No	225	0.60 (0.42 to 0.86)
Previous SSA treatment	Yes	157	0.52 (0.34 to 0.81)
	No	145	0.60 (0.39[a] to 0.94)
Tumour grade	1	194	0.57 (0.39 to 0.84)
	0	107	0.49 (0.29 to 0.83)

a Reported as 0.30 in Yao *et al.*[34]
Source: Novartis submission, figure 5.6 (p. 70).[33]

TABLE 62 Baseline characteristics for individuals with GI NETs only

Characteristic	Everolimus + BSC (*n* = 118)	Placebo + BSC (*n* = 57)
Age (years), median (range)	63.0 (22–83)	60.0 (33–83)
Male (%)	40.7	54.4
Tumour functioning	100% non-functioning	100% non-functioning
Tumour differentiation	Well differentiated: 50.8%; moderately differentiated: 5.1%; not defined: 44.1%	Well differentiated: 61.4%; moderately differentiated: 3.5%; not defined: 35.1%
WHO PS	0: 75.4%; 1: 24.6%	0: 84.2%; 1: 15.8%
Previous treatments	SSAs: 59.0%; chemotherapy: 18.6%; surgery: 69.5%; radiotherapy: (confidential information has been removed); locoregional + ablative therapy: (confidential information has been removed)	SSAs: 63.0%; chemotherapy: 12.3%; surgery: 84.2%; radiotherapy: (confidential information has been removed); locoregional + ablative therapy: (confidential information has been removed)

Source: data on file from Novartis[33] and Singh *et al.*[73]

TABLE 63 Baseline characteristics for individuals with lung NETs only

Characteristic	Everolimus + BSC (*n* = 63)	Placebo + BSC (*n* = 27)
Age (years), median (range)	Confidential information has been removed	Confidential information has been removed
Male, *n*/*N* (%)	Confidential information has been removed	Confidential information has been removed
Tumour functioning	100% non-functioning	100% non-functioning
WHO PS, *n*/*N* (%)	Confidential information has been removed	Confidential information has been removed
Previous treatments, *n*/*N* (%)	Confidential information has been removed	Confidential information has been removed

Source: data on file from Novartis.[33]

TABLE 64 Adverse events in lung NETs

AE	*n*/*N* (%)			
	All grades		Grades 3 + 4	
	Everolimus + BSC (*N* = 62)	Placebo + BSC (*N* = 27)	Everolimus + BSC (*N* = 62)	Placebo + BSC (*N* = 27)
Abdominal pain (all)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Abdominal pain (upper)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Anaemia	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Asthenia	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Cardiac disorder	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Cough	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Diarrhoea	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Dry mouth	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Dysgeusia	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Dyspnoea	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Ear and labyrinth disorders	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Eye disorders	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Nausea	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Peripheral oedema	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Stomatitis	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Vomiting	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

Source: data on file from Novartis.[33]

Appendix 8 Evidence informing the companies' economic models

Novartis

The characteristics of the models submitted by Novartis are summarised in *Table 65*. See *Table 76* for the results.

Pancreatic neuroendocrine tumours

Efficacy, effectiveness and safety evidence

The systematic review by Novartis involved searching major electronic libraries (see sections 4 and 5 of the company submission[33]) on 21 July 2016, as well as hand searches of conference proceedings on 8 August 2016. The two identified trials have been described earlier in this report (see *Chapter 4*, *Results*). Here, only the major results and design features for the purposes of economic analysis are summarised.

RADIANT-3,[34] a Phase III double-blind RCT, assessed 10 mg of everolimus given orally plus BSC relative to matched placebo plus BSC in 410 adult, mTOR inhibitor-naive patients with progressive and advanced pNETs. Participants were randomised on a 1 : 1 ratio to the two treatments in a stratified fashion according to their baseline status in terms of prior chemotherapy (receipt vs. no receipt) and WHO PS (0 vs. 1/2).

According to the effectiveness section of the Novartis submission,[33] the median follow-up period in RADIANT-3[34] was 17 months, with median treatment durations of (confidential information has been removed) for everolimus compared with 3.74 months for placebo. However, in the economic analysis section, the median treatment duration for everolimus is reported as 8.61 (Novartis submission, p. 101[33]). At the time that the primary publication was written (cut-off date of 28 February 2010), 32% of participants in the everolimus group and 13% of participants in the placebo group were still receiving the allocated treatment; 44% in the everolimus group had stopped because of disease progression and 80% in the placebo group had stopped for the same reason.[34] Participants in the placebo group whose disease subsequently progressed were eligible to cross over to open-label everolimus. Of those patients initially randomised to placebo, 85% received open-label everolimus. In addition, both groups received BSC, which involved SSA use in 37.7% and 39.9% of participants in the everolimus and placebo groups, respectively.

The primary analysis (based on assessment by a local investigator) found that median PFS was 11.0 months (95% CI 8.4 to 13.9 months) for everolimus compared with 4.6 months (95% CI 3.1 to 5.4 months) for placebo, with a HR for disease progression or death for everolimus of 0.35 (95% CI 0.27 to 0.45). The assessment by central review found a HR of 0.34 (95% CI 0.26 to 0.44). The final OS analysis, which was unadjusted for crossover to everolimus, performed with data available on 5 March 2014, produced a median OS of 44.0 months for the everolimus group and 37.7 months for the placebo group and a HR for everolimus of 0.94 (95% CI 0.73 to 1.20). In the Novartis submission[33] it was acknowledged 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, (confidential information has been removed) of everolimus group received antineoplastic therapies after discontinuation of the study drug compared with (confidential information has been removed) of the placebo group. In total, 23% of patients in the everolimus group and 19.2% in the placebo group received a targeted therapy, whereas 29% of participants in each arm received chemotherapy.

The company conducted an OS analysis in which it adjusted for the effect of crossover from the placebo to the everolimus group, 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,

TABLE 65 Characteristics of models submitted by Novartis[33]

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 of PFS and OS with baseline Weibull form	SD, PD, death	SD with no AEs; SD with AEs: everolimus; SD with AEs: sunitinib; PD; death (0). Source: vignettes (Swinburn *et al.*[130])	Drug administration, drug acquisition, AEs, resource use (physician visits, procedures/tests and hospitalisations) and post-progression therapy costs. Source: Novartis data on file; NHS reference costs 2014–15 and PCTs combined[177]	PFS HR, OS HR, RDI, treatment duration (use of PFS for treatment costs)	HR: indirect comparison of HRs of (updated) A6181111[81] (sunitinib) vs. RADIANT-3[34] (everolimus) outcome data (Bucher method). Parametric baseline function from company data on file for RADIANT-3	• The model adjusted OS outcomes for treatment switching in the placebo arm using the RPSFT method. • Were PFS, OS and treatment duration estimated from publicly available data? OS: everolimus, company data from RADIANT-3; sunitinib, aggregated data (Kaplan–Meier curve) from internal SMC submission. PFS: yes, data from RADIANT-3 and A6181111[81] (updated) • Were the mean number of treatment cycles provided? No – assumptions based on PFS were used • Resource use data were obtained from a UK resource utilisation survey of 32 expert clinicians • Weibull baseline (everolimus) OS curve selected by comparison with SEER data. PFS Weibull curve selected for consistency with OS curve

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, non-functional, GI/lung NETs; from Phase III RADIANT-4[35] trial	Everolimus + BSC vs. BSC	30 years	Partitioned survival with monthly cycles (three states). Restricted log-normal distribution for PFS and OS (base case)	SD, PD, 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[35] were used in the modelling of PFS (by central review) and OS. For PFS, the primary analysis data cut-off point (28 November 2014) was used and, for OS, data from the second OS interim analysis data cut-off point (30 November 2015) were used	• Did the model adjust for treatment switching in all arms? In RADIANT-4 treatment switching was not allowed • Were PFS, OS and treatment duration estimated from publicly available data? RADIANT-4[35] • 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 calculated using patient-level data from RADIANT-4' (Novartis' submission,[35] p. 144)

PD, progressive disease; SEER, Surveillance, Epidemiology, and End Results Program; SD, stable disease; SMC, Scottish Medicines Consortium.

which assumes that the effect of treatment on OS is the same whenever the patient receives the treatment, for example at the start of the trial, after disease progression or after completing the core phase of the study. Although the duration of follow-up in RADIANT-3[34] was 72–78 months, the RPSFT 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 to 3.95).[62]

The other RCT identified by the company's systematic review was A6181111,[81] which compared 37.5 mg of sunitinib daily plus BSC against placebo plus BSC.[81] As with RADIANT-3,[34] A6181111[81] was conducted in patients with progressive, advanced and well- or moderately differentiated pNETs and measured the same primary outcome, PFS. Similarly, participants randomised to placebo were allowed to cross over to open-label active treatment, sunitinib, following disease progression. In total, 51% of participants in the sunitinib arm ($n = 44/86$) and 69% of participants in the placebo arm ($n = 59/85$) entered the open-label extension study.[81] The median treatment duration was 4.6 months for sunitinib and 3.7 months for 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 AEs (17% and 8%).[81] In a separate report referred to by Pfizer in its submission, it is stated that 38, that is, two-thirds, of the placebo group who crossed over did so following disease progression, whereas 21 in the placebo group started sunitinib after the study closure[88] (see *Chapter 4*, *Results*, for further details of A6181111[81]).

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 compared with placebo in RADIANT-3[34] and A6181111[81] using the method of Bucher *et al.*[41] The relative effect of the treatments on OS was estimated using ITT analysis 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 to 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 to 1.28).[88]

Novartis reported a PFS HR of 1.08 (95% CI 0.59 to 1.99; blinded independent review committee) and an ITT OS HR of 1.32 (95% CI 0.81 to 2.16) and a RPFST model-adjusted OS HR of 1.39 (95% CI 0.17 to 11.72).

The company also found that the HR for SSA use as part of BSC was 1.04 (95% CI 0.48 to 2.26) for everolimus 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 indirect comparison analysis resulted in an overall OR of 4.47 (95% CI 0.5 to 39.4) for an overall rate of grade 3–4 AEs of 0.35 for everolimus compared with an indirectly estimated overall rate of 0.71 for 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 AEs in question occurred only once for each individual. As the types of grade 3–4 AEs for which sunitinib had an excess risk compared with everolimus occurred less frequently (i.e. neutropenia, hypertension, leukopenia and palmar–plantar erythrodysaesthesia syndrome occurred in < 1% of participants) than those for which everolimus had worse outcomes (i.e. diarrhoea, stomatitis, thrombocytopenia, anaemia, hyperglycaemia, fatigue, infections, pneumonitis and nausea occurred in 3–7% of participants), the excess risks estimated by the Bucher method across individual AE categories added up to a larger total with everolimus than sunitinib. Thus, although sunitinib had a higher incidence of any of the 13 grade 3/4 AEs considered, the IC of individual categories produced absolute AE rates that implied the opposite, that is, that everolimus was associated with more of any of these events. As described in the critique of their submission (see *Chapter 5*), the company addressed this contradiction in an ad hoc manner in the economic evaluation.

In its submission, Novartis also included the results of a published indirect comparative study between everolimus and sunitinib that analysed placebo-controlled outcome data from RADIANT-3[34] and A6181111[81] using the MAIC method.[124] A detailed discussion of this evidence is presented in *Chapter 4* (see *Results*). The MAIC PFS HR for everolimus compared with sunitinib was estimated to be 0.84 (95% CI 0.46 to 1.53).

This estimate was smaller although statistically indistinguishable from the PFS HR estimate of 0.90 (0.53 to 1.53) before matching and the PFS HR of 1.08 from the Bucher analysis by Novartis, described above. Matching to the A6181111[81] sample reduced the relative effectiveness of everolimus compared with sunitinib from the unadjusted OS HR of 0.69 (0.46 to 1.05) to the MAIC OS HR of 0.81 (0.49 to 1.31).

The MAIC pooled OR for the subset of eight AEs (neutropenia, hypertension, palmar–plantar erythrodysaesthesia syndrome, diarrhoea, stomatitis, thrombocytopenia, anaemia and fatigue) was 1.16, which is smaller than the corresponding Bucher indirect comparison estimate of 1.37 (calculated by PenTAG from data in the Novartis submission; see *Appendix 21*). 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 for the subset of common categories (0.38 vs. 0.37, respectively) (in contrast, the Bucher rates were 0.15 and 0.29, respectively; PenTAG calculations of Novartis data submitted to NICE[33]). In contrast, a MAIC pooled placebo-adjusted OR for sunitinib compared with everolimus of 1.37 (calculated by the AG) for the 14 grade 3/4 AEs had been reported previously by Signorovitch *et al.*[124] using older RADIANT-3[34] data.

The company concluded that there was no evidence of any difference between everolimus and sunitinib in terms of PFS, OS and SSA use. 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 in which both treatments had equal PFS and OS effectiveness. In addition, it cautioned about the potential bias as a result of heterogeneity between the populations in the trials (RADIANT-3[34] and A6181111[81]) used in the Bucher indirect comparison, which was used as the source of the economic model parameters.

The AE estimates were obtained using the primary analysis cut-off date of 28 February 2010. In addition, Novartis presented updated results on AEs that occurred in the double-blind and extension phases of RADIANT-3,[34] with a cut-off date of 5 March 2014. These are not discussed here as they were not used in the Novartis economic evaluation.

The company also presented commercial-in-confidence data from a non-randomised, unpublished study, the OBLIQUE trial, in advanced pNETs patients treated with 10 mg of everolimus in routine practice. The study involved 46 patients who were followed up for 6 months from treatment initiation, with HRQoL measured using the EORTC QLQ-C30, EORTC QLQ GINET21 (European Organisation for Research and Treatment of Cancer 21-item Quality of Life Questionnaire for gastrointestinal neuroendocrine tumours) and the EQ-5D. This study found that HRQoL was maintained over the observation period. In particular, the mean EQ-5D score was 0.72 (95% CI 0.67 to 0.77) at baseline, 0.67 (95% CI 0.61 to 0.73) at 3 months and 0.73 (95% CI 0.67 to 0.78) at 6 months. This study is important as it is the only source identified by the AG containing utility values for patients on everolimus in the advanced pNETs population (see *Chapter 6*, *Systematic review of utilities*, for the 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[34] and A6181111.[81]

Novartis review of economic models and their results

Novartis conducted a systematic literature review of economic evaluation studies, including studies on resource utilisation, costs and utilities. It identified two studies as being 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 the previous company submission to the SMC[133,178] and All Wales Medicines Strategy Group (AWMSG).[179,180]

One of the identified studies was the poster publication by Johns *et al.*,[122] reviewed in *Appendix 10*, which reported an ICER of £22,587 per QALY gained for sunitinib compared with placebo. The other study was the SMC[178] and AWMSG[180] submission on everolimus, which in the SMC analysis[178] was found to have an ICER of £14,562 per QALY gained compared with sunitinib and £24,998 per QALY gained compared with BSC; in the analysis for the AWMSG,[180] the respective values were £12,894 and £24,999.

The above evidence is likely to be outdated because of recently updated data and analyses, particularly in relation to evidence adjusted for treatment crossover, and therefore an updated review and analyses are warranted.

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[34] to estimate the proportion of patients in stable disease 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 earlier in this appendix (see also *Chapter 4*, *Indirect treatment comparison: pancreatic neuroendocrine tumours*). OS for both treatments was derived using the same approach as for PFS. The estimated PFS and OS curves were used to partition the total proportion of patients alive at any given time into the proportion in the progression-free state and the proportion in the progressive state. The former proportion was obtained directly from PFS and the latter indirectly, by subtracting the proportion of PFS from the corresponding OS proportion for the duration of the 74-month trial observation period and up to 20 years.

Novartis explored different parametric failure time distributions to model PFS and OS in the everolimus arm of RADIANT-3,[34] including exponential, Weibull, Gompertz, log-normal and log-logistic models. To select the base case, three criteria were used: the BIC, 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 the 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 of 6% after diagnosis in the SEER database was used to judge whether or not a model extrapolation beyond the end of the trial follow-up period 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 PFS with everolimus in preference to the log-logistic and log-normal distributions, as these crossed the OS curve in the early part of the trial follow-up period. 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 assumptions 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 RADIANT-3[34] and A6181111[81] 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 arm and the placebo arm in each trial.

The company warns that, because of crossover to the active treatment in the placebo arms of the two trials, the OS HR derived from the Bucher indirect comparison may be biased because of differences in the method used to adjust for treatment crossover in RADIANT-3[34] and A6181111,[81] which was conducted by Pfizer and available only to Novartis from aggregate results submitted to the SMC[181] and AWMSG.[124] In particular, Novartis argues that, as illustrated by the comparative log-log plots of the two analyses (see figure 6.2 in the Novartis NICE submission[33]), the extent of recensoring needed for valid adjustment of the placebo arm of RADIANT-3[34] using the RPSFT method produced a placebo OS curve (left-hand graph) that was much shorter than the corresponding curve for placebo (right-hand graph) in the Pfizer RPSFT analysis of A6181111[81] data. This led Novartis to propose that Pfizer may not have applied recensoring in its analyses, which is needed for a valid estimation of treatment effect.[128] The AG sought to verify this 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 from replicating the Pfizer RPFST analysis and determining whether or not the RPFST analyses by the two companies were comparable.

On the basis of the Bucher indirect comparison results showing that the HR for OS (RPSFT adjusted: 1.39, 95% CI 0.166 to 11.723) and PFS (local review: 0.833, 95% CI 0.490 to 1.417; central blinded investigator review: 1.079, 95% CI 0.586 to 1.990) for everolimus compared with sunitinib had wide CIs around 1, Novartis adopted a fixed HR value of 1 in the base case, that is, the assumption of no difference in effect between the two treatments in terms of both PFS and OS outcomes.

As discussed earlier, these OS figures and the log-log plots from A6181111[81] are the same as the latest OS results for that trial,[88] which were presented in the Pfizer submission[32] to NICE. Using the latest RPSFT-adjusted OS HR of 0.34 for sunitinib compared with placebo and the corresponding estimate for everolimus used by Novartis to derive the base-case (Bucher) HR of 0.60 for everolimus compared with sunitinib results in a (Bucher) HR of 1.76 for everolimus compared with sunitinib [Pfizer conducted a MAIC analysis of everolimus compared with sunitinib and found a MAIC OS HR of (confidential information has been removed), although this was derived by matching to the A6181111[81] population and therefore is not comparable to the figures in this section, which are matched to the RADIANT-3[34] population; Pfizer submission, p. 68[32] and see earlier in this appendix].

Adverse events The model measured only the costs and effect on HRQoL (disutility) of treatment-related grade 3/4 AEs as the 'grade 1 and 2 events [observed in RADIANT-3[34]] would not be associated with any meaningful management costs or impact on HRQoL' (Novartis submission, p. 97[33]). Overall AE rates of 7% for the everolimus arm of the model and 26% for the sunitinib arm from cycle 0 to cycle 25, set to 0% thereafter, were applied (columns P and Q in 'Survival' sheet of Novartis's pNETs Microsoft Excel model). The everolimus rate was obtained from RADIANT-3[34] data, whereas the sunitinib rate was obtained by scaling up this rate on the basis of the OR of 4.479 for sunitinib compared with everolimus for any grade 3/4 AEs from the Bucher indirect comparison conducted by Novartis (see *Appendix 14*, *Novartis*). However, new grade 3/4 data provided by Pfizer[32] as part of its submission to NICE suggest that the rate for sunitinib is too high. Updating the Bucher analyses submitted by Novartis with the new Pfizer data results in a pooled grade 3/4 HR of 1.37 for everolimus. 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 AE.

Although the model does not explicitly account for the effect of AEs on treatment use, it included a measure of RDI for the targeted therapies recorded during the study period in RADIANT-3[34] and A6181111.[81]

Similarly, the costs of AEs in the model were assumed to apply only to the first 25 cycles. The role of AEs 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 of the relative incidence of AEs between sunitinib and everolimus from MAIC analysis of AE data from an earlier cut-off point[124] than the data cut-off point in the Bucher indirect comparison analysis (see table 4.5 in the Novartis submission[33]) that informed its economic model. Although the two sources may refer to different populations, that is, the MAIC was adjusted to the A6181111[81] population and the Bucher indirect comparison analysis was adjusted to the RADIANT-3[34] population, comparison of the two sets of estimates suggests that the Bucher indirect comparison 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 because, in the previous submission to the SMC, the appraisal committee's opinion was that the method was 'non-standard with uncertainty as to the robustness of this type of analysis' (Novartis submission, p. 49[33]). However, the overall balance of grade 3/4 AE risk implied by the individual AE rates obtained from the Bucher indirect comparison analysis was inconsistent with the pooled OR using the same method. Novartis used the Bucher AE rates adjusted for this inconsistency.

Since Novartis assumed that everolimus and sunitinib had equal PFS and OS outcomes, the resulting cost differences were driven, and the QALY differences completely determined, by the difference in the profile of AEs experienced under the two treatments. As discussed earlier in this appendix, the rates of individual types of AEs were determined by indirect comparison using the Bucher method. This led to differences in grade 3/4 AE rates between the two treatments that were inconsistent with the ranking of the two treatments in terms of pooled AEs: although the pooled OR indicated that sunitinib was associated with a higher incidence of AEs, the individual rates for the 13 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 AE in RADIANT-3[34] for everolimus and by the Bucher pooled OR for sunitinib in its pNETs economic model. The same approach was used to estimate the costs of AEs.

Costs and benefits were discounted at 3.5%, as indicated in the NICE reference case[37] (see *Appendix 9*).

Utility values

The utility values in the model were obtained using a time trade-off 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 did not include details about any particular treatment but instead presented states that described stable disease (with and without AEs, including diarrhoea, palmar–plantar erythrodysaesthesia syndrome, hyperglycaemia, nausea/vomiting, pneumonitis, rash, stomatitis and thrombocytopenia) or progressive disease.[131] This study was sponsored by Novartis. A discussion of this study is presented in the review of utility values in *Appendix 15* and *Chapter 6*, *Systematic review of utilities*.

The company used the disutilities estimated from the preference elicitation exercise to impute treatment-specific utility values for stable disease for the two treatments, after applying the weighted average method based on AE rates discussed in *Chapter 6*, *Systematic review of utilities*. The same progressive disease utility value was applied to both treatment arms. The average severity of events experienced with everolimus was marginally larger than that experienced with sunitinib (i.e. 0.647 vs. 0.656).

Some of the utility values for stable disease with AEs were based on assumption. These values are presented in *Table 66*. The assumption adopted by the company that hypertension, which was not measured in the preference elicitation study, had an average disutility equal to the average utility for all AEs in stable disease (0.128, = 0.771 – 0.643) is particularly implausible as national EQ-5D data in large samples suggest that the disutility of hypertension in patients with cancer in the last 5 years is negligible.[182] The disutility of anaemia, which was imputed in the same way as for hypertension, is higher than the 0.085 identified in previous reviews of chemotherapy-induced anaemia.[183] Likewise, the imputation of the 0.128 disutility value for all AEs for grade 3/4 fatigue by Novartis is questionable in view of lower time trade-off estimates found in previous studies.[183,184]

No disutility for end-of-life care costs was included in the analysis nor was any adjustment for the effect of age on background utility considered. The overall mean utility values after including treatment-specific AE profiles and the utility value for progressive disease used in the company's analysis are presented in *Table 67*.

Costs Novartis included the 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 AEs and death.

TABLE 66 Mean utility values included in the model for stable disease with specific grade 3/4 AEs

AE	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[a]	0.583	0.023	Swinburn *et al.*[131]
Leukopenia	0.690	0.024	Assumed similar to thrombocytopenia
Diarrhoea	0.600	0.025	Swinburn *et al.*[131]
Stomatitis	0.557	0.024	Swinburn *et al.*[131]
Thrombocytopenia	0.690	0.024	Swinburn *et al.*[131]
Anaemia	0.643	0.023	Average of all AEs
Hyperglycaemia	0.771	0.020	Higher than SD with no AEs, which is unlikely; thus, assumed similar to SD with no AEs
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.*[131]
Nausea	0.710	0.021	Swinburn *et al.*[131]

SD, stable disease; SE, standard error.
a Hand–foot syndrome = palmar–plantar erythrodysaesthesia syndrome.
Source: publicly available values used in the Novartis submission.[33]

TABLE 67 Summary of utility values for the cost-effectiveness analysis

	Source			
	Swinburn *et al.*[131]		A6181111[81]	
Health state	Utility value, mean (SE)	95% CI	Utility value, mean (SE)[a]	95% CI
SD without AEs	0.771	0.731 to 0.810	NA	NR
SD with AEs (everolimus)	0.647 (0.023)	0.601 to 0.693	0.730 (00.73)	NR
SD with AEs (sunitinib)	0.656 (0.024)	0.610 to 0.702	NA	NR
PD	0.612	0.564 to 0.659	0.596 (0.06)	NR

NA, not applicable; NR, not reported; PD, progressive disease; SD, stable disease; SE, standard error.
a SEs not reported for the sunitinib trial values; these were therefore assumed to be 10%.

The acquisition cost of everolimus of £2673.00 for 30 tablets of 10 mg adopted in the model was based on 2016 BNF prices.[36] The company presented analyses with and without a (confidential information has been removed) PAS discount, which reduced the drug acquisition cost to (confidential information has been removed). The cost of everolimus in each (monthly) cycle was calculated as the product of the monthly cost of everolimus acquisition and administration, that is, a dispensing fee, and the proportion of patients on treatment at each cycle in the everolimus arm of RADIANT-3,[34] in which everolimus treatment was given for a median duration of 8.61 months and a mean duration of (confidential information has been removed). The cost of everolimus was adjusted by the RDI of 85.9% recorded in RADIANT-3,[34] which accounted for everolimus treatment interruptions and dose reductions.

The acquisition cost of sunitinib was £2522.40 for 30 tablets of 37.5 mg, based on 2016 BNF prices.[36] The company assumed a PAS discount 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.[81]

In its base-case analysis, Novartis assumed that the cost of sunitinib acquisition and dispending was incurred for the same number of mean treatment cycles as for everolimus, on the basis that its ITC 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[81] and RADIANT-3.[34] The company performed a sensitivity analysis using an alternative figure of 9.66 months for sunitinib treatment duration, which the company attributed to the literature without providing a reference. It also cites a submission by Pfizer to the AWMSG in which Pfizer is reported to have assumed that 'patients receive an average of 293 days of treatment per year'.[179] However, in its submission to NICE, Pfizer reported an average duration of sunitinib treatment of 8.3 months in clinical practice (253 days; Pfizer submission, p. 17[32]). In addition, the median treatment duration for sunitinib in A6181111[81] was 4.64 months as opposed to the (confidential information has been removed) of everolimus use in RADIANT-3.[34]

The cost of drug administration involved a dispensing fee to cover a hospital pharmacist's time required to dispense an oral medication, obtained from the Personal Social Services Research Unit,[142] and the cost of delivering chemotherapies for intravenously administered drugs, obtained from NHS reference costs.[141] The same administration cost was thus applied to everolimus and sunitinib.

As for the costs of monitoring treatment and disease, data on 13 advanced pNETs (six well differentiated and seven 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, were used in the company model. The main publication[113] reporting the methods and findings of the survey is included in the systematic review of cost-effectiveness studies (see *Appendix 10*, *Results*). The survey asked clinicians about the treatment received by and health-care resources used for the two most recent patients they had treated, for each of three disease stages: 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 that tumour progression was recorded. The first progression period 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 stable disease phase of the model and the second progression phase as the progressive disease phase of the model. The survey produced actual resource utilisation data for eight (60%) pNETs patients in the stable disease phase and no patients in the progressive disease phase. Because of limited data available on NETs in general in the progressive disease 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 years age range and had an ECOG PS of 0–1 ($n = 6$; 46% – $n = 4$ had no recorded status).

Data were collected on resource use, including clinician visits, procedures and tests (e.g. CT scans, biomarker tests, including chromogranin A, and other tests) and hospitalisations. In addition, data on symptomatic (SSA and other) drug use in stable disease and symptomatic treatment and chemotherapy in progressive disease were collected. The clinicians were asked to estimate the duration spent in stable disease for patients, whereas for progressive disease they were asked to assume that patients would spend 12 months in that state. By dividing the reported amount of resource use for the whole stable disease and progressive disease periods by their respective duration, the average cost of a monthly cycle was derived for use in the model. As more clinician visits were obtained for the first cycle of the progressive disease phase, the Novartis model allowed for different health-care costs in the first and subsequent cycles after progression. Unit costs were obtained from NHS reference costs.[141]

The resulting values used for populating the model are presented in *Table 68*, which is reproduced from the Novartis submission.[33] In total, 84% of the total health-care costs in stable disease (£87; physician visits plus tests plus hospitalisations) are associated with physician visits (£55 per month) and CT scans (£18 per month). The progressive disease state for the first month after disease progression generates total health-care costs of £376 (first cycle), with a cost of £170 per month subsequently; the difference is due to

TABLE 68 Health-care resource utilisation and costs in the stable and progressive disease states

Resource	Unit cost (£)	Unit	Stable disease		Progressive disease first 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 physician)	158.54	Visit	0.274	43.39	0.744	117.91	0.338	53.58
Follow-up (another physician)	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 radiography	42.12	Procedure	0.000	0.00	0.013	0.54	0.013	0.54
Neuron-specific enolase	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	1.19	Test	0.024	0.03	0.026	0.03	0.026	0.03
Plasma vasoactive intestinal peptide 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	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 total free T4	1.19	Test	0.016	0.02	0.026	0.03	0.026	0.03

continued

TABLE 68 Health-care resource utilisation and costs in the stable and progressive disease states (*continued*)

Resource	Unit cost (£)	Unit	Stable disease		Progressive disease first cycle		Progressive disease subsequent cycle	
			Frequency per cycle	Cycle cost (£)	Frequency per cycle	Cycle cost (£)	Frequency per cycle	Cycle cost (£)
CBC blood test	3.01	Test	0.121	0.36	0.179	0.54	0.179	0.54
Blood urea nitrogen	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

CBC, complete blood count; SRS, somatostatin receptor scintigraphy; T4, thyroxine.
Source: Novartis submission, table 6.10 (p. 105)[33] citing resource utilisation survey conducted in the UK[113] and *NHS Reference Costs 2014 to 2015*.[141]

0.4 additional visits to the primary physician and one additional visit to other physicians in the first month after progression. In subsequent months of the progressive disease state, 95% of the costs are incurred from physician visits (£106 per month), CT scans (£22 per month) and hospitalisations (£34 per month).

The costs of managing AEs covered treatment-related grade 3/4 AEs that occurred in the stable disease phase of the model. Only AEs that were recorded in > 2% of patients in any of the active treatment arms of A6181111[81] and RADIANT-3[34] were accounted for. Details of the AE types, the methods used for deriving the AE probability estimates for the sunitinib arm, involving the Bucher indirect comparison analysis in *Chapter 4* (see *Indirect treatment comparison: pancreatic neuroendocrine tumours*), and the duration for which AEs were measured in the model are described in *Appendix 14* and *Chapter 6* (see *Utility values for the Peninsula Technology Assessment Group model*). As described in *Chapter 6*, the AE probabilities were based on the assumption that the 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[81] trial sponsored by Pfizer.

Moreover, as described earlier in the utility section, the Bucher indirect comparison produced sunitinib AE rates whose aggregate magnitude was smaller than the respective magnitude in the everolimus arm in RADIANT-3,[34] whereas the opposite occurred when the count of different AEs was combined to derive an overall AE rate for sunitinib using the same Bucher method. This led Novartis to calculate the disutility and cost of a typical AE as a weighted average of the costs of the different AEs multiplied by the relative contribution to the overall sum of AE rates for each treatment arm in the model. The inputs into this weighted average are presented in *Table 69*. In line with the weighted average disutility of AEs used in the Novartis model, the cost of a typical AE in the everolimus arm is more expensive, by 15%, than the average cost of an AE under sunitinib treatment. Novartis estimated an overall AE OR of 4.47 for sunitinib compared with everolimus, but the data on AEs with sunitinib in the A6181111[81] trial that the company

TABLE 69 Grade 3/4 AE rates included in the model and associated costs

	Everolimus				Sunitinib		
Grade 3/4 AE	Unit cost (£)	AE rate[a]	Weighted frequency	AE cost (£)	AE rate from the ITC[a,b]	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[c]	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

a Includes a 0.5 correction because of cells with zero counts.
b Relative frequency calculated from the ITC.
c Hand–foot syndrome = palmar–plantar erythrodysaesthesia syndrome.
Source: table 6.11 of the Novartis submission,[33] with revised labels for clarity and correction (see footnotes).

used were obtained from previous publications and, for certain AE types, differed from those reported by Pfizer in its submission to NICE; with the updated figures, the AG obtained a OR estimate of 1.37 instead. Based on the monthly (confidential information has been removed) probability of AEs with everolimus estimated by Novartis from RADIANT-3[34] individual patient data, which the company applied for the first 25 cycles of the stable disease model under everolimus (with a probability of 0 applied for subsequent cycles), the Bucher OR estimated by Novartis produced a monthly probability of AEs with sunitinib of 26% in those cycles; with the OR calculated by the AG, the monthly probability of AEs with sunitinib changes to 10%.

This means that the costs of the additional risks of an AE with sunitinib are partly offset by the lower severity of these AEs relative to everolimus. Moreover, updating Novartis's data on AEs with sunitinib with data submitted by Pfizer[32] to NICE reduces the additional costs of AEs with sunitinib. These additional costs decline over time as fewer people in both arms remain in the stable disease state. Furthermore, in the base case they decline at the same rate in both arms, as Novartis assumed that PFS is the same across the two arms, until cycle 25 (at 2 years after treatment starts), after which no AE costs are incurred.

The use of symptomatic treatment, defined as SSA, in the stable disease phase was estimated from the proportion, 37.7%, of people who received the treatment before progression in the everolimus arm of RADIANT-3[34] and the Bucher indirect comparison OR of 1.04 (95% CI 0.478 to 2.262) estimated for everolimus compared with sunitinib (Novartis submission, section 4.7.2.3;[33] see earlier in this appendix). This resulted in a SSA treatment rate with sunitinib of 36.8%, which was multiplied by the monthly cost of treatment with SSAs, as detailed in *Table 70*. The costs used by Novartis were based on BNF drug acquisition prices.[36] In contrast, average drug acquisition prices paid by hospitals, as recorded in the electronic market information tool (eMIT) database,[137] are 8–26% lower for the symptomatic treatments considered by Novartis (final column of *Table 70*). As for symptomatic treatment in progressive disease, a rate of SSA use of 25% was assumed based on the results of the health-care resource use survey of UK experts[113] described earlier, 1.9 administrations of octreotide per cycle, at a mean daily dose of 30 µg for the first 15 days and 450 µg thereafter, and 90% RDI.

The costs of subsequent treatments following disease progression were included for chemotherapy, radiotherapy and chemoembolisation. Information on subsequent therapy used in the sunitinib arm of A6181111[81] was not recorded in the trial (Pfizer, response to AG data request, August 2016). Novartis stated that the rates of subsequent treatments used in its model were obtained from those recorded in the RADIANT-3[34] trial of everolimus compared with placebo; these were applied to both the sunitinib and the everolimus arms of the model. However, the rates used in the model (reproduced in *Table 71*) and those observed in RADIANT-3[34] and reported in the appendix of the Novartis submission[33] do not seem to correspond.

TABLE 70 Costing and dosing assumptions for SSA usage

SSA	Costing assumption (£)	Administration cost (£)	Costing assumption based on eMIT prices (not considered in the Novartis model submission) (£)
Octreotide LAR (Sandostatin LAR)[a]	799.33	239.12	632.40
Octreotide (Sandostatin) – 500 mg	14.12	239.12	NA
Lanreotide (Somatuline Autogel)[a]	736.00	239.12	NA
Octreotide (Sandostatin) 500 µg/ml, 1-ml ampoule	27.09	239.12	25.10

NA, not available.
a Based on 50% of patients receiving octreotide LAR and 50% receiving lanreotide. In the model it was assumed that 39.9% of patients received a SSA, thereby incurring an average cost £767.66 × 0.39 = £306.30.
Source: non-confidential data from the Novartis submission[33] (column 3), eMIT prices[137] and the BNF 2016[36] (column 2).

TABLE 71 Post-progression treatment utilisation and costs allocated to the initial post-progression state

Treatment	Unit cost (£)	Initial drug administration cost (£)	Subsequent drug administration 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

End-of-life care costs were included as a single fixed amount of £4346 occurring at the time that patients died in the model. This figure was obtained from a published study estimating the per-patient health-care costs observed in the terminal phase of life of cancer patients in England and Wales,[143] 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.

Costs were expressed in 2015 prices.

Gastrointestinal and lung neuroendocrine tumours

Efficacy, effectiveness and safety evidence

In RADIANT-4,[35] 205 patients were randomised to 10 mg daily of everolimus plus BSC and 97 were randomised to placebo plus BSC. Randomisation was carried out with stratification by previous SSA 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 PS (0 vs. 1). The median follow-up period in the study was 21 months and the median duration of treatment with everolimus was 40.4 weeks. Median PFS was 11.0 months (95% CI 9.2 to 13.3 months) in the everolimus arm and 3.9 months (95% CI 3.6 to 7.4 months) 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 to 0.67).

Participants in RADIANT-4[35] were not allowed to undergo treatment crossover after disease progression. Interim OS analysis found a reduction in the risk of death with everolimus of 36% (HR 0.64, 95% CI 0.40 to 1.05), but the data were not mature enough to estimate median OS in any arm. Grade 3/4 drug-related AEs observed in the trial included stomatitis, diarrhoea, infections, anaemia, fatigue and hyperglycaemia (see *Chapter 4*, *Results* for details).

Review of the 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 utilisation or costing and utilities associated with health states or treatments in the GI/NETs patient population. No studies were found.

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 earlier for the Novartis model of pNETs

and including PFS (cut-off date 28 November 2014) and OS (cut-off date 30 November 2015) data from RADIANT-4.[35] For this purpose and to extrapolate the OS and PFS outcome distributions beyond the end of the follow-up period in RADIANT-4,[35] a parametric survival curve was chosen from six 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, in which one distribution was estimated using data from both trial arms but different estimates for each parameter in the distribution were obtained for the two arms, and a variant in which the data from both arms were analysed with the same distribution but all but one of the parameters (i.e. the scale) were restricted to be the same for the everolimus and placebo arms.

More broadly, Novartis assessed the empirical adequacy of three classes of treatment effect models for PFS and OS data. One was the shifted failure time model, which assumes that 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 model, which assumes that the treatment proportionally alters the (instantaneous) risk of the event occurring; this model class includes the exponential, Weibull and Gompertz models. The third model class considered was the AFT model, which assumes that treatment affects the survival time proportionally; this model class includes the log-logistic, log-normal and gamma models. By applying the counterfactual criteria of Bagust and Beale[185] to model section, Novartis was able to discriminate the AFT model class as providing valid PFS model candidates, whereas the proportional hazards and AFT model classes were valid for modelling OS. The counterfactual criteria consist of 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 for which the counterfactual placebo survival curve matches 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 had 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 the SEER database, despite the caveats acknowledged by the company and discussed earlier with regard to the Novartis pNETs model. The other requirement was that curves did not cross, which, in the analysis of OS, was justified on the basis that 'there is no reason to believe that the OS for everolimus plus BSC would be less than that for placebo plus BSC at any point in time' (Novartis submission, p. 137[33]).

The PFS model selected for the base case was the (restricted) log-normal model, whereas the (restricted) gamma, (restricted) log-logistic and (unrestricted) log-normal models were used for sensitivity analyses. The (restricted) log-logistic distribution was chosen to model OS in the base-case analysis, with the (restricted and unrestricted) log-normal model used in sensitivity analysis. Novartis considered unrestricted variants as more flexible options than the restricted forms of each survival distribution but in practice their added flexibility ended up ruling them out as candidate models for PFS and OS data because of curve crossing between the everolimus arm and the placebo arm. Therefore, it is questionable whether or not 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 RADIANT-4,[35] 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[35] were not allowed to cross over from placebo to open-label everolimus after disease progression, data on subsequent treatments submitted to NICE by Novartis as part of the economic model (table 7.13, p. 154[33]) show that 9% of patients in RADIANT-4 received everolimus as subsequent treatment after disease progression. 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 crossover to everolimus (in spite of including, in the BSC arm of the model, the costs of subsequent everolimus treatment used by placebo arm participants) in RADIANT-4[35] may be invalid.

Adverse events

The model included the costs of grade 3/4 AEs reported in RADIANT-4[35] that had an incidence of ≥ 2%. This resulted in the inclusion of stomatitis, diarrhoea, fatigue, infections, peripheral oedema, anaemia, pyrexia and hyperglycaemia. The proportions of participants 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 the stable disease phase for everolimus and 0.0147 from the first to the 30th cycle in the SD phase for BSC. Other cycles were assigned AE probabilities of zero. Given that HRQoL outcomes that allowed derivation of health state utilities were measured in RADIANT-4,[35] these AE probabilities were not used to calculate base-case utility values but they were used to calculate alternative utility values in sensitivity analysis following the approach described earlier for pNETs (see *Chapter 5*, *Economic evaluation of everolimus in pancreatic neuroendocrine tumours*).

Model implementation

In order to incorporate the costs of subsequent treatment, different costs were used in the model in the first and in subsequent cycles after disease progression. The costs of drug administration were applied to both initial and subsequent treatments. AE costs were applied only in the stable disease state. The costs of terminal care were also included as a single cost as participants die in the model. Costs and QALYs were discounted at a 3.5% annual rate.

Utility values

Health state utility values for stable disease and progressive disease were obtained from FACT-G outcome data collected in RADIANT-4.[35] This involved using the ordinary least squares mapping algorithm estimated by Longworth *et al.*[134] and Young *et al.*[186] 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.[37] The AG has been able to reproduce the utility estimates used in the base-case analysis from publicly available summary data on FACT-G domain scores reported by RADIANT investigators[74] and a linearised version of the best-fitting non-linear algorithm, based on domain responses[134] (see *Chapter 6*, *Systematic review of utilities*). The base-case analysis used the value of 0.779 for stable disease and 0.725 for progressive disease in both treatment arms, although the company also estimated treatment-specific stable disease utility values of 0.767 for everolimus plus BSC and 0.807 for placebo plus BSC and progressive disease values of 0.714 and 0.747, respectively, and used these values in scenario analyses. The stated reason for the choice of base-case values was that the differences in utilities between everolimus plus BSC and placebo plus BSC in RADIANT-4[35] 'were not statistically significant or clinically meaningful' (Novartis submission, p. 159[33]). As acknowledged by the company, the utility values for progressive disease are unlikely to be valid measures of the post-progression period as they are based on HRQoL outcomes of a subgroup of people who had progressed by the time that the study had ended and which covered only the early phase of the progressive disease state. This led the company to explore lower values in sensitivity analyses.

No adjustment was applied to utilities for end-of-life care or the effect of ageing on HRQoL.

Costs

The costs of drug acquisition, dispensation and administration associated with everolimus and BSC were included in the analysis. Analyses of costs using list prices and alternative potential PAS discounts were presented.

The cost of drug acquisition of 10 mg daily of everolimus, as given in RADIANT-4,[35] was calculated using the 2016 BNF price of £2673 for 30 tables of 10 mg each.[36] Alternatively, the PAS discount of (confidential information has been removed) 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 individual

patient data from RADIANT-4.[35] The Kaplan–Meier median treatment duration was (confidential information has been removed) months and by month 38 (confidential information has been removed) remained on treatment. A RDI obtained from RADIANT-4[35] data of 79.4% was applied to the everolimus treatment costs.

The costs of orally administered treatment were based on hospital pharmacy staff time, with unit costs obtained from the Personal Social Services Research Unit.[142] The costs of intravenously administered therapies as part of BSC were applied using unit costs obtained from NHS reference costs.[141]

Included in BSC were analgesics, antiemetics, antidiarrhoeals, external beam radiation therapy 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[35] data. Novartis selected the most commonly observed specific treatment as a representative for each category for the purposes of calculating the costs of BSC in the model. The usage rates of therapies constituting BSC used in the model are presented in *Table 72*.

Health-care 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.[120] The methods used in the survey are described earlier for Novartis's pNETs model. The validation exercise considered current management practice in non-functional GI and lung NETs separately and involved five 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 73*, weighted in proportion to the mix of GI and lung participants in RADIANT-4.[35]

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

TABLE 72 Usage rates of therapies constituting BSC in the model

BSC therapy	Usage rates (derived from RADIANT-4[35]) (%)	
	Everolimus + BSC	Placebo + BSC
Analgesics: representative treatment lidocaine	12.7	6.2
Other pain medication: corticosteroids and glucocorticoids – representative treatments dexamethasone (corticosteroids) and prednisone (glucocorticoids)[a]	Corticosteroids 31.7, glucocorticoids 41.5	Corticosteroids 10.3, glucocorticoids 11.3
Antiemetics: representative treatment prochlorperazine	2.9	3.1
Antidiarrhoeals: representative treatments Biofermin, *Saccharomyces boulardii*[b]	5.8	5.2
EBRT	1	0
SSAs: representative treatment octreotide LAR	2	1

EBRT, external beam radiation therapy.
a Two treatment categories were included because they were the most frequently used concomitant medications in the trial that can be used to alleviate pain.
b Two treatments were included because both were used equally as frequently in trial participants.
Source: Yao *et al.*[35] and table 7.8 of the Novartis submission.[33]

TABLE 73 List of resource use in stable disease and progressive disease and associated unit costs

Item	Resource use in SD		Resource use in PD		Unit cost (£)
	Everolimus + BSC	BSC alone	Everolimus + 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
Neuron-specific enolase	0.056	0.055	0.106	0.000	1.19
Chromogranin A	0.277	0.146	0.344	0.130	1.19
5-hydroxyindoleacetic acid	0.166	0.104	0.213	0.059	1.19
CBC blood test	0.805	0.271	1.038	0.211	3.01
Blood urea nitrogen	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

CBC, complete blood count; PD, progressive disease; SD, stable disease; SRS, stereotactic radiosurgery.
Source: table 7.10 of the Novartis submission.[33]

alone (Novartis submission, p. 159[33]). In addition, patients in the progressive disease 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 who started the model under BSC alone were under observation; see details in *Table 74*).

Novartis stated 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 alone would be treated after disease progression, the relative use of these post-progression therapies was calculated using the RADIANT-4[35] trial data' (Novartis submission,[33] section 7.5.5.1). Costs for post-progression treatments in the model were applied according to the number of treatment cycles that they were observed to be given for

TABLE 74 Resource use relating to post-progression treatments

	Central review C, %	
Post-progression treatment	Everolimus + BSC	Placebo + BSC
Octreotide LAR	29.8	22.7
Lanreotide	8.5	8.0
Everolimus	4.3	9.1
PRRT	5.0	3.4
IFN	1.4	0.0
Hepatic artery embolisation	5.0	6.8
Chemoembolisation	0.7	3.4
Radiofrequency ablation	0.7	1.1
SIRT	0.0	2.3
Temozolomide	14.2	11.4
Capecitabine	14.2	11.4
Streptozocin	2.8	1.1
Fluorouracil	2.8	1.1
Observation	32.7	33.3

IFN, interferon; PRRT, peptide receptor radionuclide therapy; SIRT, selective internal radiation therapy.
Source: Yao *et al.*,[35] reproduced from table 7.13 of the Novartis submission.[33]

in RADIANT-4,[35] assuming standard dosages rounded to the nearest dose that was consistent with no wastage (*Table 77*).

Octreotide LAR was applied a unit cost of £998.41 per month based on 2016 BNF prices.[35] This price is 20% higher than the £806.42 average price available to hospitals according to the eMIT database[137] (accessed October 2016). Another aspect to note is the rate of use of everolimus in the placebo arm of 9.3% compared with a rate of 4.3% in the everolimus arm, both of which were given for a treatment duration of 6.18 cycles in the model (see *Table 74*). Clinical expert advice received by the AG suggests that there is currently no access to peptide receptor radionuclide therapy in England, although there was previously, and that chemotherapy would be used instead in most patients.

A fixed cost of £4346 was applied when patients died in the model to account for the costs of terminal care. This figure was derived from the literature.[143]

To estimate the costs of AEs, the probability of any AE, derived from the pooled incidence of grade 3/4 AEs with an incidence of ≥ 2% in either arm of RADIANT-4[35] (see *Chapter 4*, *Outcomes from randomised controlled trial evidence for gastrointestinal and lung neuroendocrine tumours*, *Adverse events*), was multiplied by the weighted average cost 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.[141]

Advanced Accelerator Applications

The main characteristics of the models submitted by the company are presented in *Table 75*. The main results are presented in *Table 76*.

TABLE 75 Characteristics of models submitted by AAA[31]

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 pNETs subgroup of patients in the ERASMUS study – patients with inoperable SSTR+ GEP NETs	177Lu-DOTATATE vs. everolimus and sunitinib (also octreotide LAR – out of scope)	20 years (lifetime)	Cost–utility analysis, QALYs. Three-state Markov model with partitioned-survival. Four-week corrected cycles. Proportional hazards model PFS and OS with baseline Weibull form	Pre-progression survival (PFS), post-progression survival (PPS), death	EORTC QLQ-C30 mapped to EQ-5D: PFS 0.80, PPS 0.79. AE disutility from various literature sources (grade 3/4 only); applied per cycle	Drug acquisition, drug administration, monitoring, AE. Resource utilisation rates from the NETTER-1 CSR.[175] Base case includes 177Lu-DOTATATE drug acquisition cost reduction for real-world dose intensity (86.4%). BSC = 30 mg of octreotide LAR	PFS HRs, OS HRs, PFS and PPS health state utilities, 177Lu-DOTATATE dose intensity, 177Lu-DOTATATE drug cost	ERASMUS CSR[187] for baseline PFS and OS risk curves (direct extraction). PFS and OS adjusted for an extreme value. MTC for adjusted proportional hazards. RADIANT-3[34] for everolimus outcome data; Raymond *et al.*[81] for sunitinib data; NETTER-1, RADIANT-3[34] and Raymond *et al.*[81] for AE proportions. PFS utility sourced from the ERASMUS study	• No comparison with BSC • No reported treatment switching between arms in NETTER-1. Treatment switching was not allowed in RADIANT-4[35] • PFS and OS for 177Lu-DOTATATE were not drawn from a publicly available source (NETTER-1 CSR) • To link the MTC network the treatment effect of octreotide LAR was assumed to be equivalent to that of placebo • Everolimus and sunitinib treatment continued until progression, not for their mean treatment duration • No nuclear scientists involved in administration of lutetium – cost underestimated?

continued

TABLE 75 Characteristics of models submitted by AAA[31] (*continued*)

Company/ indication	Population	Comparators	Horizon	Model structure	Health states/events modelled	Utilities	Costs	Key individual parameters (sensitivity analysis)	Source of effectiveness parameters	Comments
AAA, GI NETs within GEP NETs	Patients with inoperable, SSTR + mid-gut carcinoid tumours (NETTER-1 study)	177Lu-DOTATATE vs. everolimus (also octreotide LAR – out of scope)	20 years (lifetime)	Cost–utility analysis, QALYs. Three-state Markov model with partitioned-survival. Four-week corrected cycles. Proportional hazards model of PFS and OS with baseline Weibull form	Pre-progression survival (PFS), post-progression survival (PPS), death	EORTC-QLQ-C30 mapped to EQ-5D: PFS 0.79, PPS 0.74. AE disutility from various literature sources (grade 3/4 only); applied per cycle	Drug acquisition, drug administration, monitoring; AEs. 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 = 30 mg of octreotide LAR	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 sensitivity analysis	NETTER-1 CSR (v1) for baseline PFS and OS risk curves (direct extraction). MTC for adjusted proportional hazards. RADIANT-2 and -4 for everolimus outcome data;[35,119] NETTER-1 and RADIANT-4[35] for AE proportions. PFS utility sourced from UK Trust registry; PPS sourced from the ERASMUS study	• No comparison with BSC • No reported treatment switching between arms in NETTER-1. Treatment switching was not allowed in RADIANT-4[35] • PFS and OS for 177Lu-DOTATATE were not drawn from a publicly available source (NETTER-1 CSR) • To link the MTC network the treatment effect of octreotide LAR was assumed to be equivalent to that of placebo • Everolimus and sunitinib treatment continued until progression, not for their mean treatment duration • No nuclear scientists involved in administration of lutetium – cost underestimated?

CSR, clinical study report; EQ-5D, EuroQol-5 Dimensions.

TABLE 76 Results of the company model submissions

Study	Regimens compared	Patient characteristics	Time horizon	PFS (years)	Life-years (undiscounted unless otherwise stated)	Discounted (3.5%) incremental QALYs	Discounted (3.5%) incremental costs (£)	ICER (£)	Notes on the ICER
Novartis, pNETs	Everolimus, sunitinib	pNETs, as in RADIANT-3[34] (everolimus) and A6181111[81] (sunitinib)	20 years	Everolimus 14.348; sunitinib 12.512	Everolimus 3.298; sunitinib 2.85	0.021	–1,635.86. (Confidential information has been removed) (PAS)	Dominant Dominant (PAS)	Costs and QALYs discounted by 3.5%. PAS with (confidential information has been removed) discount for everolimus
Novartis, GI NETs	Everolimus + BSC, BSC	Mean age 61.7 years (RADIANT-4[35])	30 years	Everolimus 11.01; BSC 5.50	Everolimus 5.793; BSC 4.775	0.777	33,902	£43,642 (list price). (Confidential information has been removed) (PAS price)	Costs and QALYs discounted by 3.5% per year and are in 2014–15 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 years	177Lu-DOTATATE: 1 year 80.84%, 5 years 11.58%, 10 years 0.34%; everolimus: 1 year 61.99%, 5 years 0.79%, 10 years 0.00%	Discounted: 177Lu-DOTATATE 4.26; everolimus 2.49	1.42	Confidential information has been removed	Confidential information has been removed	Base case excludes cost of palliative care; includes concomitant drugs and a dose intensity adjustment for lutetium
AAA, pNETs within GEP NETs	177Lu-DOTATATE, everolimus, sunitinib	From NETTER-1 CSR: mean age 63.7 years; weight 74.05 kg. Population: unresectable or metastatic pNETs with disease progression	20 years	177Lu-DOTATATE: 1 year 90.06%, 5 years 19.53%, 10 years 0.58%; everolimus: 1 year 83.97%, 5 years 6.56%, 10 years 0.02%; sunitinib: 1 year 78.53%, 5 years 3.80%, 10 years 0.00%	Discounted: 177Lu-DOTATATE 6.91; everolimus 4.16; sunitinib 6.84	2.18	177Lu-DOTATATE: vs. everolimus: (confidential information has been removed); 177Lu-DOTATATE vs. sunitinib: (confidential information has been removed)	177Lu-DOTATATE vs. everolimus: (confidential information has been removed); 177Lu-DOTATATE vs. sunitinib: (confidential information has been removed)	Base case excludes cost of palliative care; includes concomitant drugs and a dose intensity adjustment for lutetium

CSR, clinical study report.

TABLE 77 Unit costs of post-progression treatments

Post-progression treatment	Unit cost (£) (unit)	Source	Treatment duration				
			Everolimus + BSC		BSC alone		
			Number of units per cycle	Number of cycles	Number of units per cycle	Number of cycles	Source
Octreotide LAR – 30 mg	998.41 (per month)	BNF 2016[36]	1.087	4.06	1.087	4.46	RADIANT-4[35]
Lanreotide – 120 mg	937.00 (per month)	BNF 2016[36]	1.087	1.80	1.087	2.27	RADIANT-4[35]
Everolimus – 10 mg	89.10 (per day)	BNF 2016[36]	30.438	6.18	30.438	6.18	RADIANT-4[35]
PRRT	2247.10 (per procedure)	*NHS Reference Cost 2014 to 2015*[141]	0.400	5.74	0.400	0.03	RADIANT-4[35]
IFN – 5 million IU	28.37 (per day)	BNF 2016;[36] IntronA Summary of Product Characteristics	13.045	3.84	13.045	3.84	RADIANT-4[35]
Hepatic artery embolisation	3993.90 (per procedure)	*NHS Reference Cost 2014 to 2015*[141]	1.000	1.00	1.000	1.00	RADIANT-4[35]
Chemoembolisation	3993.90 (per procedure)	*NHS Reference Cost 2014 to 2015*[141]	1.000	1.00	1.000	1.00	RADIANT-4[35]
Radiofrequency ablation	937.54 (per procedure)	*NHS Reference Cost 2014 to 2015*[141]	1.000	1.00	1.000	1.00	RADIANT-4[35]
SIRT	2026.86 (per procedure)	*NHS Reference Cost 2014 to 2015*[141]	1.000	1.00	1.000	1.00	RADIANT-4[35]
Temozolomide – 360 mg	152.40 (per day)	BNF 2016;[36] Strosberg *et al.*[67] Sacco *et al.*[188]	5.435	2.34	5.435	3.08	RADIANT-4[35]
Capecitabine – 2650 mg	£6.42 (per day)	BNF 2016;[36] Strosberg *et al.*[67] Sacco *et al.*[188]	15.219	2.34	15.219	3.08	RADIANT-4[35]
Streptozocin – 895 mg	0.00 (per day)	Assumption that cost is covered by the CDF	2.174	1.23	2.174	1.45	RADIANT-4[35]
Fluorouracil – 750 mg	10.40 (per day)	BNF 2016;[36] Sun *et al.*;[189] Sacco *et al.*[188]	4.348	1.23	4.348	1.45	RADIANT-4[35]
Observation	0.00	NA	0.000	0.00	0.000	0.00	NA

IFN, interferon; NA, not applicable; PRRT, peptide receptor radionuclide therapy; SIRT, selective internal radiation therapy.

Efficacy and effectiveness evidence

Advanced Accelerator Applications conducted a systematic review of 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[145] was included in the review, NETTER-1, which compared 177Lu-DOTATATE plus 30 mg of octreotide with 60 mg of octreotide in individuals with GI NETs.

Advanced Accelerator Applications 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. AAA considered the study and participant characteristics in all studies in the two networks to be comparable, including RADIANT-2,[190] which was excluded from our systematic review (see *Chapter 4*) because all participants have functioning tumours, which is outside the licence for everolimus. These MTCs are illustrated in *Figures 35* and *36*.

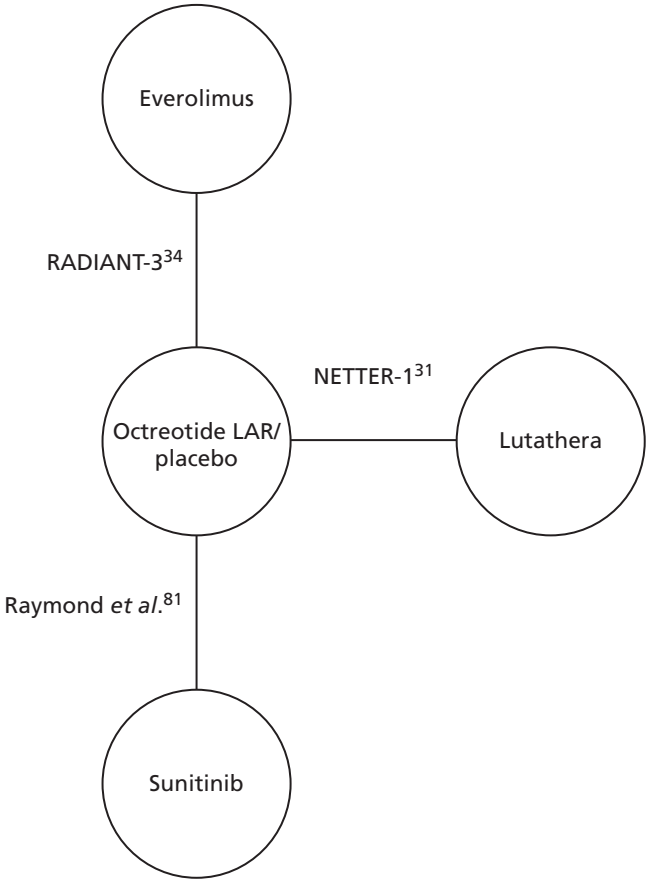

FIGURE 35 Indirect comparison network for PFS and OS in pNETs. Source: figure 12 (pp. 71–2) of the AAA submission.[31]

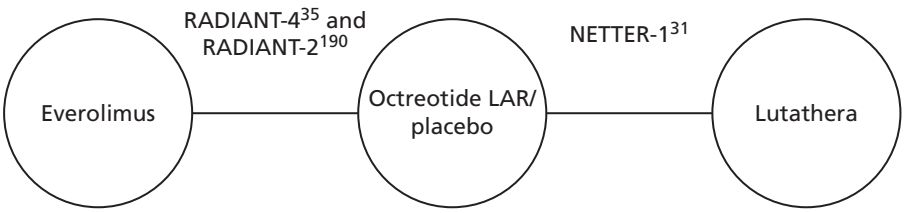

FIGURE 36 Indirect comparison network for PFS and OS in GI NETs. Source: figure 13 (pp. 71–2) of the AAA submission.[31]

Advanced Accelerator Applications made three major assumptions in performing its MTC. These were that:

1. 60 mg of octreotide can be assumed to be equivalent to placebo and placebo plus 30 mg of octreotide (in order to connect NETTER-1 to the other trials) in the GI NETs network
2. 60 mg of octreotide is equivalent to placebo and placebo plus BSC (in order to connect NETTER-1 to the other trials) in the pNETs network
3. data from the NETTER-1 trial can be used to inform the network for pNETs even though no participants within the NETTER-1 trial had pNETs.

Advanced Accelerator Applications undertook a Bayesian analysis with Markov chain Monte Carlo (MCMC) simulation in R. It ran fixed- and random-effects models with HRs as response variables, using the poisson/log model and the binomial/cloglog model. AAA reported assessing convergence using trace plots, autocorrelations and 'other standard convergence diagnostics' (AAA submission, p. 210[31]), but did not state explicitly whether or not convergence was achieved in the models.

The results of the MTCs are shown in *Tables 78* and *79*.

TABLE 78 Pancreatic NETs HRs (95% credibility intervals) synthesised from the MTC

Intervention	PFS	OS
177Lu-DOTATATE vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
Everolimus vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
Sunitinib vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
177Lu-DoTATATE vs. everolimus	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE vs. sunitinib	Confidential information has been removed	Confidential information has been removed
Everolimus vs. sunitinib	Confidential information has been removed	Confidential information has been removed

TABLE 79 Gastrointestinal NETs HRs (95% credibility intervals) synthesised from the MTC

Intervention	PFS	OS
177Lu-DOTATATE vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
Everolimus vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE vs. everolimus	Confidential information has been removed	Confidential information has been removed

We have a number of reservations regarding the MTCs conducted by AAA:

- RADIANT-2[190] should be excluded from the MTC for GI NETs as the population in this trial all have functioning tumours, which is outside the marketing licence for everolimus in GI NETs.
- NETTER-1 should be excluded from the pNETs network as this trial did not include any patients with pNETs
- For the evaluation of GI NETs, the populations included for OS differ across the three studies (midgut NETs in NETTER-1, all NETs in RADIANT-2 and GI and lung-NETs in RADIANT-4[35]).
- There is no justification for the assumption that 60 mg of octreotide LAR is equivalent to placebo, placebo plus 30 mg of octreotide and placebo plus BSC.
- There is no consideration of the extent of treatment switching within RADIANT-2[190] (58% switched to active treatment), RADIANT-3[34] (73% switched to active treatment) and A6181111[81] (69% switched to active treatment), which limits the interpretation of the results for OS.
- The 95% credibility intervals (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 identified four single-arm non-RCTs,[145,162–165,170] yet focused on the Dutch subset of the ERASMUS study.[162–164] 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 80*.

Review of the economic models and their results in the submission

The submission details a systematic review of the economic literature, which identified 11 cost-effectiveness studies relevant to the decision problem.

Individual search strategies were developed for the following databases:

- MEDLINE (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- The Cochrane Library (Wiley): Cochrane Database of Systematic Reviews (CDSR), CENTRAL, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment database and NHS EED.
- EconLit

The electronic database search was supplemented by hand searching the Cost-effectiveness Analysis (CEA) Registry, NICE HTA, PBAC (Pharmaceutical Benefits Advisory Committee) and CADTH (Canadian Agency for Drugs and Technologies in Health) submissions and conference proceedings.

In total, 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; 10 were cost-effectiveness analysis studies and one was a budget impact study. All 11[122,126,127,144,191–194] were assessed as being of good quality.

TABLE 80 Primary outcomes from the ERASMUS non-randomised open label study

Outcome	Midgut	Hindgut	Foregut	Pancreas
ORR, % (95% CI)	34 (28 to 41)	46 (19 to 73)	50 (22 to 78)	56 (48 to 65)
Median PFS, months (95% CI)	29.6 (24.8 to 34.4)	29.3 (22.3 to 39.0)	NR	30.5 (24.9 to 36.2)
Median OS, months (95% CI)	55.4 (49.8 to 70.1)	NR	NR	70.8 (63.2 to ND)

ND, not determined; NR, not reached.

Seven cost-effectiveness analysis studies 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 evaluated those with carcinoid syndrome and VIPoma and one evaluated GI (midgut) NETs.

The methodology used in the company's systematic review of the economic literature was sound and comprehensive. However, the company did not include a description of the results or discuss the 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.

Data and methods

Efficacy and effectiveness data used in the model

Baseline rates of progression and OS 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 AIC and BIC, combined with clinical plausibility on visual inspection.

A partitioned survival model was implemented in Microsoft Excel with Weibull coefficients for PFS and OS generated in Stata® (StataCorp LP, College Station, TX, USA) 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, HRs generated from the MTC were applied to the baseline survival curves (*Table 81*). Background mortality was not included in the base-case analysis but was included in scenario analysis.

Adverse events

Serious adverse events (grades 3 and 4) were incorporated into the model using incidence data from clinical trials (*Table 82*). For each treatment an AE profile was developed whereby each event, when appropriate, carried a cost of management and an associated utility decrement.

Treatment-specific adjustments to baseline PFS utility were calculated using decrements weighted according to event incidence in the trials (*Table 83*).

TABLE 81 Hazard ratios from the MTC of interventions (deterministic median) applied to baseline risk

Intervention	PFS (95% CI)	OS (95% CI)
Everolimus pNETs vs. placebo	Confidential information has been removed	Confidential information has been removed
Sunitinib pNETs vs. placebo	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE GI NETs vs. placebo	Confidential information has been removed	Confidential information has been removed
Everolimus GI NETs vs. placebo	Confidential information has been removed	Confidential information has been removed

TABLE 82 Incidence (%) of SAEs in clinical trials

SAE	177Lu-DOTATATE (NETTER-1[187])	Everolimus (pNETs) (RADIANT-3[34])	Sunitinib pNETs[81]	Everolimus (GI NETs) (RADIANT-4[35])
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			

TABLE 83 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

Decrements for AEs were applied to every cycle for which patients remained progression free, including post treatment for those patients administered 177Lu-DOTATATE.

The utility decrement weightings for SAEs followed the trend advised by the AG expert clinicians: BSC > 177Lu-DOTATATE > everolimus > sunitinib. 177Lu-DOTATATE dose adjustment as a result of AEs or missed treatments in NETTER-1 was incorporated into the costing of 177Lu-DOTATATE in the base case by applying a RDI reduction in mean drug acquisition cost. No such adjustment was made for everolimus or sunitinib. AE utility decrements were applied to all treatment strategies while patients were progression free. As these decrements should be applied to the treatment period only, this approach overestimates the period of disutility from AEs. Although the disutility penalty is greatest for everolimus and sunitinib, the mean duration of treatment of 177Lu-DOTATAE is less than that of everolimus and sunitinib in practice. In any case, the ICERs are insensitive to this limitation.

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 SAEs. HRQoL scores were collected for stable and progressive disease in the base case from pNETs/GI NETs patients administered 177Lu-DOTATATE in the ERASMUS study (*Table 84*). However, the exception is the base-case estimate of stable disease in GI NETs, for which the estimate was sourced from a UK registry. The company did not explain why this approach was adopted.

Patients in the ERAMUS trial were Dutch and the number of participants and their characteristics were not stated. Responses were collected every 12 weeks from first treatment to 72 weeks. HRQoL scores from the EROTC QLQ-C30 questionnaire used in the ERASMUS trial were mapped to EQ-5D scores.[134] 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% white; mean age 60 years). Overall, the synthesis of health state utility estimates is potentially weak because of the use of multiple sources, multiple quality-of-life assessment tools and cohorts from single-arm studies/registries rather than RCTs.

Adverse events were not modelled using an additional health state; instead, disutilities were applied to the baseline PFS estimates according to the incidence of AEs in the trial of each treatment (see *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 to be 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 well-being; this was included in a univariate deterministic sensitivity analysis.

Costs

The included cost categories were drug acquisition, drug administration, disease monitoring and AE management. No provision was made for any hospitalisation of patients owing to deterioration of their 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 (30 mg) following progression and until death.

Drug acquisition prices and posology were sourced from the BNF[36] (everolimus, sunitinib and octreotide), except for 177Lu-DOTATATE, for which information was supplied by AAA (*Table 85*).

Drug prices were incorporated into the base case at the NHS list price; no discount or PAS prices were explored in sensitivity analyses. A RDI adjustment to reflect downwards dose modifications or skipped doses observed in the NETTER-1 trial (0.864) was applied to the acquisition cost of 177Lu-DOTATATE. No equivalent adjustments were made for everolimus or sunitinib. This reduced the cost of the 177Lu-DOTATATE strategy, which decreased the ICERs compared with 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 its submission in which the involvement of nuclear medicine department

TABLE 84 Utilities used in the base case by primary NETs site and health state

Site	PFS	PPS
pNETs	0.80[a] (95% CI 0.79 to 0.81)	0.79[a] (95% CI 0.76 to 0.82)
GI NETs	0.79[b] (95% CI 0.77 to 0.82)	0.74[a] (95% CI 0.72 to 0.76)

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.

TABLE 85 Drug posology and acquisition price

Treatment	Dose and frequency	Unit cost in base case
177Lu-DOTATATE	Four administrations of 7.4 GBq (200 mCi), administered once every 8 weeks	29.6 GBq (800 mCi) = (confidential information has been removed)
Everolimus	10 mg administered once daily	30 tablets, 10-mg pack = £2673
Sunitinib	37.5 mg administered once daily	30 tablets, 12.5-mg pack = £784.70
Granisetron[a]	3 mg administered before administering 177Lu-DOTATATE	10 tablets, 1-mg pack = £32.89
Vamin 18 – 18%[a]	Given before administering 177Lu-DOTATATE	Vamin 18 (electrolyte free), net price 1 litre = £23.38

a Supportive treatments administered alongside 177Lu-DOTATATE.

resources are anticipated. It is also inconsistent with expert clinical opinion that we received, which indicated that specialist involvement and admission with an overnight stay is routine.

Everolimus and sunitinib are self-administered orally and therefore attracted a zero administration cost.

The resource utilisation for monitoring of disease was assumed to be the same for all treatment strategies. The unit costs are shown in *Table 86*.

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 SAE types. Seven were 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 to be equal to the cost of the highest cost event (stomatitis, £385.17). The cost of managing AEs was included for every cycle in stable disease, rather than while on treatment. Note the earlier assumption that everolimus and sunitinib treatment are 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 were included in univariate deterministic sensitivity analysis.

The price year used in the analysis was not stated but it may reasonably be assumed to be 2015.

TABLE 86 Resource utilisation rates and unit costs

Resource use[31]	Frequency[31]	Unit cost in base case (£)[137]
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

CBC, complete blood count; ECG, electrocardiogram.

Appendix 9 Reference case

TABLE 87 National Institute for Health and Care Excellence reference case[37]

Element of health technology assessment	Reference case	Novartis[33] (pNETs)	Novartis[33] (GI and lung NETs)	AAA[31] (pNETs)	AAA[31] (GI NETs)
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 HRQoL in adults	Yes	Yes	Yes	Yes
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	No	Yes	Yes	Yes
Source of preference data for valuation of changes in HRQoL	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

Appendix 10 Review of cost-effectiveness evidence

The purpose of this appendix is to review existing evidence on the cost-effectiveness of sunitinib, everolimus and lutetium relative to chemotherapy or BSC in patients with unresectable or metastatic, progressive NETs.

Methods

Searches

Bibliographic literature searching was conducted on 19 May 2016 and forward citation searching was completed on 17 August 2016. The searches took the following form: (terms for neuroendocrine or pancreatic or GI or lung) AND (metastatic or unresectable or advanced) AND (terms for the interventions under review) AND (a costs or economic literature search filter). The searches were not date limited, were not limited by language and were not limited to human-only studies.

The following databases were searched: MEDLINE (Ovid), EMBASE (Ovid), NHS EED (Wiley Online Library), Web of Science (ISI – including conference proceedings) and EconLit (EBSCO*host*). The search strategies are recorded in *Appendix 1*.

Screening

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review (see *Chapter 4*, *Inclusion and exclusion criteria*), with the following exceptions (as specified in the appraisal protocol):

- non-randomised studies were 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 were included (economic evaluations that report only average cost-effectiveness ratios were included only if the incremental ratios could be easily calculated from the published data)
- studies that measure only costs but not health benefits were 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 to be eligible for inclusion, were examined by one reviewer (RMM) to identify other potentially relevant references. These references were retrieved and checked for eligibility in the same way as for full texts identified from the database searches.

Quality assessment

Studies meeting the criteria for inclusion were assessed by one reviewer (RMM) using the checklist developed by Evers *et al.*[195] This checklist is intended as a criteria list for the quality assessment of economic evaluations in systematic reviews, thereby making these reviews transparent, informative and comparable. Studies based on decision models were further quality assessed using the checklist developed by Philips *et al.*[196]

Synthesis

Economic studies were summarised and synthesised using tabulated data and narrative synthesis. The narrative synthesis described the major contributions of reviewed studies to the economic evidence on targeted treatments in patients with advanced, progressive NET and the methodological strengths and weaknesses. The findings were summarised with reference to the elements of the NICE reference case.[37]

Results

Identified studies

The electronic database search for cost-effectiveness evidence identified 1143 records; six additional records were identified by other means. After deduplication, 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 37*.

Four of the eight full texts were journal articles and the remaining four were posters presented at conferences. Three[120,121,123] of the four articles were full economic evaluations and were included in the review. The remaining article[197] was an analysis of the costs of administration of lanreotide and octreotide; because of the limited scope of this study, and as the revision of the NICE scope removed these two treatment options from the present technology assessment review, this study was excluded from the review.

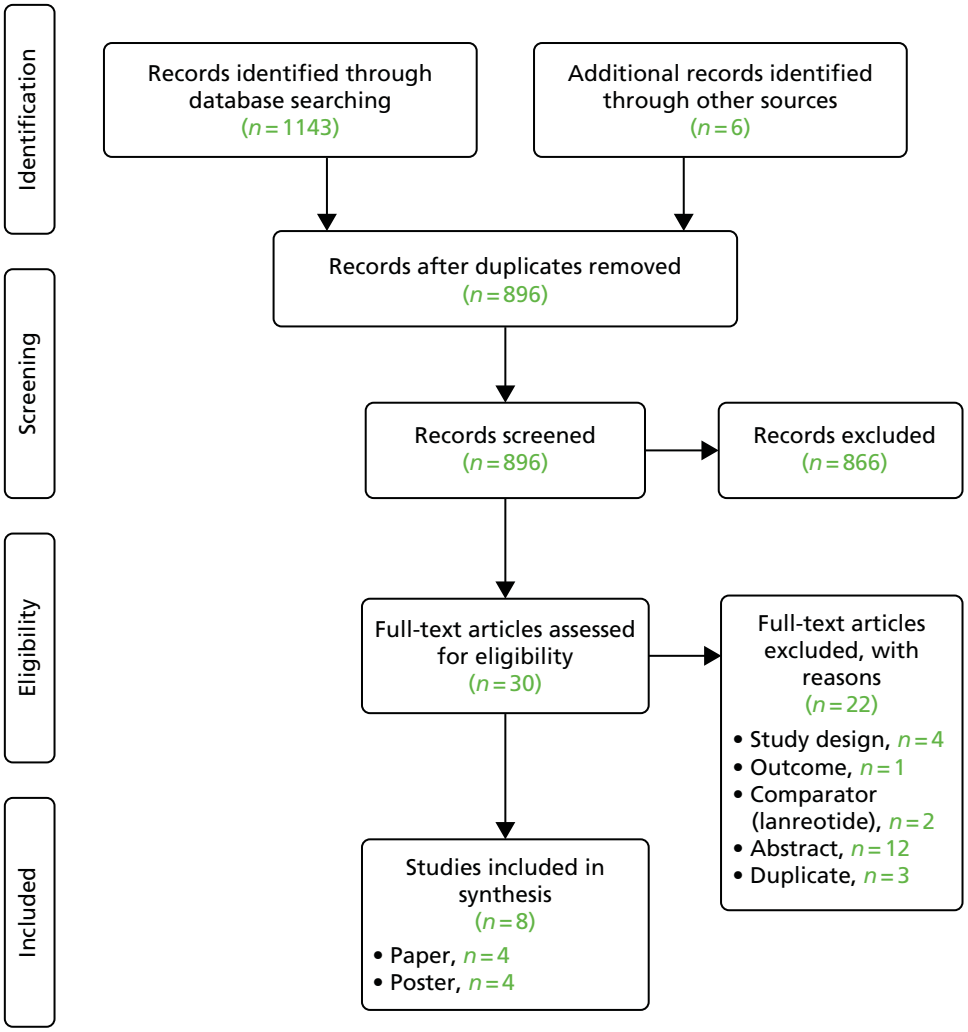

FIGURE 37 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Of the four identified conference poster presentations, one described the only study conducted in the UK[122] and provided detailed methods and results and was therefore included in the review; another reported limited methodological information and results and was conducted in the Portuguese health-care setting[198] and was therefore excluded. The remaining two posters were evaluations of lanreotide and octreotide[118,199] and were therefore excluded. Given the limited evidence found, and as 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 compared with everolimus in the US health-care setting,[120] one was an evaluation of sunitinib compared with BSC in the Mexican health-care system[121] and one was an evaluation of sunitinib compared with BSC in the Polish health-care system. The included study presented as a conference poster was an evaluation of sunitinib compared with BSC for pNETs patients in Scotland and Wales.[122] One of the excluded posters was the only report found, in poster or journal article form, that related to an economic evaluation of treatments for GI NETs.[118]

Table 88 describes the characteristics of the included studies. All studies were sponsored by the industry or co-authored by an individual affiliated with a company manufacturing or commercialising one of the evaluated treatments.

Pancreatic studies

Summary characteristics of the included studies are presented in *Table 89*. The main results of these studies are presented in *Table 90*. The critique of each of these studies is guided by the quality assessment reported in *Table 91*.

Casciano *et al.*[120]

The only study comparing targeted therapies evaluated everolimus and sunitinib in patients with advanced (unresectable or metastatic) progressive pNETs from a US health insurer perspective. In the absence of a head-to-head study of the two treatments, this study was based on the results of a previous indirect comparison of AE, PFS and OS outcomes with everolimus and sunitinib across their respective pivotal Phase III trials.[124] Data on outcomes with everolimus relative to placebo were those reported in RADIANT-3,[34] whereas the sunitinib outcomes were obtained from A6181111.[81]

The analysis modelled the experience of a cohort of patients who receive either everolimus plus BSC or sunitinib plus BSC, from the start of treatment until 20 years post treatment. Patients were assumed to be in an initial stable disease health state where they could remain until death or they experienced disease progression and moved to a deteriorated health state, progressive disease, with higher costs and lower utility values. In turn, those who experienced disease progression would, according to the model, remain there until death. This model was implemented as a semi-Markov model in which patients could move between the three health states (stable disease, progressive disease and death) at discrete time points every month. In each of these monthly cycles patients would accumulate costs and utilities specific to the health state; different costs and utilities were accumulated for stable disease between the two initial treatments (sunitinib and everolimus), whereas costs and utilities for progressive disease 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 stable disease states that were differentiated only by the presence or absence of AEs, which did not affect the transition probabilities to the other health states (progressive disease and death) but only the costs and utilities associated with the cycle. As the rate of AEs varied with each cycle, in effect this was a Markov model with three health states, with variable costs and utility pay-offs for the stable disease state.

The transition probabilities across states with each successive cycle were derived by partitioning survival into OS time and survival time free from disease progression. To estimate the PFS and OS curves for each treatment, the MAIC method was used.[124] In this application, this consisted of weighting individual patient data from one placebo-controlled trial (i.e. RADIANT-3[34] trial of everolimus) to match the distribution of

TABLE 88 Characteristics of the included studies

Author	Country	Regimens	Population	Study type	Perspective	Outcomes considered	Horizon	Model based?	Sponsor
Casciano 2012[120]	USA	Sunitinib vs. everolimus	Advanced (i.e. unresectable and/or metastatic) progressive pNETs (mean years)	Cost–utility analysis	Hospital	Total health-care costs per patient, cost per QALY gained	20 years	Yes	Funded by Novartis
Muciño Ortega 2012[121]	Mexico	Sunitinib with BSC vs. BSC only	Advanced well-differentiated pNETs	Cost–utility analysis	Mexican (Public) Social Health Insurance Institution, IMSS	Total health-care costs per patient, cost per QALY gained	10 years	Yes	Funded by Pfizer
Johns 2012[122]	UK	Sunitinib with BSC vs. BSC only	Advanced pNETs	Cost–utility analysis	NHS	Total care costs, cost per QALY gained	10 years	Yes	Funded by Pfizer
Walczak 2012[123]	Poland	Sunitinib with BSC vs. BSC only	Advanced well-differentiated pNETs with disease progression	Cost–utility analysis	Public payer for health services, i.e. PNHF; additional analysis presented from the perspective of PNHF and the patient	Total health-care costs per patient, cost per QALY gained	Lifetime	Yes	Funded by Pfizer

IMSS, Instituto Mexicano del Seguro Social; PNHF, Polish National Health Fund.

TABLE 89 Characteristics of the 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 2012[120]	Advanced pNETs, USA	Everolimus vs. sunitinib	20 years	Semi-Markov – partitioned survival with monthly cycles. Proportional hazards model of PFS and OS with baseline Weibull form	SD without AEs, SD with AEs, PD, death	SD with no AEs, SD with AEs: everolimus, SD with AEs: sunitinib, PD, death (0)	Drug acquisition and administration. For each health state (entry and follow-up states): symptomatic care, procedures/ tests, physician visits and hospitalisations. Also post-progression treatments and death (end-of-life care)	PFS HR, active treatment dose intensity, post-progression treatment costs, AE costs	HR: MAIC of HRs of (updated) A6181111[81] (sunitinib) vs. RADIANT-3[34] (everolimus) outcome data[124]	• Discount rate of 3% for costs and QALYs • There was no adjustment for treatment switching to everolimus in sunitinib arm • PFS, OS and treatment duration estimated from publicly available data for sunitinib and private company individual patient data on everolimus • Mean treatment cycles were provided
Muciño Ortega 2012[121]	Advanced well-differentiated pNETs, Mexico	Sunitinib + BSC vs. BSC	10 years	Markov – partitioned survival with 2-weekly cycles Proportional hazards model of PFS and OS with baseline Weibull form	SD, PD, death	Treatment-specific SD values from mapping EORTC-QLQ-C30 data from A6181111[81,123] into EQ-5D scores with the McKenzie and van der Pol[132] algorithm	Drug acquisition and AE management. For each health state: procedures/tests, physician visits and palliative care. The source of resource use data was a survey of 15 oncologists in public hospitals in four different cities	HR PFS, HR OS, cycle costs of routine care before progression, acquisition costs of sunitinib per cycle, utility of post progression	HRs for OS and PFS from A6181111[81]	• Discount rate 5% • The model did not report adjustments for crossover in any treatment arm • PFS and OS were estimated from publicly available data from the main trials
Johns 2012[122]	Advanced or metastatic pNETs	Sunitinib + BSC vs. BSC	10 years (described as 'lifetime')	Markov – partitioned survival. Proportional hazards model of PFS and OS with baseline Weibull form	SD, PD, death	Treatment-specific SD values from mapping EORTC-QLQ-C30 data from A6181111[81] into EQ-5D scores using the McKenzie and van der Pol[132] algorithm	Drug acquisition, grade 3/4 AE management, BSC patient management, outpatient visits, CT scans and end-of-life care	OS: ITT vs. crossover adjusted, utility PD, sunitinib drug acquisition, HR PFS	HRs from (updated) A6181111[81] (sunitinib)	• Discount rate 3.5% • OS RPSFT adjusted for crossover • Cycle length not stated

continued

TABLE 89 Characteristics of the included studies (*continued*)

Study	Population	Comparators	Horizon	Model structure	Health states/events modelled	Utilities	Costs	Key individual parameters (sensitivity analysis)	Source of effectiveness parameters	Comments
Walczak 2012[123]	Unresectable or metastatic, well-differentiated pNETs with disease progression, Poland	Sunitinib + BSC vs. BSC	Lifetime	Markov – partitioned survival with 4 weekly cycles Proportional hazards model of PFS and OS with baseline Weibull form	SD, PD, death	Treatment-specific SD values from mapping EORTC-QLQ-C30 data from A6181111[81] into EQ-5D scores	Direct medical costs: sunitinib, the administration of the drug, diagnostic and monitoring costs, SSAs, BSC, grade 3/4 severe AEs, palliative care and end-of-life care	Sunitinib treatment duration	HRs for OS and PFS from A6181111[81] (data at 2009 cut-off)	• Discount rate of 5% for costs and 3.5% for QALYs • OS RPSFT adjusted for crossover • Systematic review of the effectiveness, safety and HRQoL literature; date of search March 2012

PD, progressive disease; SD, stable disease.

TABLE 90 Results of the included 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	Notes on ICER
Casciano 2012[120]	Everolimus vs. Sunitinib	As in A6181111[81] (sunitinib) based on MAIC	20 years	Everolimus 1.196; sunitinib 1.043	Everolimus 3.29; sunitinib 2.85	Everolimus 11.896; sunitinib 10.967	0.304	US$12,673	US$41,702	Costs, QALYs and ICERs are discounted at a 3% annual rate and prices are in 2010 US$ Was treatment duration also based on MAIC?
Muciño Ortega 2012[121]	Sunitinib + BSC vs. BSC	As in A6181111[81]	10 years	Sunitinib + BSC 1.02; BSC 0.52	Sunitinib + BSC 2.76; BSC 1.58 (discounted)	NR	0.70	US$20,854	US$29,807	Costs, QALYs and ICER are discounted at 5% annual rate and prices are in 2011 US dollars
Johns 2012[122]	Sunitinib + BSC vs. BSC	As in A6181111[81]	10 years	TTP: sunitinib + BSC 1.10; BSC 0.57 (discounted)	Sunitinib + BSC 3.49; BSC 1.16 (discounted)	NR	1.39	£31,416	£22,587	Costs, QALYs and ICER are discounted at 3.5% annual rate and prices are in 2010 British pounds
Walczak 2012[123]	Sunitinib + BSC vs. BSC	As in A6181111[81]	Lifetime	NR	NR	NR	0.98	€21,770	€20,441	Costs are discounted at 5% and QALYs are discounted at 3.5%. Prices according to the Polish National Health Fund regulations applicable in 2012 (exchange rate to euros from 2011). Median duration of drug use, accounting for discontinuation as a result of an AE, disease progression and death, was used to estimate the cost of sunitinib and SSAs

NR, not reported; TTP, time to progression.

TABLE 91 Review of published economic evaluation studies using the Evers *et al.* checklist[195]

Criteria	Casciano 2012[120] pNETs	Muciño Ortega 2012[121] pNETs	Walczak 2014[123] pNETs	Johns 2012[126] pNETs	Ayaggari 2016[118] GI NETs
1. Is the study population clearly described?	No	Yes	Yes	Yes	Yes
2. Are competing alternatives clearly described?	Yes	Yes	Yes	Yes	No
3. Is a well-defined research question posed in an answerable form?	Yes	Yes	Yes	Yes	Yes
4. Is the economic study design appropriate to the stated objective?	No	Yes	No	No	Yes
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	No	No	No	Yes	Yes
6. Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes	Yes
7. Are all important and relevant costs for each alternative identified?	No	No	Yes	No	No
8. Are all costs measured appropriately in physical units?	Yes	No	No	No	Yes
9. Are costs valued appropriately?	Yes	Yes	Yes	No	Yes
10. Are all important and relevant outcomes for each alternative identified?	No	No	No	No	No
11. Are all outcomes measured appropriately?	No	No	No	No	No
12. Are outcomes valued appropriately?	No	Yes	No	No	No
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	No	Yes	Yes	Yes
14. Are all future costs and outcomes discounted appropriately?	Yes	Yes	No	Yes	Yes
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Yes	Yes	No	Yes
16. Do the conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes
17. Does the study discuss the generalisability of the results to other settings and patient/client groups?	No	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	No
19. Are ethical and distributional issues discussed appropriately?	No	No	No	No	No

summary baseline characteristics in the other trial (A6181111[81] 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.[34] For AEs, cycle-specific event rates were derived from the observed grade 3/4 AE rates for each successive cycle in the everolimus arm of RADIANT-3,[34] 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 the treatment of NETs in the USA, who were asked about the experiences of a total of 40 patients recently treated by them.[120] 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 were taken to reflect the stable disease health state in the model (as the patient population was defined as having advanced, progressive NETs), whereas the second progression period, which was assumed to correspond to the progressive disease heath state of the model, was mostly based on hypothetical treatment scenarios.[120]

Drug acquisition costs for 10 mg/day of everolimus and 37.5 mg/day of sunitinib, which were given in RADIANT-3[34] and A6181111[81] until disease progression or dose reduction or discontinuation because of intolerance, were adjusted for dose intensities of 85.9% and 91.3% respectively. Other costs were related to BSC, which included SSA, physician visits, imaging and laboratory tests, hospitalised treatment for grade 3/4 AEs, post-progression therapy and end-of-life care.

Health state utility values were obtained from a time trade-off preference elicitation study in heathy individuals of health state descriptors (vignettes) constructed by physicians for the purpose of this economic model evaluation. Values for stable disease and progressive disease were elicited as well as disutilities of a selected number of AEs.[131] This was used to calculate a stable disease utility value constituted by an AE-free utility value common to both treatments from which a weighted average of disutilities according to their AE profiles in RADIANT-3[34] and A6181111[81] was subtracted, as well as a progressive disease utility value common to both treatment arms of the model.

Treatment with everolimus and sunitinib resulted in a mean PFS duration of 1.19 and 1.04 years, respectively (0.15-year difference), and 3.30 and 2.85 life-years, respectively (0.45-year difference). Everolimus increased the number of annually discounted (at 3%) QALYs relative to sunitinib by 0.304 and increased the discounted (at 3%) health-care costs by US$12,673 (in 2014 prices, purchasing power-adjusted price £9276) per patient, corresponding to a cost per QALY gained of US$41,702 (£30,524).

The results were most sensitive to the PFS HR, treatment dose intensity, costs of progressive disease and AE costs. PSA revealed a 69% probability that the ICER for everolimus was < 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). Therefore, the study was inconclusive, although the authors argue that these results suggest that everolimus is cost-effective.

Critique

This study provided evidence on the costs and health benefits of choosing one of two targeted therapies available to treat advanced, progressive pNETs. It provides 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.*[41]) 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 cost 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. Another key limitation is the source of utility data, which were derived from time trade-off 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 in their chose of values by the fact that their source of effectiveness data for everolimus, RADIANT-3,[34] did not collect such HRQoL patient-reported outcomes, they could have employed the HRQoL outcomes reported in the A6181111[81] trial of sunitinib, with mapping algorithms used to derive EQ-5D values. Finally, the authors acknowledged the lack of adequate resource utilisation data for progressive disease.

Muciño Ortega *et al.*[121]

A study in Mexico compared sunitinib plus BSC with BSC alone, using the data from A6181111.[81] The study used the same three-state Markov model structure as in the study by Casciano *et al.*[120] but used 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 a 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 the model parameters were obtained from a time-to-event analysis using Weibull parametric models of PFS and OS data in A6181111.[81] The relative treatment effects of sunitinib were estimated relative to these models as proportional hazards. AE rates in the model were obtained from the same trial.

The analysis included the costs of drug acquisition and medical management, including specialist consultations, laboratory and imaging tests, pain management and palliative care. The resource utilisation data 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 A6181111,[81] using the EORTC QLQ-C30. Such data were mapped onto EQ-5D scores using the linear algorithm of McKenzie and van der Pol.[132] 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 0.70 extra (discounted) QALYs. 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 £22,977). The corresponding incremental cost per QALY gained was US$29,808 (£18,475; £19,168 in 2015 prices; adjusted for purchasing power parity £32,842). The parameters that had the most influence on these results, in order of importance, were routine medical management costs before progression, the HR for PFS, the HR for OS, sunitinib acquisition costs, the utility of the post-progression health state and routine medical management costs after disease progression.

Critique

This study's main strengths are 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 cost parameters associated with AEs reported in A6181111[81] and heath state utility values from patients' responses to a disease-specific (EORTC QLQ-C30) tool mapped onto the EQ-5D.

The main limitation of the study is its analysis of OS, in which crossover to sunitinib in patients in the placebo arm was not adjusted for. Crossover occurred in 69% of patients under placebo;[122] as the relevant comparison in this analysis is between a situation in which sunitinib is available and an alternative situation in which it is not, the analysis is likely to underestimate life-year and QALY gains by sunitinib over BSC (provided that 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 (through NICE), October 2016, personal communication].

Another limitation of this study is its reliance on the opinions of a panel of oncologists to obtain resource use data on 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 the results; there is no report of any testing of the proportional hazards assumptions on which the results rely heavily and no sensitivity analysis was performed using different parametric functions to extrapolate OS and PFS.

It is an open question, therefore, whether or not the estimated extension of life free of disease and overall life extension found by this study of 0.49 and 1.18 years, 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 generalisable to the UK setting because of marked differences in the cost of medical staff inputs relative to drug acquisition costs between Mexico and the UK. Nevertheless, the study provides valuable evidence on health state utility values in pancreatic patients.

Johns *et al.*[122]

The only published cost-effectiveness analysis in the UK is a conference poster by Johns *et al.*[122] presenting the evidence submitted by Pfizer to the SMC in January 2011 and to the AWMSG in March 2011, which resulted in a positive recommendation for the drug as treatment for advanced pNETs in Scotland and Wales. This analysis used the most recent data at the time from the Phase III A6181111[81] trial of sunitinib compared with placebo to model incremental costs and QALY gains using the same methods of Muciño Ortega,[121] but with the addition of an adjustment to OS outcomes in the placebo arm for the effect of crossover to sunitinib in the blinded and extension phases of the study.

It was reported that adjustment of OS data for crossover using the RPSFT model resulted in a HR at the latest cut-off date of 0.499 (95% CI 0.351 to 0.947), citing a conference abstract source.[94] However, it was reported that the cost-effectiveness analysis was based on an estimate of the RPSFT model HR of 0.24 (95% CI 0.08 to 1.07) based on an 'intermediate data cut' dated December 2009 and citing 'Pfizer data on file'.[122] This analysis used a proportional hazards model for both PFS and OS time-to-event analyses, in which PFS was analysed using a Weibull parametric regression form with a binary covariate indicating the randomly allocated treatment group and in which OS in the sunitinib arm was modelled using a Weibull form and the placebo OS outcomes were obtained from applying the HR from the RPSFT to the Weibull placebo distribution. However, the Weibull parameter values used to extrapolate PFS and OS rates in the model were not reported.

It was reported that the probabilities of AEs and treatment discontinuation were obtained from A6181111.[81] Resource utilisation data for BSC and AE management, with only grade 3/4 events considered, were obtained from UK clinical expert opinion, without citing any sources. Utilities were obtained from mapping the EORTC QLQ-C30 patient data from A6181111[81] onto the EQ-5D using the algorithm of McKenzie and van der Pol.[132] 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 value of 0.60 used for the progressive disease phase in both arms was the mean utility value measured during the last study cycle for patients who experienced disease progression. The quoted statement is unclear about the role that the baseline utility value played in the analysis, especially as it is utility values post baseline and before progression that are relevant for estimating utility in the stable disease phase.

The study reported that treatment with sunitinib resulted in an increase in discounted PFS years, discounted life-years and discounted QALYs by 0.53, 2.33 and 1.39, respectively, whereas it resulted in incremental costs of £31,416 (in 2010 prices), almost two-thirds of which was the cost of acquisition of sunitinib. The resulting ICER was £22,587 (£24,244 at 2015 prices). Besides the use of ITT values for the OS HR as opposed to crossover-adjusted values, which was most influential, the parameters to which the results were most sensitive included the post-progression utility, sunitinib acquisition cost and the PFS HR. The authors stated 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 an assessment of its quality. Indeed, it is not possible to replicate the results with the information presented in the poster, because, for example, the Weibull

parameter values used to extrapolate the PFS and OS curves in the model were not reported. It is noteworthy that this study adjusted placebo OS outcomes for crossover to sunitinib, although the reported choice of data cut-off date appears to be different from the latest cut-off date. This study suggests that adjustment for crossover from placebo to the targeted treatment in RCTs in this area may determine whether or not a treatment is cost-effective.

On the other hand, the study suffers from the 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 the authors followed the methods detailed in the study by Muciño Ortega *et al.*[121] In common with other studies, this analysis suffers from a lack of actual resource use data, as it was based entirely on expert opinions. According to these results, the cost per QALY gained for sunitinib may be between £20,000 and £30,000.

Walczak *et al.*[123]

The same study question was investigated from a Polish health payer's perspective in a separate study by Pfizer.[123] Walczak *et al.*[123] provided a detailed account of the use of systematic methods to search for effectiveness evidence on sunitinib compared with BSC, following principles in the Cochrane Collaboration and the Polish Agency for Health Technology Assessment. The search was conducted in March 2012. Only one study, A6181111,[81] met the inclusion criteria, which specified the reporting of effectiveness, safety and HRQoL outcomes in a head-to-head parallel-group RCT of the two treatment options for advanced, progressive pNETs.

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 AWMSG in 2011 by Pfizer and reported by Johns *et al.*[122] In addition, as in the study by Johns *et al.*,[122] the Polish analysis adopted the estimates of OS effectiveness based on an interim data cut-off date of 15 April 2009,[81,84] with a HR of 0.18 (95% CI 0.06 to 0.68), as opposed to the latest estimates available at the time, with a cut-off date of June 2010,[94] which resulted in a HR of 0.49 (95% CI 0.35 to 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 crossover (counterfactual placebo OS rates). The authors reported that a Weibull function with a binary treatment indicator was fitted to the PFS data from A6181111[81] to extrapolate PFS rates in the two trial arms, and ultimately partition OS time into stable disease and progressive disease, which equals the difference between extrapolated OS and extrapolated PFS rates (i.e. mean time in progressive disease for sunitinib: 2.98 – 1.89 = 1.09 years, and for BSC: 0.54 – 0.49 = 0.05 years; see *Table 9*.). However, the authors reported the parameter values in *Table 92*, which suggests that Weibull functions were fitted to each arm separately.

The costs of drug acquisition, drug administration, diagnosis and monitoring (including a CT scan every 2 months for the first 6 months and every 3 months thereafter until disease progression), SSA use, BSC, grade 3/4 AE management and palliative care were measured. Sunitinib and SSA treatment costs were measured using the median treatment duration, with treatment stopped because of AEs, disease progression or death. Alternatively, treatment duration until disease progression was used in a scenario analysis. A compliance rate of 91.3%, obtained from the main trial report,[81] was used, with compliance defined as the number of doses administered relative to the number of planned doses at 37.5 mg daily. End-of-life care was also measured using the costs of hospice-at-home care for the last week of life.

The study found that treatment with sunitinib plus BSC produced an extra 0.98 QALYs and had an ICER of €20,441 (£33,866 at purchasing power parity in 2005 prices) per QALY gained relative to BSC only. The parameter to which the results were most sensitive was the duration of sunitinib use.

Critique

Walczak *et al.*[123] documented a systematic search of the RCT literature comparing sunitinib with BSC, which identified only one study, the Phase III A6181111[81] trial. The authors reported a detailed assessment of the quality of this study and an account of the main findings.

TABLE 92 Parameter values for Weibull[a] extrapolating models of PFS and OS in base-case pNETs

		Walczak *et al.*[123]		Casciano *et al.*[120]	
Outcome	Parameter/summary statistic	Sunitinib	BCS	Sunitinib	Everolimus
PFS	Shape	0.79	1.16	1.195	1.195
	Scale	19.89[b]	6.31[b]	7.27[c]	6.103[c]
	Predicted mean (years)	1.89	0.49	0.97[d]	1.15[d]
OS	Shape	1.63	1.63	1.379	1.379
	Scale	40.04[b]	7.20[b]	5.88[c]	7.263[c]
	Predicted mean (years)	2.98	0.54[e]	2.89[f]	3.57[f]

a Scale × time (months or days) ^ shape.
b Scale in months, as reported by Walczak *et al.*[123]
c Scale in days, as reported by Casciano *et al.*[120]
d These figures contrast with those of Casciano *et al.*,[120] who reported mean PFS of 1.19 years (14.35 months) and 1.04 years (12.51 months) for everolimus and sunitinib respectively.
e The study reported using a HR of 0.18. Using the latest HR estimate referred to by the authors, 0.499,[94] results in a mean life expectancy of 1.49.
f Figures are based on the integral of the survival Weibull formula; i.e. the gamma function, which overestimates mean survival as it extends over an infinite time horizon; to see the extent of the inaccuracy, compare the results for mean years of OS for sunitinib in this table, 2.89 years, and those reported by Casciano *et al.*,[120] 2.85 years, which are summarised in *Table 92*, i.e. an overestimation of 1.4%. The percentage overestimation of the values for Walczak *et al.*[123] is similarly small although larger than that for Casciano *et al.*,[120] as Walczak *et al.*'s[123] time horizon is shorter than that of Casciano *et al.*,[120] i.e. 10 years vs. 20 years.

A strength of this study is its application of a method to adjust OS outcomes for crossover of patients in the placebo arm to the targeted therapy arm in A6181111.[81] However, the authors reported the 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. RADIANT-3[34] may have been identified by the systematic search had it been designed to include such targeted therapy.

As with 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 the proportional hazards assumption so that the available estimate of effectiveness, which was in HR form, could be adopted in the analysis. For PFS however, no such justification existed, as there was no crossover adjustment to deal with, and the authors should have provided at least a sensitivity analysis of the parametric extrapolation functions used for each arm.

There was also inadequate reporting of model inputs for the duration of sunitinib treatment and of model outputs in terms of life-years and mean PFS time.

Overall, this is the only complete report of an economic evaluation in Europe. However, given the different country setting and relative prices, 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.

Gastrointestinal studies

The only study identified in the GI location evaluated lanreotide relative to octreotide,[118] both of which are outside the NICE scope for the current assessment. For the present purposes, it is relevant that this study adopted the same three-state semi-Markov structure as the analyses in pNETs reviewed in the previous sections, using a 3-year and lifetime time horizons. This study was presented in a conference poster format and, given the limited information thus provided, was not subject to any formal critique.

Appendix 11 Subgroup and scenario analyses

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.

Scenario analyses

A range of scenario analyses were conducted, including:

- For pNETs and GI and lung NETs, 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 pNETs, using OS data from ITT analysis instead of the RPSFT-adjusted OS data used in the base case.
- Using an alternative set of utility values presented in *Chapter 6*, *Tables 21* and *22*.
- Using an 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, whereas 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 function, whereas OS under the two strategies was changed to the log-logistic function. All other model specifications remained as in the base case.
- Limiting 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 crossover and active subsequent treatment use.
- A scenario analysis including first-cycle drug acquisition costs, which were omitted in the base case.
- A scenario analysis for GI (midgut) and GI and lung NETs with different costs of disease monitoring corresponding to the numbers of physician visits adopted in 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 and 2.6 times the base-case value in stable disease and 1.5 times the base-case value in progressive disease.
- Applying a 0% discount to costs and benefits.

Local assessment

When we changed the PFS data for everolimus from central review data to 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 93*).

TABLE 93 Peninsula Technology Assessment Group scenario analysis results using 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

Intention-to-treat analysis for pancreatic neuroendocrine tumours

Using the ITT data from the A6181111[81] and RADIANT-3[34] trials of pNETs produced ICERs that were three times as high for everolimus (reaching an ICER of £136,000) and twice as high for sunitinib (£37,000) as their respective base-case values (*Table 94*). These changes reflect the influence of adjusting for the effects on OS of crossover to the targeted treatment in the placebo arms of both trials, which occurred in 69% of placebo arm participants in the sunitinib trial and 85% of participants in the everolimus trial.

Alternative set of utility values

Increasing the utility values for stable disease in pNETs by 0.09 and keeping the values in progressive disease practically unchanged, to correspond to the values in Swinburn *et al.*,[200] reduced the ICER for everolimus by 10% to £41,246, as expected given the larger quantity of life lived in stable disease under the everolimus strategy than under the BSC-only strategy. Similarly, the ICER for sunitinib was reduced by 6% to £19,411 (*Table 95*).

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%.

Alternative set of overall survival and progression-free survival curves

When the parametric survival models for everolimus and BSC alone were changed from proportional hazards to AFT forms, the ICER for sunitinib in pNETs remained more or less the same, whereas that for everolimus in pNETs decreased by 33% to £28,098 (*Table 96*). In contrast, everolimus in GI and lung NETs became less effective than BSC alone in terms of discounted QALYs, despite its larger life expectancy, that is, 7.11 compared with 6.84 years; this result is explained by the different periods of time over which quality of life benefits take place, so that, when the discount rate is switched to 0%, everolimus becomes the strategy with the highest number of QALYs (data not shown). Thus, the relative advantage of everolimus in terms of health outcomes tends to occur after an earlier disadvantage. At the 3.5% annual discount rate, such an advantage occurs too late in time and everolimus becomes inferior to BSC in GI and lung NETs.

TABLE 94 Peninsula Technology Assessment Group scenario analysis results based on OS ITT data in pNETs

Treatment	Treatment or comparator	ICER (£)
Everolimus	BSC	136,455
Sunitinib	BSC	37,217

TABLE 95 Peninsula Technology Assessment Group scenario analysis results using 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

TABLE 96 Peninsula Technology Assessment Group scenario analysis results for alternative OS and PFS curves

Tumour location	Treatment	PFS	OS	Comparator	PFS	OS	ICER (£)
Pancreas	Everolimus	Log-logistic	Log-normal	BSC	Log-normal	Exponential	28,098
	Sunitinib	Exponential	Exponential	BSC	Log-normal	Exponential	20,726
GI and lung	Everolimus	Lognormal	Loglogistic	BSC	Log-normal	Loglogistic	BSC dominant

Analysis limited to progression-free survival

Because of the inherent uncertainty in the OS data caused by treatment crossover from placebo to targeted treatments and its immaturity in the 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, the ICER for sunitinib in pNETs increased by 75% to £35,448, whereas the ICER for everolimus in pNETs increased by 26% to £57,493 (*Table 97*). In GI and lung NETs, the ICER for everolimus increased from its base-case value of £44,557 to £73,086. Everolimus has an ICER in patients with midgut NETs that is 21% larger than that in GI and lung NETs, suggesting less value for money in this patient subgroup and higher cost-effectiveness in the non-midgut GI and lung NETs population. Furthermore, the ICER for 177Lu-DOTATATE is less than half that for everolimus at £30,115, which suggests that peptide receptor radionuclide therapy treatment may have better longer-term outcomes than everolimus.

Background mortality adjustments to the overall survival and progression-free survival curves

Adjusting for background mortality has a limited effect on the results in pNETs and GI and lung NETs. In GI (midgut) NETs, the ICER for everolimus declines from about £200,000 in the base case to £78,330 with background mortality adjustment (*Table 98*). This reflects the high degree of uncertainty in the extrapolation of survival outcomes in the GI (midgut) location, for which we did have access to OS but had

TABLE 97 Peninsula Technology Assessment Group scenario analysis results limiting the 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

TABLE 98 Peninsula Technology Assessment Group scenario analysis results adjusting for 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

to impute it from the available PFS data for this subgroup. In addition, in GI (midgut) NETs, the base-case analysis that includes 177-Lu-DOTATATE adopts a background mortality adjustment because of the immaturity of the OS data in NETTER-1, from which the effectiveness data for 177Lu-DOTATATE is derived. Thus, in *Table 98* we present the ICER for this treatment without adjusting for background mortality, which reduces its ICER from £62,158 to £43,348.

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) NETs has a minor effect on the results, as evidenced by results in *Tables 99* and *100*.

Scenario analysis with a 0% discount rate

As evidenced previously by the results of the scenario analysis in which the parametric survival curves were altered to more optimistic forms, the discount rate has an influential effect on the results as treatments tend to yield significant benefits in the long term. This may be seen for both pNETs and GI and lung NETs in *Table 101*.

TABLE 99 Peninsula Technology Assessment Group scenario analysis results accounting for first-cycle costs of subsequent treatments

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

TABLE 100 Peninsula Technology Assessment Group scenario analysis results accounting for first-cycle costs of 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

TABLE 101 Peninsula Technology Assessment Group 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

Appendix 12 Visual fit to (instantaneous) survival event risk

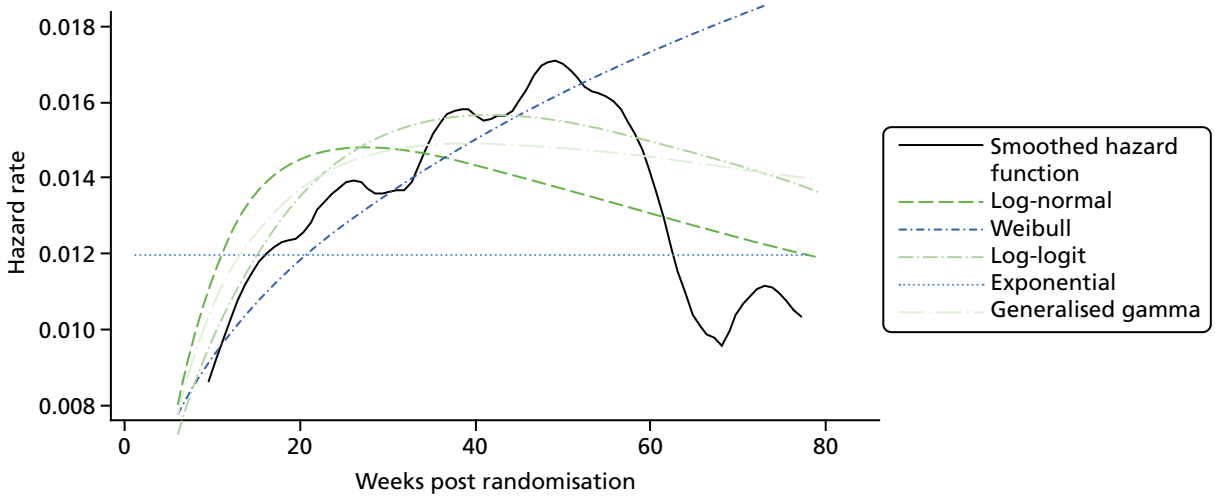

FIGURE 38 Everolimus arm in RADIANT-3:[34] observed and predicted PFS hazard functions by the best-fitting models.

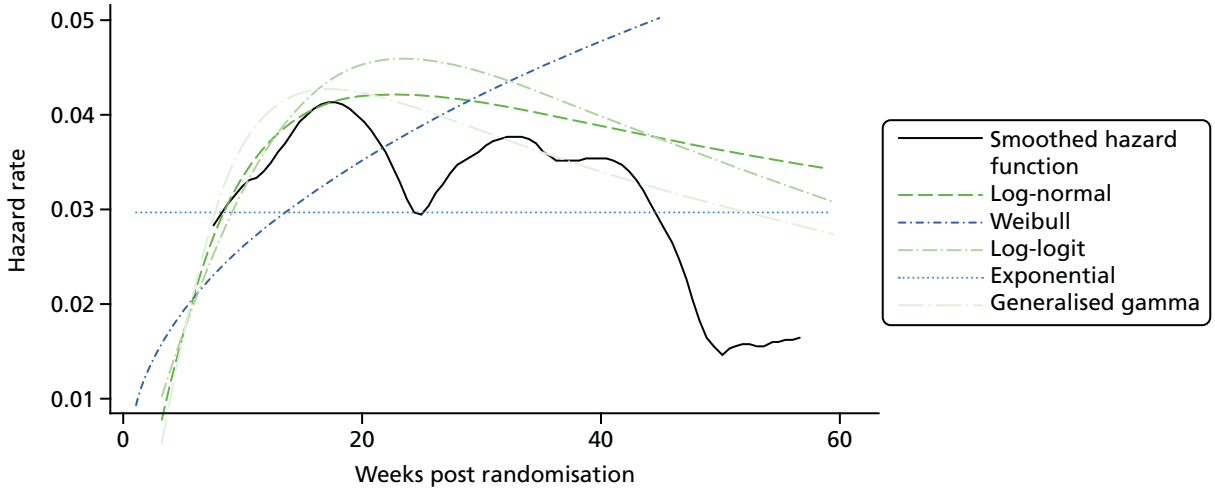

FIGURE 39 Placebo arm: observed and predicted PFS hazard functions by the best-fitting models.

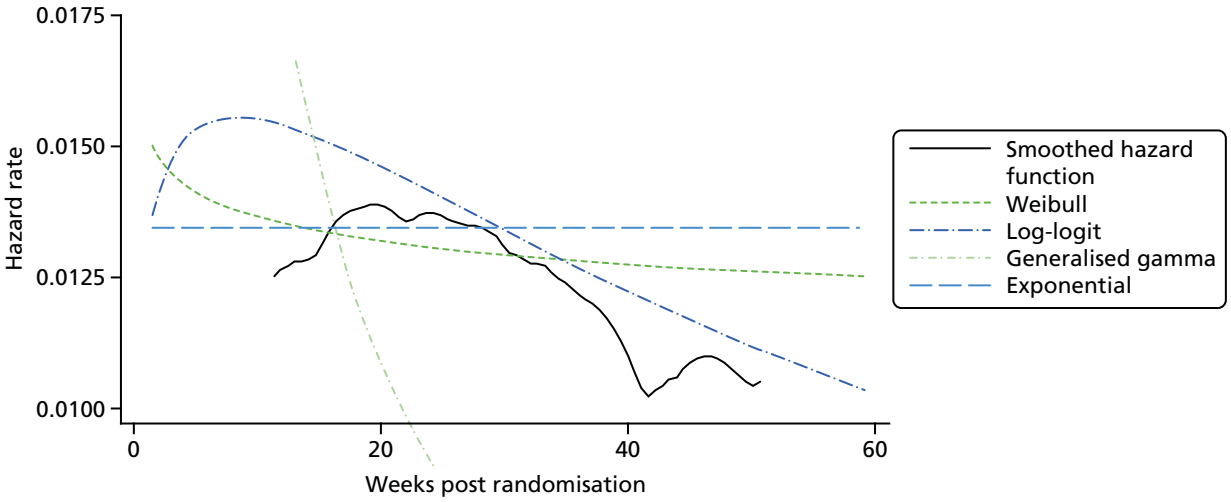

FIGURE 40 Sunitinib arm: observed and predicted PFS hazard functions by the best-fitting models.

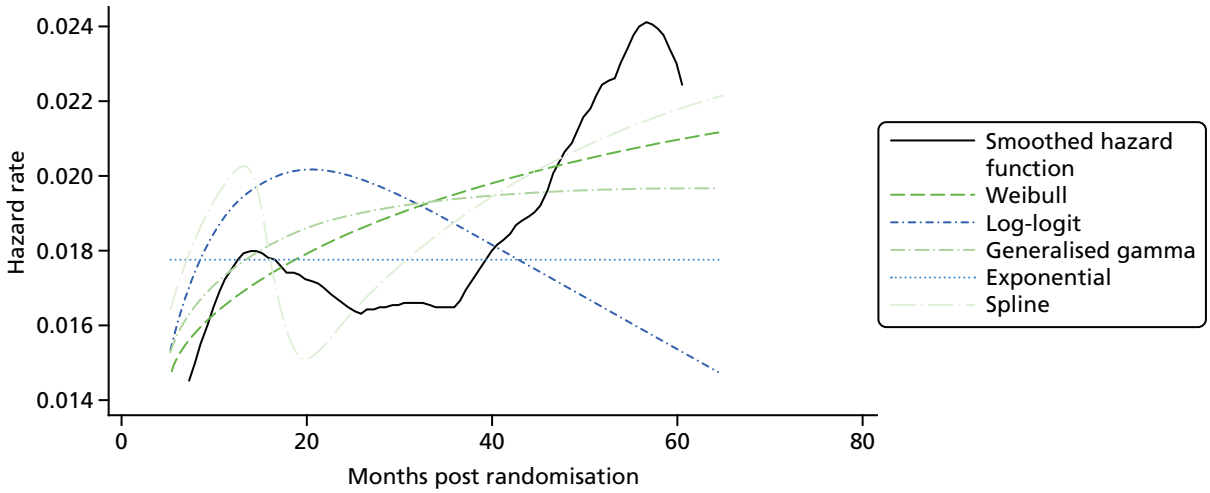

FIGURE 41 Everolimus arm: observed and predicted PFS hazard functions by the best-fitting models.

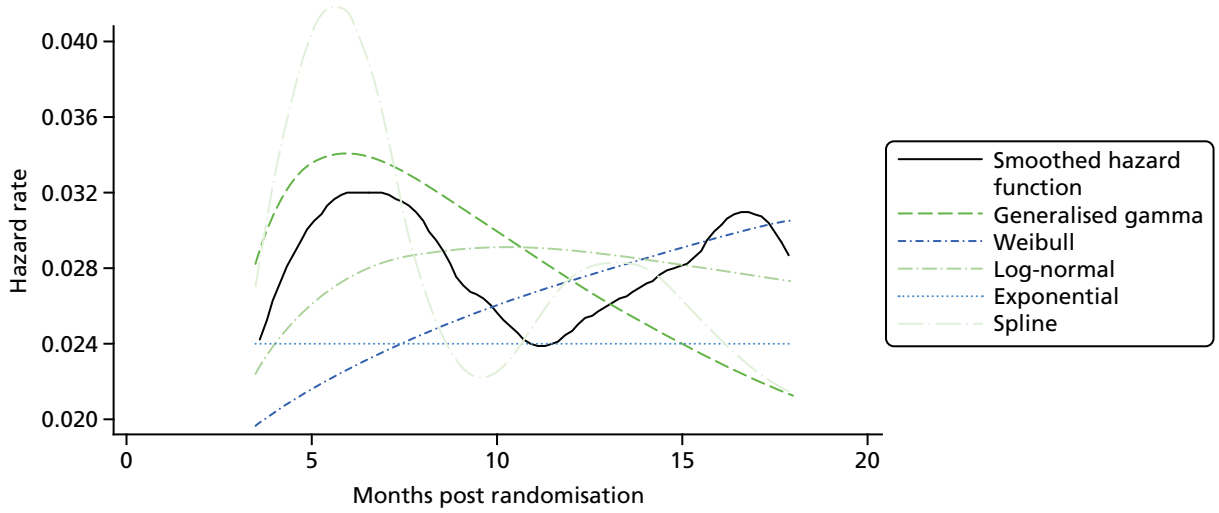

FIGURE 42 Placebo arm in RADIANT-3:[34] observed and predicted OS hazard functions by the best-fitting models.

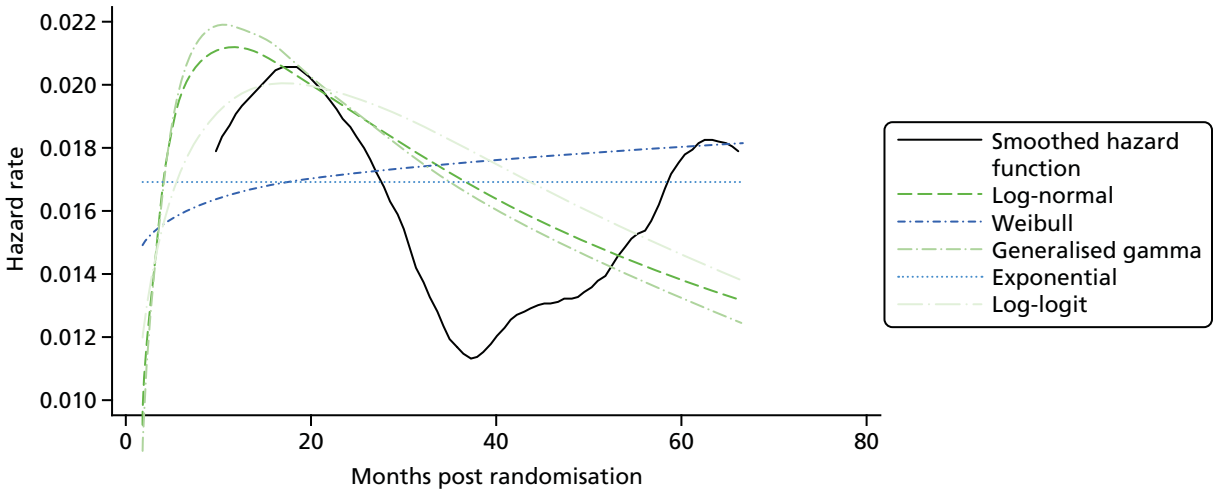

FIGURE 43 Sunitinib arm in A6181111:[81] observed and predicted OS hazard functions by the best-fitting models.

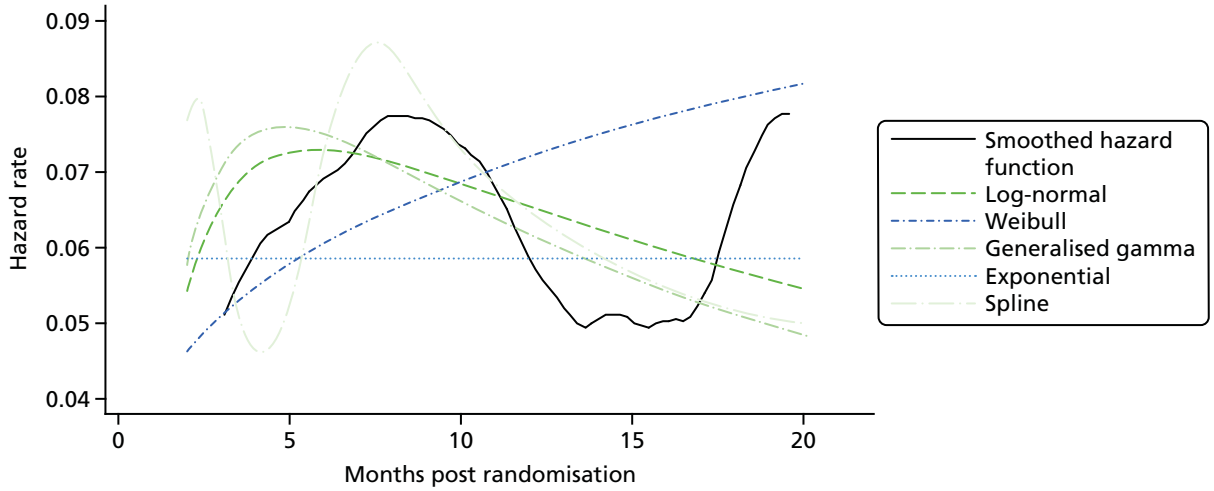

FIGURE 44 Everolimus arm in RADIANT-4:[35] observed and predicted PFS hazard functions by the best-fitting models.

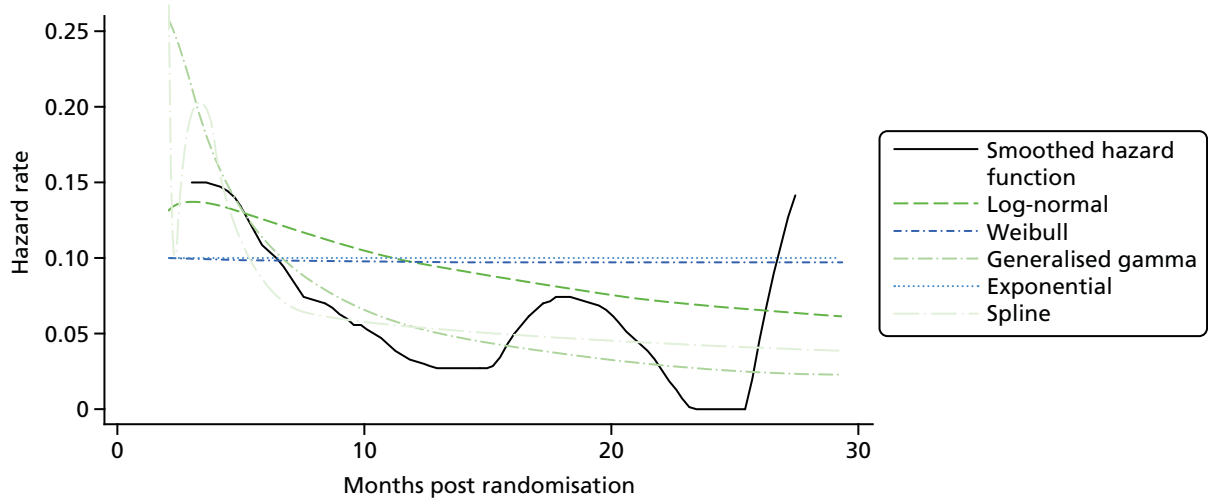

FIGURE 45 Placebo arm in RADIANT-4:[35] observed and predicted PFS hazard functions by the best-fitting models.

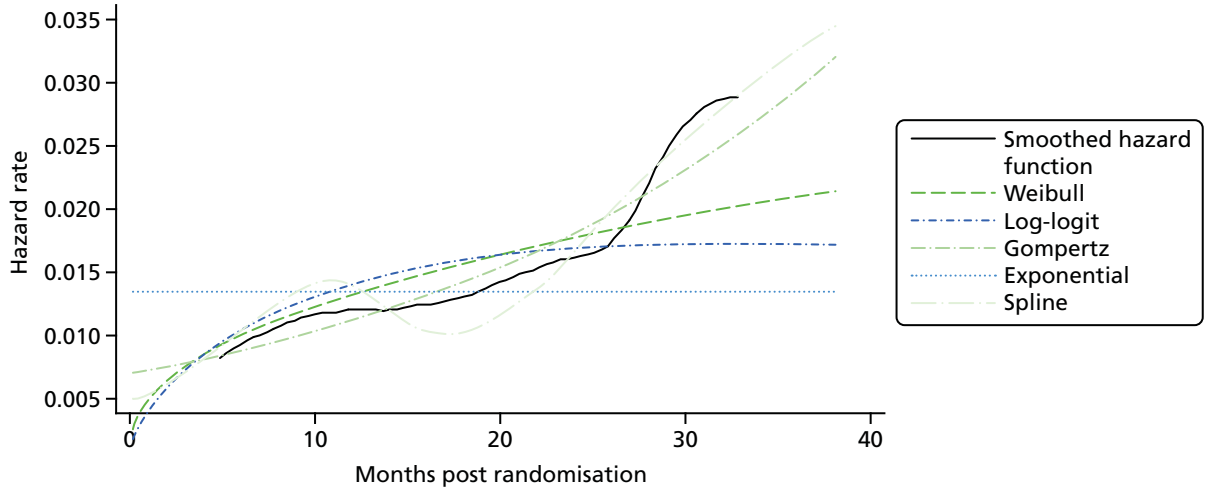

FIGURE 46 Everolimus arm in RADIANT-4:[35] observed and predicted OS hazard functions by the best-fitting models.

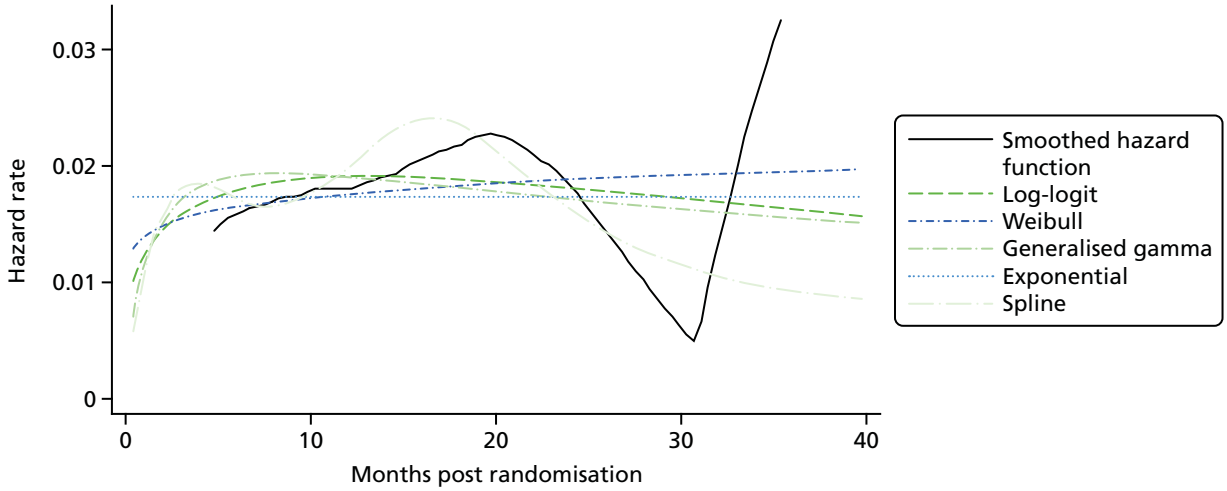

FIGURE 47 Placebo arm in RADIANT-4:[35] observed and predicted OS hazard functions by the best-fitting models.

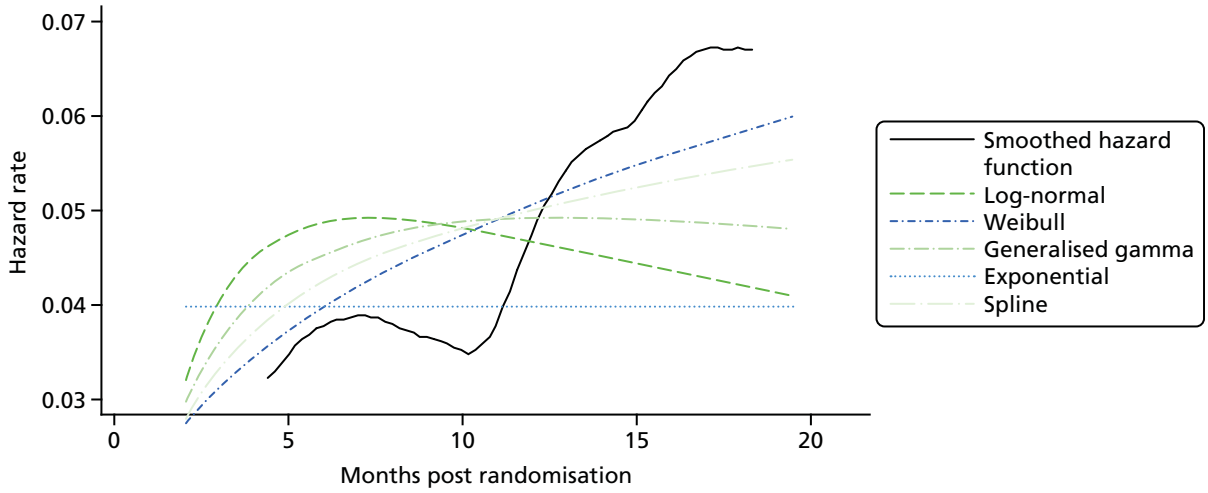

FIGURE 48 Everolimus arm in RADIANT-4[73] (midgut): observed and predicted PFS hazard functions by the best-fitting models.

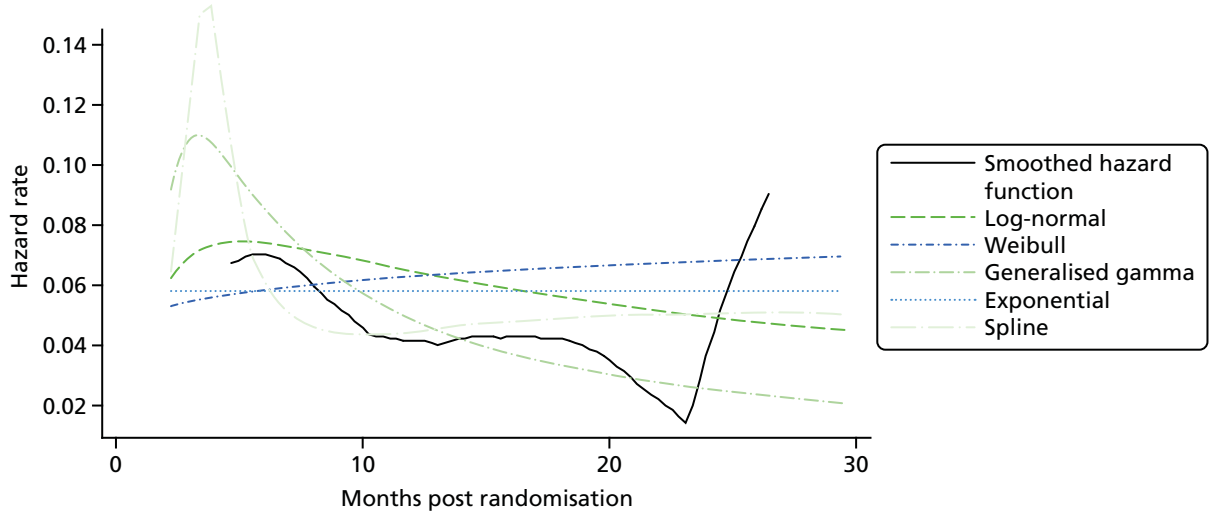

FIGURE 49 Placebo arm in RADIANT-4[73] (midgut): observed and predicted PFS hazard functions by the best-fitting models.

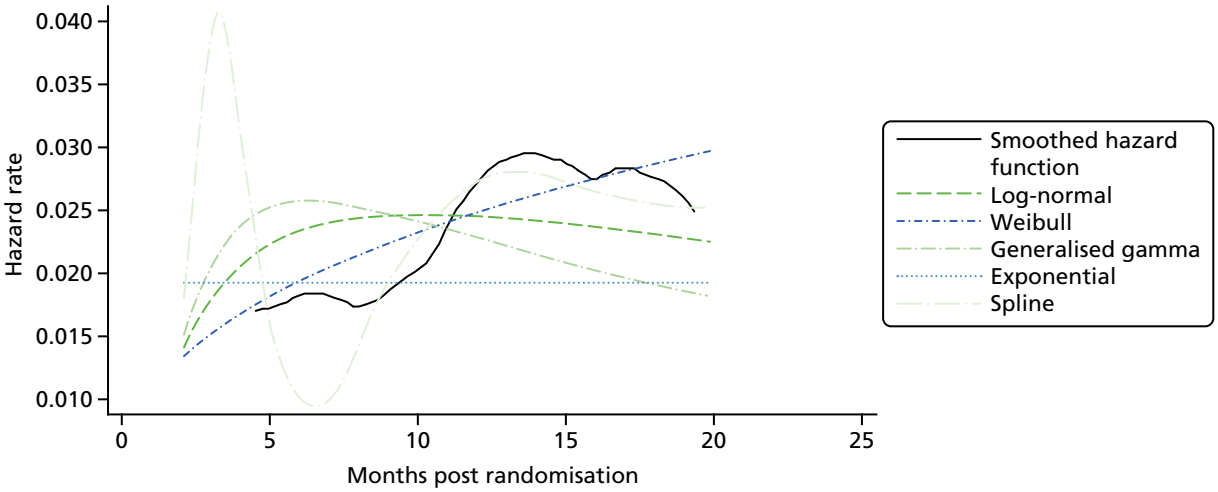

FIGURE 50 177Lu-DOTATE arm in NETTER-1: observed and predicted PFS hazard functions by the best-fitting models.

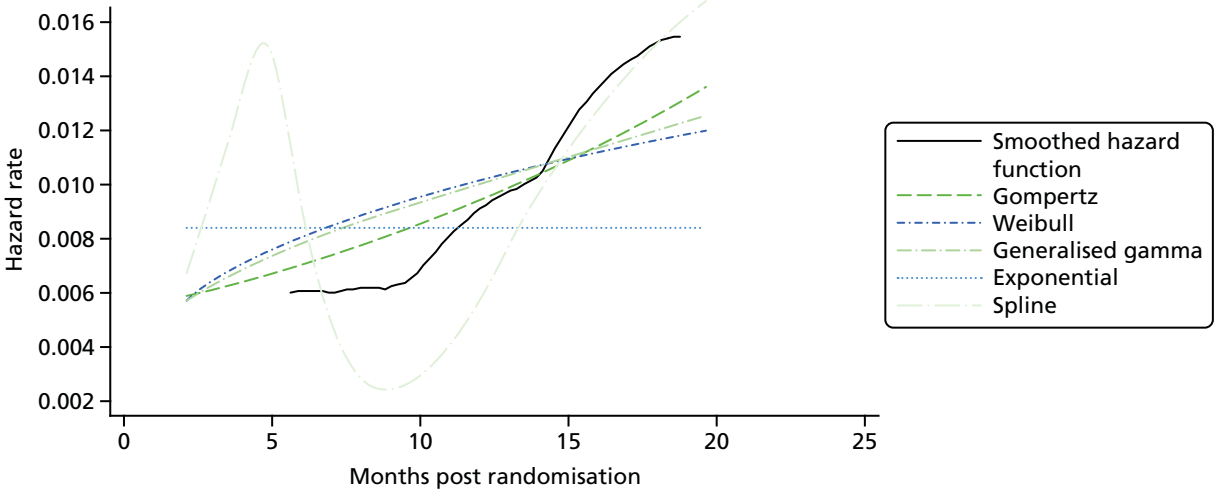

FIGURE 51 177Lu-DOTATE arm in NETTER-1: observed and predicted OS hazard functions by the best-fitting models.

Appendix 13 Progression-free survival and overall survival: extrapolation of 177Lu-DOTATATE outcomes in the NETTER-1 trial

177Lu-DOTATATE in the NETTER-1 trial (Advanced Accelerator Applications submission to the National Institute for Health and Care Excellence)

Progression-free survival

Although the models did not differ in their goodness of fit to the PFS outcomes of 177Lu-DOTATE in NETTER-1 (*Figure 52*), the Weibull model exhibited the closest fit to its associated risk of death or disease progression (see *Figure 50*). The exponential fell in the middle of the range of PFS rates of the candidate distributions.

The parameter of the PFS distribution was adjusted for the difference in expected PFS between the 60 mg of octreotide arm of NETTER-1 and the placebo arm of RADIANT-4[35] (midgut population), following the method described earlier for the analysis of pNETs (see *Chapter 6*, *Model parameters*). 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 *Chapter 6*. Restricting the mean area under the Kaplan–Meier curve of the placebo arm in RADIANT-4[35] to the maximum length of follow-up of OS in the 60 mg of octreotide arm in NETTER-1 (which had a shorter follow-up than RADIANT-4[35]), that is, 25.18 months, led to a restricted mean PFS of 9.97 months in the placebo arm of RADIANT-4[35] and 13.23 months in the 60 mg of octreotide arm in NETTER-1. In terms of *Equation 1*, the adjusted hazard and exponential survival functions with 177Lu-DOTATATE are:

$$\hat{\lambda} = \left(\frac{1}{0.019341} * \frac{13.23}{9.97} \right)^{-1} = 0.014576 \tag{4}$$

and

$$S(\hat{\lambda}) = exp^{-0.014576t}. \tag{5}$$

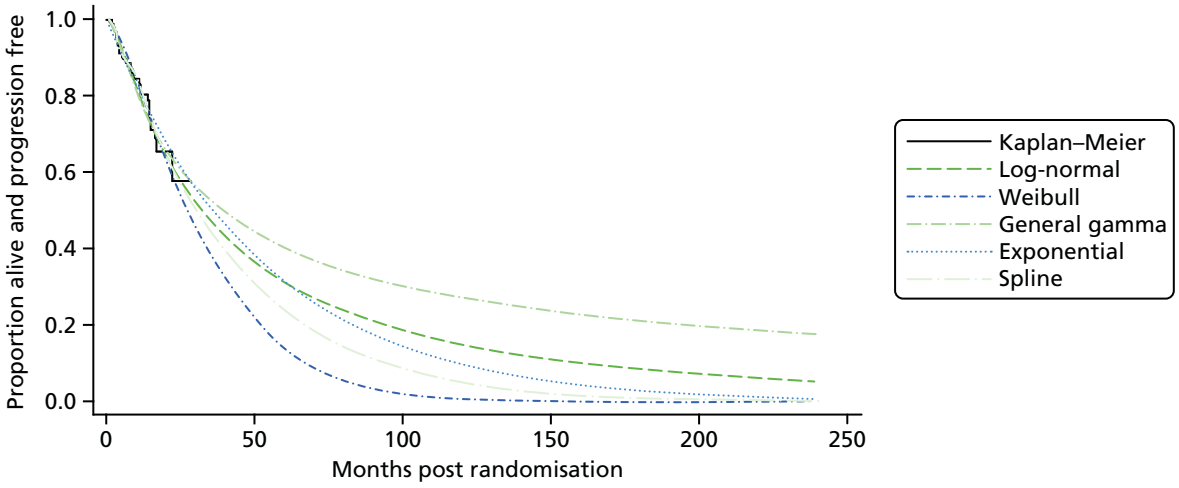

FIGURE 52 Progression-free survival in the 177Lu-DOTATE arm of NETTER-1: extrapolation to 20 years.

The OS curve of the 177Lu-DOTATE arm of NETTER-1 adopted for the base case on the basis of the diagnostic results was the exponential (see *Table 23*). The parametric OS curve of 177Lu-DOTATE was adjusted for the 9.1%-shorter expected OS in the 60 mg of octreotide arm of NETTER-1 than in the placebo arm of RADIANT-4[35] (midgut population), using the methods described above for pNETs (see *Chapter 6*, *Model parameters*).

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[35] (midgut only), this rate becomes 25%. In contrast, the respective unadjusted rate for the Weibull function (*Figure 53*) 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.

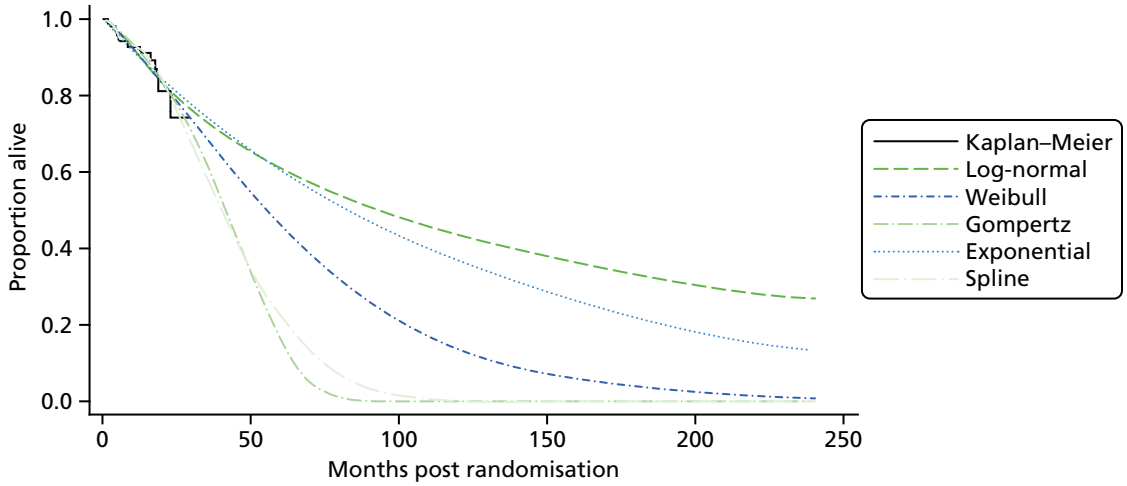

FIGURE 53 Overall survival in the 177Lu-DOTATE arm of NETTER-1: extrapolation to 20 years.

Appendix 14 Company reviews of clinical effectiveness

All three of the manufacturers – AAA, Novartis and Pfizer – submitted clinical evidence for consideration for this MTA.

Advanced Accelerator Applications

Advanced Accelerator Applications 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' (AAA submission to NICE,[31] p.18). The literature searching carried out for this submission was sufficient, as were the inclusion/exclusion criteria used for screening. It is unclear whether or not title and abstract screening was completed in duplicate. Full-text screening was completed by two reviewers. As part of the inclusion criteria [table 16 of the AAA submission (p. 58)], AAA included SSAs (octreotide and lanreotide). SSAs were removed from the NICE scope on 18 August 2016. In its submission, AAA stated that conference abstracts were excluded (company submission, table 16, p. 58). It is unclear, therefore, why AAA included the NETTER-1 trial as, at the time, not only was it published only in abstract form (and so it would not be identified by AAA's systematic review) but also its comparator was outside 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 *Chapter 4*, *Studies identified*). The AG conducted a non-systematic review for non-RCT evidence for 177Lu-DOTATATE and identified 32 studies (see *Appendix 2*, *Results for non-randomised controlled trial evidence*). AAA identified four non-RCTs of 177Lu-DOTATE.[145,162–165,170] All four non-RCTs were included. It is unclear why AAA did not include the additional 28 studies that the AG had identified.

Network meta-analysis

Advanced Accelerator Applications did not undertake a meta-analysis as it found only one trial of 177Lu-DOTATATE. Instead, it performed an ITC for GI NETs, comparing everolimus with 177Lu-DOTATATE, and a MTC for pNETs, comparing everolimus, sunitinib and 177Lu-DOTATATE, for the outcomes of PFS and OS.

Five trials identified in the systematic review were excluded from the analyses by AAA for the following reasons: 96% of participants at baseline had stable disease (CLARINET),[176] no data were provided on the number of participants with stable/progressive disease (PROMID)[201] or the trials could not be connected to either the GI NETs or the pNETs network.[202–204]

The three trials used in the ITC for GI NETs were RADIANT-2,[190] RADIANT-4[35] and NETTER-1[31] (*Figure 54*). The three trials used in the MTC for pNETs were RADIANT-3,[34] A6181111[81] and NETTER-1[31] (*Figure 55*).

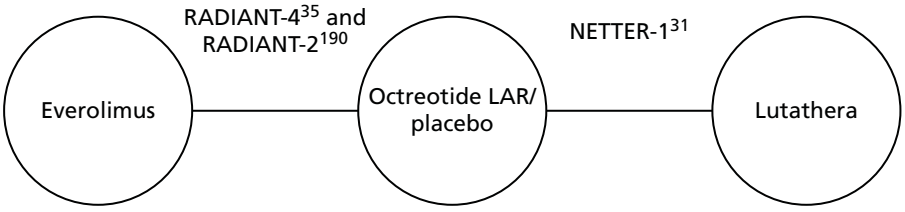

FIGURE 54 Gastrointestinal NETs network for the MTC conducted by AAA for PFS and OS. Source: figure 13 (pp. 71–72) of the AAA submission.[31]

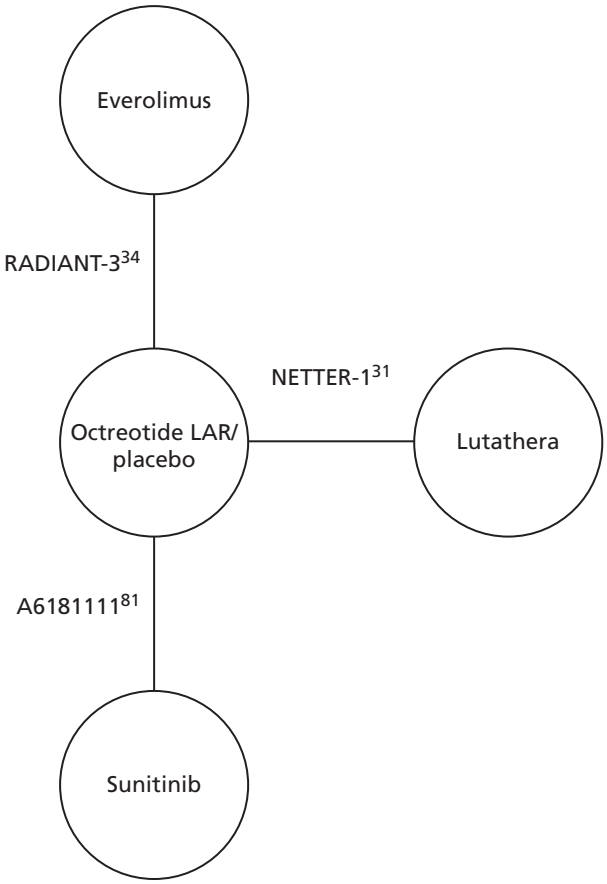

FIGURE 55 Pancreatic NETs network for the MTC conducted by AAA for PFS and OS. Source: figure 12 (pp. 71–72) of the AAA submission.[31]

Study and participant characteristics were compared across studies by AAA for GI NETs and pNETs. For somatostatin receptor status, AAA stated that in NETTER-1 all participants were SSTR+, but reported that it was unable to obtain this information for RADIANT-2, RADIANT-3,[34] RADIANT-4[35] and A6181111.[81] It was therefore assumed by AAA that the relative effectiveness between treatments does not alter according to somatostatin receptor status. As we do not know the somatostatin receptor status of participants in the other trials, we cannot be sure whether or not this assumption is correct.

For GI NETs, AAA highlighted that the tumour functioning status differs between participants in the RADIANT-2, RADIANT-4[35] and NETTER-1 trials. It stated that tumour function is not reported in RADIANT-2, that all participants in RADIANT-4 had non-functioning tumours and that, 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 of everolimus and 177Lu-DOTATATE for participants with functioning and non-functioning tumours, AAA assumed that there is no difference. AAA stated that the participant populations from RADIANT-2, RADIANT-4[35] and NETTER-1 are aligned with each other and with the NICE scope in terms of disease progression. AAA noted that, although all patients in RADIANT-4 and NETTER-1 had received prior therapy, it was unclear whether or not this was the case in RADIANT-2. From expert clinical opinion, the AG notes that the prognosis for a patient differs depending on his or her tumour functioning status. As we do not know the different proportions or participants with functioning and non-functioning tumours in the different trials, we cannot be sure whether or not AAA's assumption is correct regarding the relative effectiveness of everolimus and 177Lu-DOTATATE for participants with functioning and non-functioning tumours.

Advanced Accelerator Applications detailed the data used in the networks from each trial by NET location. For GI NETs, the company considered the populations to be in close alignment for PFS but commented that there are differences in the populations for OS (*Table 102*).

For pNETs, AAA reported that, although NETTER-1 and A6181111[81] included participants with functioning and non-functioning tumours, RADIANT-3[34] did not report the tumour functioning status of their participants. As for GI NETs, AAA therefore assumed that the relative effectiveness of everolimus compared with 177Lu-DOTATATE does not differ by tumour functioning status. AAA stated that the participant populations in NETTER-1, RADIANT-3[34] and A6181111[81] had progressive disease, which was assumed to be aligned with the NICE scope. AAA noted that, although all patients in NETTER-1 had received prior therapy, it was unclear whether this was the case in RADIANT-3[34] and A6181111.[81]

Advanced Accelerator Applications considered tumour location for RADIANT-3[34] and A6181111[81] to be aligned for PFS and OS, but that the population from NETTER-1 (GI NETs) was not aligned. Nevertheless, AAA included the GI NETs population from NETTER-1 in its MTC for pNETs (*Table 103*).

For both tumour locations, AAA noted that there was 'considerable variation' in the baseline characteristics across trials, yet considered the trials to be similar enough to synthesise the data.

Advanced Accelerator Applications made three major assumptions in performing their MTC: (1) that 60 mg of octreotide can be assumed to be equivalent to placebo and placebo plus 30 mg of octreotide (to connect the NETTER-1 trial to the other trials in the GI NETs network), (2) that 60 mg of octreotide is equivalent to placebo and placebo plus BSC (to connect the NETTER-1 trial to the other trials in 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 in the NETTER-1 trial had pNETs. The third assumption is clearly untenable based on the difference in typical expected survival outcomes in pNETs and GI (midgut) NETs.

Advanced Accelerator Applications undertook a Bayesian analysis with MCMC simulation in R for both analyses using methods set out in Dias *et al.*[205] 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 criterion (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 and random-effects binomial/cloglog model. For each analysis, AAA report simulating four 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

TABLE 102 Gastrointestinal NETs location data used by AAA from RADIANT-2, RADIANT-4[35] and NETTER-1

Trial	PFS	OS
NETTER-1	Midgut	Midgut
RADIANT-2[119]	colorectal cancer	All NETs
RADIANT-4[35]	GI	Lung + GI

TABLE 103 Pancreatic NETs location data used by AAA from RADIANT-3,[34] A6181111[81] and NETTER-1

Trial	PFS	OS
NETTER-1	Midgut	Midgut
RADIANT-3[34]	Pancreas	Pancreas
A6181111[81]	Pancreas	Pancreas

diagnostics' (AAA submission, p. 210[31]), but do not state explicitly whether or not convergence was achieved in the models. Consistency of the networks could not be assessed as there were no closed loops, meaning that direct evidence for treatments compared within a RCT could not be compared with indirect evidence for that treatment comparison.

Advanced Accelerator Applications reported very little difference between the DICs from the four models for each network [table 27 (p. 83) of the AAA submission[31]); therefore, the results from the random-effects Poisson model are presented for both tumour locations and outcomes. Point estimates and 95% CrIs are reported for all treatment comparisons in tables 23–26 (pp. 81–82) of the submission.[31] The main results are summarised in *Tables 104* and *105*.

Limitations of Advanced Accelerator Applications's mixed treatment comparison

We acknowledge the following important limitations of the MTC conducted by AAA, which limit the extent to which the findings can be relied on: (1) RADIANT-2 should be excluded from this MTA as the population in this trial all have functioning tumours, which is outside the marketing licence for everolimus for GI NETs, (2) NETTER-1 should be excluded from the pNETs network as it does not include any patients with pNETs, (3) for the evaluation of GI NETs, the populations differ across the three studies for OS (midgut NETs in NETTER-1, all NETs in RADIANT-2, GI and lung NETs in RADIANT-4), (4) there is no justification for the assumption that 60 mg of octreotide LAR is equivalent to placebo, placebo plus 30 mg of octreotide and placebo plus 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 the results for OS, (6) the 95% CrIs are very wide, indicating a great deal of uncertainty, more so than the results from the

TABLE 104 Gastrointestinal NETs HRs (95% CrIs)

Intervention	PFS	OS
177Lu-DOTATATE vs. octreotode/placebo	Confidential information has been removed	Confidential information has been removed
Everolimus vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE vs. everolimus	Confidential information has been removed	Confidential information has been removed

TABLE 105 Pancreatic NETs HRs (95% CrIs)

Intervention	PFS	OS
177Lu-DOTATATE vs. octreotode/placebo	Confidential information has been removed	Confidential information has been removed
Everolimus vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
Sunitinib vs. octreotide/placebo	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE vs. everolimus	Confidential information has been removed	Confidential information has been removed
177Lu-DOTATATE vs. sunitinib	Confidential information has been removed	Confidential information has been removed
Everolimus vs. sunitinib	Confidential information has been removed	Confidential information has been removed

RCTs suggest and (7) the 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.

Comparison with the Assessment Group's 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 plus BSC with 60 mg of octreotide to allow RADIANT-4[35] 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 that it was appropriate to link the RADIANT-4[35] and NETTER-1 trials by assuming that placebo plus BSC (as used in RADIANT-4[35]) is equivalent to 60 mg of octreotide (as used in NETTER-1). However, in a sensitivity analysis, the AG made the strong assumption that placebo plus BSC can be considered equivalent to 60 mg of octreotide, but this ITC should be interpreted with caution.

From data requests sent by the AG to AAA, the AG was able to obtain GI-only NETs data from RADIANT-4[35] (rather than GI plus lung NETS data, as used in AAA's ITC), but only for PFS and some AEs. Therefore, the results of the ITC undertaken by the AG are different from those of the ITC undertaken by AAA, as RADIANT-2 was excluded from the AG analysis, only GI NETs data were included from RADIANT-4[35] and an ITC for OS was not conducted by the AG as these data were not received from the company.

For PFS, the HR for 177Lu-DOTATATE compared with everolimus was estimated as 0.37 (95% CI 0.19 to 0.69) by the AG and 0.43 (95% CrI 0.05 to 4.24) by AAA. The 95% CrI in AAA's analysis is wide because a random-effects model was used. These findings are similar in magnitude; however, to accept these results it must be assumed that placebo plus BSC is equivalent to 60 mg of octreotide. The AG also conducted an indirect comparison of AEs, OS and RR.

For the pNETs network, the AG did not include data from NETTER-1 as none of the participants in this trial had pNETs. Therefore, only data from RADIANT-3[34] and A6181111[81] were included in the AG's ITC between everolimus and sunitinib. As well as PFS and OS, the AG also reported ITC results for RR and AEs. AAA considered only 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 for everolimus compared with sunitinib from AAA's analysis is (confidential information has been removed), whereas the HR from the AG's analysis is 0.83 (95% CI 0.49 to 1.42). It is likely that these differences in the widths of the 95% CrI and 95% CI occur because AAA reported the results from a random-effects model, whereas the analysis conducted by the AG assumed a fixed-effects model. As AAA did not report the results from a fixed-effects model it is not possible to check whether or not this is the reason for the uncertainty.

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' (Novartis submission, p. 33[33]). The literature searching carried out 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 *CRD's Guidance for Undertaking Reviews in Health Care*.[38] The methods used by Novartis are described in brief and are adequate for the purpose of the 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 reviewer screening 10% and all included citations.

In relation to pNETs, Novartis identified five RCTs and 41 non-RCTs. Of the five RCTs, four evaluated everolimus (RADIANT-3,[34] COOPERATE-2 (COmbination Of Pasireotide and evERolimus in Advanced Tumors of neuroEndocrine origin, second trial),[206] Yao *et al.*,[107] NCT01628913[207]) and one evaluated sunitinib (A6181111[81]). Of the four RCTs that evaluated everolimus, only RADIANT-3[34] was included in the submission as COOPERATE-2 and NCT01628913 compared everolimus with comparators outside the scope. The results from the fourth identified RCT, that by Yao *et al.*,[107] were retracted by the authors 6 months after their publication.[208] The inclusion of RADIANT-3[34] matches the RCT included by the AG for the assessment of everolimus in pNETs. RADIANT-3[34] is reported in detail in the main text of the company submission, with additional information presented in appendix 3 of the submission.[33] Novartis also refers to OBLIQUE, a currently unpublished Phase IV observational study, which assesses quality of life in individuals with pNETs receiving everolimus. Novartis also reports on non-RCTs of everolimus, which represent 16 or 17 [16 studies referred to in the main company submission document, whereas 17 studies are presented in the results table (see appendix 2 of the company submission[33])] of the 41 identified non-RCTs. The non-RCT data were tabulated (see appendix 2 of the company submission[33]) and summarised in the main report (see chapter 4.8 of the company submission[33]). The AG did not assess any non-randomised evidence for everolimus. Novartis conducted two further systematic literature reviews 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' (Novartis submission, p. 59[33]). The literature searching carried out was sufficient and the methods of the review were the same as those mentioned earlier. In terms of the GI NETs systematic review, eight RCTs and five non-RCTs were identified by Novartis, of which three RCTs and two non-RCTs also met the eligibility criteria for inclusion in the lung NETs systematic review. Of the eight RCTs and five non-RCTs, only one RCT and one non-RCT were deemed relevant by Novartis in its submission (RADIANT-4[35] and Bajetta *et al.*[209] respectively). Irrelevant RCTs were excluded based on the interventions not meeting the inclusion criteria in the scope (Yao *et al.*;[210] CLARINET;[211] Faiss *et al.*;[201] Jacobsen *et al.*[212] PROMID;[176,213] Wolin *et al.*[214]) or the population recruited not being within the marketing authorisation for everolimus (RADIANT-2[119,215–217]). Irrelevant non-RCTs were all excluded based on the interventions not being within the scope (Ferolla *et al.*,[218] Campana *et al.*,[219] Grozinsky-Glasberg *et al.*[220] and Panzuto *et al.*[221]). The AG did not include non-RCTs for everolimus. Consequently, from the two included studies from Novartis, the AG also identified RADIANT-4[35] (the RCT) but did not include Bajetta *et al.*[209] (the non-RCT). RADIANT-4[35] is reported in detail in the main text of the company submission, with additional information presented in *Appendix 7* of the submission.

Network meta-analysis

Novartis did not conduct a meta-analysis, MTC or ITC for GI and/or lung NETs as it identified only the RADIANT-4[35] trial.

For pNETs, Novartis identified three trials in its systematic review that included everolimus (RADIANT-3,[34] COOPERATE-2[206] and NCT01628913[207]), stating that, because of the different comparators in these three trials, a meta-analysis was not undertaken. Instead, an indirect comparison between everolimus and sunitinib was carried out using RADIANT-3[34] and A6181111.[81] The network for Novartis's pNETs MTC is shown in *Figure 56*.

The network was used to compare PFS, OS, concomitant SSA use and 13 grade 3/4 AEs (for which there was an incidence of ≥ 2% in either trial) between everolimus and sunitinib. For PFS, Novartis conducted

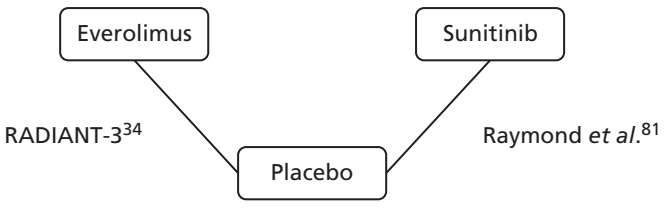

FIGURE 56 Pancreatic NETs network for the indirect comparison conducted by Novartis for PFS, OS, concomitant SSA use and AEs.

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 its submission). For OS, Novartis conducted an indirect comparison of OS based on ITT analysis 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[34] and A6181111[81] was conducted by Novartis, who deemed the trials to be similar enough to be combined. The outcomes from both trials contributing to the ITCs are presented in table 4.8 of Novartis's submission.[33]

Novartis also reported the results of a published MAIC,[124] which used individual participant data from RADIANT-3[34] and aggregate data from A6181111.[81] This method was used to allow for matching of the characteristics of participants in RADIANT-3[34] with those in A6181111[81] and to help 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 argued (p. 49 of the submission[33]) that the limitations of the MAIC method, which include 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 SMC, for which the MAIC had been included in a health technology assessment that it appraised on this clinical question, referred to the MAIC as 'non-standard', have led it to consider the more straightforward approach of Bucher *et al.*[41] for carrying out 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 in the Bucher *et al.*[41] method. In any case, the MAIC analysis serves as a robustness check of the Bucher results. The results of these analyses are summarised in *Tables 106* and *107* (see tables 4.11–4.15 in Novartis's submission[33] for all data used and the MTC results).

Novartis concluded that there are no significant differences in (locally and centrally defined) PFS, (ITT or RPSFT) OS and concomitant SSA use between everolimus and sunitinib. It reported that the indirect comparison for AEs suggests a higher odds of grade 3/4 neutropenia, hypertension, palmar–plantar erythrodysaesthesia syndrome and leukopenia events with sunitinib than with everolimus, whereas for the remaining AEs a higher odds is associated with everolimus than with sunitinib. However, none of the ORs is statistically significant and all have very wide 95% CIs.

Limitations of Novartis's indirect treatment comparison

The AG notes the following limitations with the indirect comparison carried out by Novartis: (1) it is unclear where Novartis obtained the HR for blinded independent review-defined PFS for A6181111[81] as the AG was unable to identify this from the published literature and (2) the justification for using the Bucher *et al.*[41] method of indirect comparison is not clear when a MAIC analysis would have been possible.

TABLE 106 Results of Novartis's pNETs indirect comparison of everolimus with sunitinib for PFS, OS and concomitant SSA use[a]

Outcome	Everolimus vs. placebo OR (95% CI)	Sunitinib vs. placebo OR (95% CI)	Everolimus vs. sunitinib OR (95% CI)
Local investigator-defined PFS	0.35 (0.27 to 0.45)	0.42 (0.26 to 0.66)	0.83 (0.49 to 1.42)
Blinded independent review-defined PFS	0.34 (0.26 to 0.44)	0.32 (0.18 to 0.55)	1.08 (0.59 to 1.99)
ITT OS	0.94 (0.73 to 1.20)	0.71 (0.47 to 1.09)	1.32 (0.81 to 2.16)
RPSFT OS	0.60 (0.09 to 3.95)	0.43 (0.17 to 1.20)	1.40 (0.17 to 11.72)
Concomitant SSA use	0.91 (0.61 to 1.36)	0.88 (0.45 to 1.71)	1.04 (0.48 to 2.26)

a Rounded to two decimal places by the AG.

TABLE 107 Results of Novartis's pNETs indirect comparison of sunitinib with everolimus for grade 3/4 AEs[a]

Outcome	Sunitinib vs. everolimus[a] OR (95% CI)
Neutropenia	23.71 (0.19 to 3037.28)
Hypertension	18.68 (0.15 to 2414.14)
PPE syndrome	11.62 (0.09 to 1540.16)
Leukopenia	11.62 (0.09 to 1540.16)
Diarrhoea	0.57 (0.03 to 12.113)
Stomatitis	0.23 (0.01 to 14.06)
Thrombocytopenia	0.41 (0.01 to 25.31)
Anaemia	0.04 (0 to 4.76)
Hyperglycaemia	0.35 (0.01 to 21.02)
Fatigue	0.20 (0.01 to 17.25)
Infections	0.20 (0.01 to 17.25)
Pneumonitis	0.09 (0.01 to 11.67)
Nausea	0.09 (0.01 to 11.67)
Sum	4.48 (0.51 to 39.38)

PPE, palmar–plantar erythrodysaesthesia.
a Note that in table 4.15 of Novartis's submission[33] (results for indirect comparison of AEs), the upper and lower 95% CIs were incorrectly labelled as lower and upper respectively.

The AG notes that the conclusions of the published MAIC[124] are similar to those reported by Novartis using the Bucher *et al.*[41] method, even though the methods used differ and the OS data used by Novartis are more mature than those used in the published MAIC analysis.

Comparison with the Assessment Group's indirect treatment comparison

The AG identified the same two RCTs for pNETs and used the same method for the ITC[41] as Novartis. The ITC results were exactly the same for local investigator-defined PFS between Novartis and the AG and were very slightly different for blinded independent review-defined PFS, even though the HRs and 95% CIs for RADIANT-3[34] and A6181111[81] were the same. The AG believes that this very slight difference is possibly related to Novartis using more precise data than the AG had access to. For OS, the AG used data for A6181111[81] from Pfizer's submission[32] rather than data from Raymond *et al.*,[81] which is what Novartis used. Therefore, there are some differences in the HRs and 95% CIs used between the AG and Novartis. However, both sets of results (the 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 that there is no statistically significant difference between everolimus and sunitinib.

Pfizer

Pfizer did not conduct a systematic review to identify relevant trials for this decision problem as it was confident that the only trial conducted with sunitinib in its licensed indication for pNETs was the A6181111[81] trial. This matches the identification of A6181111 by the AG as the only relevant trial for the analysis of sunitinib. Pfizer reported data primarily from the principal study publication.[81] In addition, other data sources for the A6181111[81] trial included the CSR[110] (dated 2009) and updated survival analysis from a conference abstract.[88] In its submission Pfizer reported incidence rates for AEs using the CSR as the source. The AE incidence rates published by Raymond *et al.*[81] are different and on average higher (by $n = 1$ or 2) for all grades of AEs.

Critique of the matched adjusted indirect comparison analyses by Pfizer

Pfizer presented a MAIC of everolimus and sunitinib using placebo-controlled treatment effects on PFS and OS from the A6181111 trial[81] of sunitinib compared with placebo and the RADIANT-3 trial[34] of everolimus compared with placebo. These analyses follow previously published work by Signorovitch *et al.*,[124] who first applied the MAIC method to this question. Pfizer used updated OS data and matched the sunitinib and placebo arms of A6181111[81] to the baseline characteristics in RADIANT-3.[34] The direction of matching, that is, of the A6181111[81] population to the RADIANT-3[34] population, was determined by the availability of individual patient data from the former trial and only summary data from the latter trial. In contrast, the study by Signorovitch *et al.*[124] was sponsored by Novartis and had available individual patient data from RADIANT-3[34] but only aggregate data from A6181111,[81] which determined that matching was performed in the opposite direction, that is, from RADIANT-3[34] to the A6181111[81] population.

Briefly, a MAIC involves estimating sampling weights by regression analysis and applying these weights to data from individual patients to adjust their relative contribution to the analysis of outcome data from the 'index' trial, that is, A6181111;[81] the weights reflect the likelihood that an individual with a mix of baseline characteristics is found in the population of a 'target' trial, that is, RADIANT-3.[34] In practice, logistic regression is used to obtain the weights, following the methodology of propensity score matching for observational data.[222] As a result, the weighted summary characteristics at baseline match the baseline characteristics of the target population in RADIANT-3.[34] In the present case, in which 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.[124]

Pfizer's justification for its use of MAIC, as opposed to simpler methods such as that by Bucher *et al.*, to indirectly compare sunitinib with 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 crossover in OS. As 69% and 85% of placebo patients in A6181111[81] and RADIANT–3,[34] respectively, 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 a common comparator or anchor. In contrast, by matching the sunitinib arm of A6181111[81] to the everolimus arm of RADIANT-3,[34] the MAIC is feasible.

Although 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 because of improved PFS with sunitinib, the smaller size of this trial relative to RADIANT-3[34] and the more frequent imaging schedule in A6181111[81] (8 weeks vs. 12 weeks in RADIANT-3[34]), which may result in earlier detection of disease progression. Unlike A6181111,[81] RADIANT-3[34] included patients with a PS of 2, but as they constituted only 3% of the trial sample this had a limited effect on the results produced by Pfizer.

Although randomisation produced a balanced distribution of baseline characteristics in RADIANT-3,[34] it (confidential information has been removed).

Two approaches were taken by Pfizer to the MAIC, one for PFS and another for OS. For PFS, for which 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 plus placebo arms of A6181111[81] were separately matched to the everolimus arm.
2. The HR for sunitinib compared with BSC plus placebo was estimated from the matched A6181111[81] individual patient data.
3. A Bucher indirect comparison of everolimus with sunitinib was estimated using the HR from the matched sunitinib compared with BSC plus placebo data from A6181111[81] and the reported HR for everolimus compared with BSC plus placebo in RADIANT-3.[34]

The 95% CI for the resulting MAIC HR for PFS was calculated from the standard errors of the log HR of sunitinib compared with BSC plus placebo, adjusted for the effective sample size, and of the HR of everolimus compared with BSC plus placebo in RADIANT-3,[34] as approximated from its reported point estimate and 95% CI (confidential information has been removed).

Because of contamination as a result of crossover, the MAIC for OS was conducted by directly matching the sunitinib arm to the everolimus arm. In this analysis, the following steps were followed:

1. The sunitinib arm of A618111145[81] was matched to the everolimus arm.
2. The individual patient OS data for everolimus were recreated from digitised Kaplan–Meier curves using the algorithm of Hoyle and Henley.[223]
3. The HR for sunitinib compared with everolimus was estimated from the matched individual patient data from the sunitinib arm and the recreated individual patient data in RADIANT-3.[34]

The weights applied to the sunitinib arm for MAIC with everolimus were normalised (i.e. divided) by the effective sample size (defined as the ratio of the square of the sum of weights to the sum of the square of individual weights). The purpose of this adjustment was that the 95% CI associated with the hazard ratio in step 3 accounted for the reduced amount of information available from a sample of a given size after matching.

(Confidential information has been removed) *Table 108*. Confidential information has been removed.

TABLE 108 Matched adjusted indirect comparison results for PFS and OS in the Pfizer submission vs. the Bucher estimates

	PFS		OS	
Comparison	*n*	HR (95% CI)	*n*	HR (95% CI)
Bucher IC				
Sunitinib vs. placebo	Confidential information has been removed	Confidential information has been removed	–	–
Everolimus vs. placebo	Confidential information has been removed	Confidential information has been removed	–	–
Sunitinib vs. everolimus	Confidential information has been removed	Confidential information has been removed	–	–
MAIC				
Sunitinib vs. placebo[a]	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Everolimus vs. placebo[b]	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Sunitinib vs. everolimus	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Unmatched IC				
Sunitinib vs. everolimus	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

IC, indirect comparison.
a Based on individual patient data weighted to match the population of RADIANT-3,[34] as described by summary characteristics in above.
b Based on published data.[34,81]

Confidential information has been removed. In particular, Pfizer compared the matching-adjusted Kaplan–Meier curve of the placebo arm in A6181111[81] with the respective curve from recreated individual patient data from the placebo arm of RADIANT-3[34] and (confidential information has been removed). However, given the differences in the timing of scheduled imaging assessments to determine disease status between the two trials, discussed in *Critique of the matched adjusted indirect comparison analyses by Pfizer*, adjusting for the placebo PFS outcomes in the common comparator approach seems warranted nonetheless.

In relation to its OS results, Pfizer acknowledged the limitation of the data available. In particular, the available sample for the sunitinib arm was small, especially after matching, which effectively halved its size. Confidential information has been removed.

Pfizer provided a clear justification for the MAIC evidence submitted to NICE. This was based on updating the previous analysis[124] with new OS data and on 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 details of the methods used in and results obtained from the MAIC. The discussion also acknowledges the main strengths and limitations of this analysis and provides an adequate explanation of the reasons for the (confidential information has been removed). This discussion provided the valuable insight that much of the (confidential information has been removed). This highlights the limitations associated with the small sample size in this trial.

The AG notes that MAICs in small samples have a difficult balance to strike between internally valid comparisons and generalisability to the relevant patient populations. We have discussed this issue before.[224] 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 who are represented in both A6181111[81] and RADIANT-3,[34] but may not be generalisable to the subgroup of patients not represented in RADIANT-3[34] but present in A6181111.[81] Thus, although Pfizer presents its findings as improved evidence with regard to the previous study by Novartis on the basis of its 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[81] population. This is in addition to the limitations from 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 because of the lack of a within-trial placebo control for indirect comparison and the problems of sample size. A further MAIC analysis is needed with a within-trial placebo control that is itself adjusted for crossover to active treatment. Because of the small sample size in A6181111,[81] the most fruitful approach would be to match the sample of RADIANT-3[34] to the population of A6181111,[81] as Signorovitch *et al.*[124] have done, 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 as a result of few observations.

Pfizer provided individual patient data on A6181111[81] to NICE, which the AG used to conduct some sensitivity analyses of its MAIC. Confidential information has been removed.

Appendix 15 Methods for systematic reviewing of utilities (health-related quality-of-life 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 in MEDLINE (Ovid), EMBASE (Ovid), School of Health and Related Research Health Utilities Database (ScHARRHUD) [see www.scharrhud.org (accessed 15 May 2018)], the Health Economics Research Centre (HERC) database, the EQ-5D website [URL: https://euroqol.org (accessed 16 July 2018)], the 'patient-reported outcome and quality of life instruments' database[225] and the Health Technology Assessment database and NHS EED. These searches were not limited by study design and language. A complete list of search strategies can be found in *Appendix 1*.

All references were exported into EndNote X7 where automatic and manual deduplication 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 NETs, irrespective of the tumour location. The following outcome was considered: HRQoL 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 on the 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 consisted of 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. Owing to the lack of a standardised checklist for the quality appraisal of HRQoL studies, a set of criteria was formulated to critically appraise the studies included in the systematic review. The checklist used (*Table 109*) relies heavily on the 14-item checklist designed by Mols *et al.*[226] for the appraisal of quality-of-life studies in the area of breast cancer and later used by Cornish *et al.*[227] in the area of cutaneous melanoma. Compared with the original version outlined in Mols *et al.*,[226] three items were added and one was deleted in order to adapt the checklist to this specific disease area and types 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 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[228]

Mapping

Mapping was performed to obtain utility values from the EORTC QLQ-C30 and FACT-G data identified in the literature review.

Mapping the EORTC QLQ-C30 to the EuroQol-5 Dimensions

Doble and Lorgelly[229] conducted a comprehensive external validation study on the algorithms developed to map EORTC QLQ-C30 scores to the EuroQol-5 Dimensions three-level version (EQ-5D-3L). The data set that they used consisted of EORTC QLQ-C30 and EQ-5D values from a sample of 988 patients enrolled in the Cancer 2015 longitudinal study.[230] The patients involved were treatment naive 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 model and dummy variables, were found to perform inadequately.[229] 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 disease severity. The algorithm by Versteegh *et al.*[231] and that by Longworth *et al.*[134] 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 a relatively small mean squared error when predicting EQ-5D values and corresponding QALYs.[229] Although the algorithm in Versteegh *et al.*[231] cannot be generalised easily as it can only provide utilities drawn from the Dutch value set, the algorithm developed by Longworth *et al.*[132] (see *Appendix 22*), although being computationally intensive, had the advantage of providing utility values for any country-specific tariff, making it more generalisable.

The algorithm developed by McKenzie and van der Pol,[132] although not found to provide the highest accuracy in the review of algorithms by Doble and Lorgelly,[229] has been widely used and cited in studies of cancer. The validation process showed that the McKenzie and van der Pol[132] algorithm performs well in terms of predictive power, as all of the actual EQ-5D values were found to be in the 95% CIs 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 generalisability of such results remain unanswered, particularly in relation to the application of this algorithm to patient groups with widely different age ranges and health status from those in the oesophageal cancer patient group used to validate the algorithm.

TABLE 109 Quality-of-life studies in NETs: quality appraisal checklist

Checklist question	Cramer *et al.* (2014)[231]	Pavel *et al.* (2016)[232]	Teunissen *et al.* (2004)[233]	Swinburn *et al.* (2012)[130]	Singh *et al.*, (2016)[73]	Cohen and Allred (2009) (as cited in the submission)[32]
Are sociodemographic and medical data described?	No	Yes	Yes	No	No	Yes
Are inclusion/exclusion criteria formulated?	No	Yes	Yes	No	No	Yes
Was HRQoL a primary outcome of the study?	Yes	Yes	Yes	Yes	Yes	No
Is the process of data collection described?	No	No	Yes	Yes	No	Yes
Is the type of cancer described?	Yes	Yes	Yes	Yes	Yes	Yes
Are results compared between two or more groups?	No	Yes	Yes	No	Yes	Yes
Are the mean (or median) and range of time since diagnosis given?	No	Yes	No	No	No	Yes
Are participation and response rates per group described and > 75%?	No	No	Yes	No	No	Yes
Is information on patient/disease characteristics of respondents and non-respondents presented? If there is no selective response, is this explained?	No	No	No	No	No	No
Is the use of a valid QoL questionnaire justified?	No	No	No	No	No	No
Are the mean (or median) and standard deviation for the HRQoL measures reported?	No	Yes	Yes	Yes	Yes	No
Are the results reported as item scores as opposed to summary scores?	No	No	Yes	No	Yes	Yes
Is an attempt made to identify a set of determinants with the highest prognostic value?	No	Yes	Yes	No	No	No
Is the degree of selection of the patient sample described?	No	Yes	Yes	No	No	Yes
Was it reported whether the changes in HRQoL measured were clinically statistically significant?	No	Yes	Yes	No	No	Yes

QoL, quality of life.
Note
The checklist developed by Mols *et al.*[226] was modified by the author.

As the impact of using different algorithms in cost–utility analysis could not be measured by Doble and Lorgelly,[229] 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 the FACT-G to the EuroQol-5 Dimensions

The mapping of FACT-G scores to EQ-5D utilities was performed based on the work by Longworth *et al.*,[134] who 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.*[134] show that the best-fitting algorithm (see *Appendix 22*) used in this analysis achieves a high degree of accuracy in predicting EQ-5D values. Nevertheless, Young *et al.*[186] raise concerns regarding the generalisability of such results on the grounds that the patient sample used to test the algorithms in Longworth *et al.*[134] included a surprisingly low number of patients in poor health.

In this analysis, the best-fitting algorithm by Longworth *et al.*[134] (see *Appendix 22*) was linearised and used to map published FACT-G summary domain scores into EQ-5D values for the stable disease and disease progression health states for patients in RADIANT-4.[35] These utility values were the only empirical data available on EQ-5D health state utilities in patients treated with everolimus and, as we did not have access to the original individual patient data from the RADIANT-4[35] 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 *et al.*'s[134] 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 *et al.*'s[134] non-linear, best-fitting algorithm (see *Appendix 22*).

Results

A total of 6792 records were identified. After deduplication, 5192 records were manually screened by two reviewers. After the screening process, eight studies were ultimately included in this review.[32,73,121,123,131,232–234] A modified PRISMA flow chart is provided in *Figure 57*.

The main characteristics of the studies identified through the systematic search for data on HRQoL are summarised in *Tables 109* and *110*.

Evidence identified through the systematic search for studies on health-related quality of life

Of the included studies, data extraction on an initial set of six studies was undertaken (*Table 110*). Of the six studies, one was a conference abstract on a longitudinal study;[232] one was a Phase III expanded-access study;[233] one was a prospective cohort study;[234] one was a preference elicitation study;[131] and two were economic evaluations.[121,123]

Evidence obtained by contacting the authors or the sponsors of the studies

A second set of studies was identified in the systematic search for studies on HRQoL as abstracts only, with the study outcomes not available to the public. To obtain such data, the authors or the sponsors of the studies had to be contacted directly. *Table 111* 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[78] and a CSR provided by the sponsor of the study as part of the NICE appraisal process.[32]

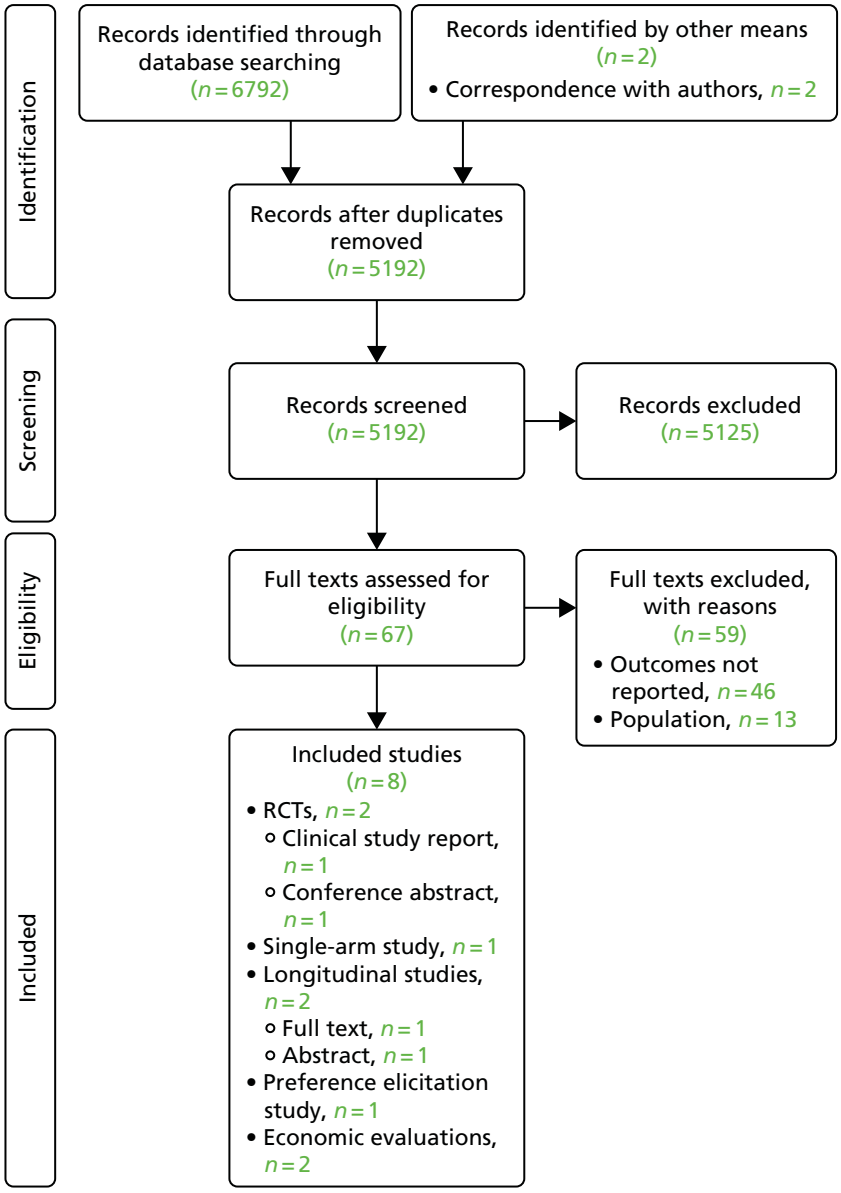

FIGURE 57 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

TABLE 110 Studies identified through the systematic search for HRQoL data: description

Study	Study design[a]	*n*	Population	Intervention	Measure (type[b] and name)	Outcomes[c]	Time period	Statistical method of analysis
Cramer 2014[232]	U	30	US NETs patients with hepatic metastases	Y-90 radioembolisation	G, SF-36	A	24 months	
Pavel 2016[233]	E	246	Patients with advanced NETs (pNETs vs. non-pNETS separately). Non-pNETs included small intestine, lung, colon and other	Everolimus	G, EQ-VAS, EQ-5D, EORTC QLQ-C30, EORTC QLQ-GI NET21	A	12 months	Last HRQoL value before treatment discontinuation was used
Teunissen 2004[234]	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 quality of life
Swinburn 2012[131]	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	NA
Walczak 2012[123]	EE	NR[d]	Adults with unresectable or metastatic well-differentiated pNETs with disease progression	Sunitinib + BSC vs. placebo + BSC	G, mapped EORTC QLQ-C30 onto EQ-5D	HS	Patients' lifetime	Markov model
Muciño Ortega 2012[121]	EE	NR[d]	Mexican non-resectable pNETs patients	Sunitinib + BSC vs. placebo + BSC	G, mapped EORTC QLQ-C30 onto EQ-5D	HS	10 years	Markov model

NA, not applicable; NR, not reported. SF-36, Short Form questionnaire-36 items; VAS, visual analogue scale.
a E, experimental; EE, economic evaluation; U, uncontrolled.
b G, generic; D, disease specific.
c A, average at fixed time point (e.g. 6 months after treatment start or at beginning of cycle 1); HS, health state.
d This study was an economic evaluation that referred to an unpublished secondary source for this information.

TABLE 111 Evidence obtained by contacting the authors: description

Study	Study design[a]	*n*	Population	Intervention	Measure (type[b] and name)	Outcomes[c]	Time period	Statistical method of analysis
Singh 2016[73]	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 2009[32]	E	144	Adults with progressive, well differentiated pNETs	Sunitinib	D, EORTC QLQ-C30	A	21 months	Repeated measures mixed-effects model

a E, experimental.
b G, generic; D, disease specific.
c A, average at fixed time point (e.g. 6 months after treatment start or at beginning of cycle 1); HS, health state.

Appendix 16 Use of chemotherapy

The analysis by Novartis in patients with pNETs adopted the values for the use of chemotherapy after disease progression presented in *Table 112*. The corresponding values for the company's evaluation of targeted therapy in GI or lung NETs are presented in *Table 113*. These values were used by the AG in the respective the novo model analyses. The frequency of use of other supportive drug therapies in the AG model-based analysis of GI and lung were obtained from RADIANT-4 data reported in the NICE submission by Novartis, as presented in *Table 114*. The frequencies of AEs in the AG analysis of pNETs, GI and lung and GI midgut patients, respectively, are presented in *Tables 115–117*.

TABLE 112 Use of chemotherapy post progression in RADIANT-3[34]

Treatment	Proportion of participants (%)	Number of cycles
5-fluorouracil	21.9	2.5
Doxorubicin	28.1	1.66
Streptozocin	31.3	2.14

TABLE 113 Use of chemotherapy post progression in RADIANT-4[35]

Treatment	Arm	Proportion of participants (%)	Number of cycles
5-fluorouracil	Everolimus + BSC	2.8	1.45
	BSC	1.1	
Streptozocin	Everolimus + BSC	2.8	1.45
	BSC	1.1	
Temozolomide	Everolimus + BSC	14.2	3.08
	BSC	11.4	
Capecitabine	Everolimus + BSC	14.2	3.08
	BSC	11.4	

TABLE 114 Use of other supportive drug therapies in RADIANT-4[35]

Treatment	Arm	Disease[a]	Proportion (%)
Analgesic (lidocaine)	Everolimus + BSC	Stable	12.7
	BSC	Stable	6.2
Corticosteroid (dexamethasone)	Everolimus + BSC	Stable	31.7
	BSC	Stable	10.3
Glucocorticoid (prednisone)	Everolimus + BSC	Stable	41.5
	BSC	Stable	11.3
Antiemetic (prochlorperazine)	Everolimus + BSC	Stable	2.9
	BSC	Stable	3.1
Antidiarrhoeal (Biofermin/*S. boulardii*)	Everolimus + BSC	Stable	5.8
	BSC	Stable	5.2

a For patients from both arms, the post-progression state frequency of use was assumed to be that corresponding to the BSC arm in stable disease, except (in sensitivity analysis) during the 1st cycle for the proportion of cases that were under active subsequent therapy (67.3% in everolimus + BSC arm, 66.7% in BSC arm), for whom the same proportion as that for everolimum + BSC arm under stable disease was assummed.

TABLE 115 Included SAEs in the pNETs evaluation by proportion (%) and treatment strategy[34,140]

AE	Everolimus (%)	Sunitinib (%)	BSC (%)
Neutropenia	0.2	5.5	0.2
Hypertension	0.2	4.4	0.2
Palmar–plantar erythrodysaesthesia	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 116 Included SAEs in the GI and lung NETs evaluation by proportion (%) and treatment strategy[35]

AE	Everolimus (%)	BSC (%)
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 117 Included SAEs in the GI (midgut) NETs evaluation by proportion (%) and treatment strategy[31,73,102]

AE	Everolimus (%)	177Lu-DOTATATE (%)	BSC (%)
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

Appendix 17 Addendum 1

Lung neuroendocrine tumours

The comparison between treatment with everolimus and treatment with BSC for lung NETs patients yielded an ICER of £31,016 (*Table 118*). Treatment of these patients with everolimus results in better survival (5.12 years vs. 2.96 for BSC). Likewise, the treatment costs in the everolimus arm are higher, driven by the drug acquisition costs in the pre-progression health state (*Table 119*).

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[138]
- exponential curves fitted to individual patient data derived from OS Kaplan–Meier curves and number of patients at risk data provided by Novartis for the lung subgroup of RADIANT-4[35]
- exponential curves fitted to individual patient data derived from lung PFS Kaplan–Meier curves presented in the American Society of Clinical Oncology (ASCO) poster by Singh *et al.*[73] [from PFS curves for all, non-prior treatment with SSA and prior treatment with SSA subgroups in RADIANT-4[35] and validated by comparing the resulting HR of 0.48 (95% CI 0.27 to 0.85) with the lung HR of 0.50 (95% CI 0.28 to 0.88) reported in the RADIANT-4[35] CSR]
- all other parameters were assumed to be the same as for the GI/lung patient population in RADIANT-4.[35]

Alternative set of utility values

When an alternative set of utility values was applied the ICER for sunitinib was £19,411 and for everolimus plus BSC was £41,246. In other locations the ICERs were > £30,000 (*Table 120*).

Analysis limited to progression-free survival

When the analysis was limited to accounting for costs and benefits up to disease progression, in patients with GI (midgut) tumours 177Lu-DOTATATE had an ICER of £30,115 and everolimus had an ICER of £88,801. In other tumour locations targeted treatments had ICERs of ≥ £35,448 (*Table 121*).

Background mortality adjustments to the overall survival and progression-free survival curves

Background mortality adjustment resulted in an ICER for sunitinib of £21,594. In all other locations targeted treatments resulted in ICERs of ≥£33,908 (*Table 122*) (the results for 177Lu-DOTATATE are presented in *Table 122* without adjustment for background mortality as the respective base-case values included an adjustment for background mortality).

TABLE 118 Peninsula Technology Assessment Group base-case results for lung NETs

Outcome measure	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 per QALY) (£)			31,016

TABLE 119 Peninsula Technology Assessment Group base-case detailed results for lung NETs

Outcome measure	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	3338	1509	1830
AEs	171	34	137
Total (pre progression)	34,013	1822	32,191
Post progression			
Drug acquisition	3748	1572	2175
Drug administration	18	6	12
Medical management	7689	4898	2791
End-of-life care	3700	3950	–250
Total (post progression)	15,155	10,426	4729
Total	49,168	12,249	36,920
ICER (cost per QALY)			31,016

TABLE 120 Peninsula Technology Assessment Group scenario analysis results using 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

TABLE 121 Peninsula Technology Assessment Group scenario analysis results limiting the 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

TABLE 122 Peninsula Technology Assessment Group scenario analysis results adjusting for 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

First-cycle costs and disease monitoring

When the costs of treatment after disease progression were included (accounted for by adjusting the first-cycle costs of the progressive disease phase), the ICER for sunitinib plus BSC was £20,624 and for everolimus was £45,288. For targeted treatments in other locations, the ICERs were ≥ £32,744 (*Table 123*).

The scenario using alternative costs for disease monitoring, as adopted by Novartis in its analysis submitted to NICE, resulted in ICERs of ≥ £32,221 across GI/lung tumour locations (*Table 124*).

Scenario analysis using a 0% discount rate

With no discounting for costs and QALYs, sunitinib plus BSC in pNETs is the only targeted treatment in the studied locations with an ICER of < £20,000. The only other treatment with an ICER of < £30,000 was everolimus pus BSC in patients with lung NETs (*Table 125*).

TABLE 123 Peninsula Technology Assessment Group scenario analysis results adjusting for first-cycle costs of disease progression

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

TABLE 124 Peninsula Technology Assessment Group scenario analysis results adjusting for first-cycle costs of 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

TABLE 125 Peninsula Technology Assessment Group 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

Probabilistic sensitivity analyses

The sampling variation in model parameter data is consistent with everolimus having an ICER that is > £30,000 in lung pNETs (*Figure 58*).

For lung NETs, the probabilistic mean ICER is £31,987. The probability that everolimus is the most cost-effective treatment for lung NETs at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY gained is 12.6% and 46.3%, respectively (*Figure 59*).

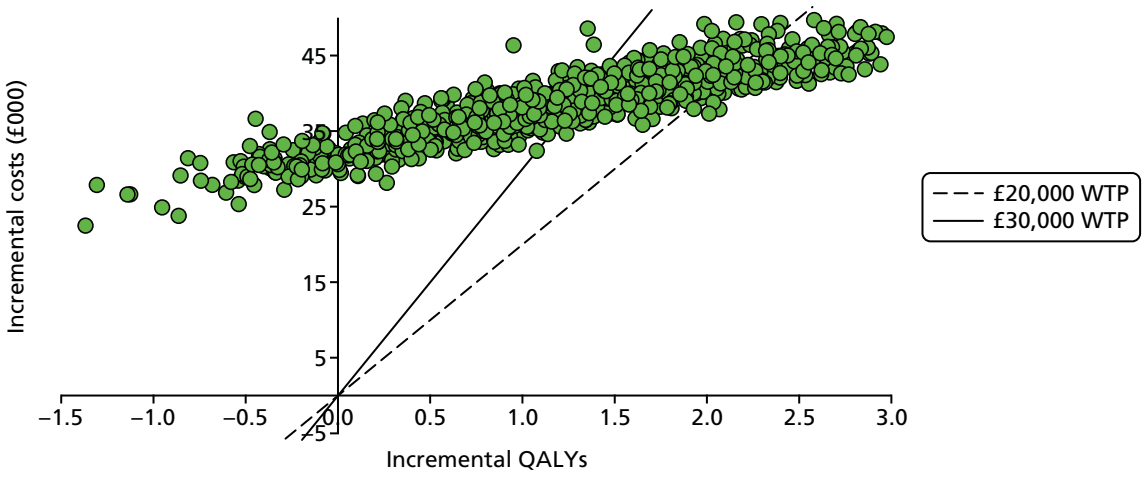

FIGURE 58 Cost-effectiveness plane: treatments in lung pNETs. WTP, willingness to pay.

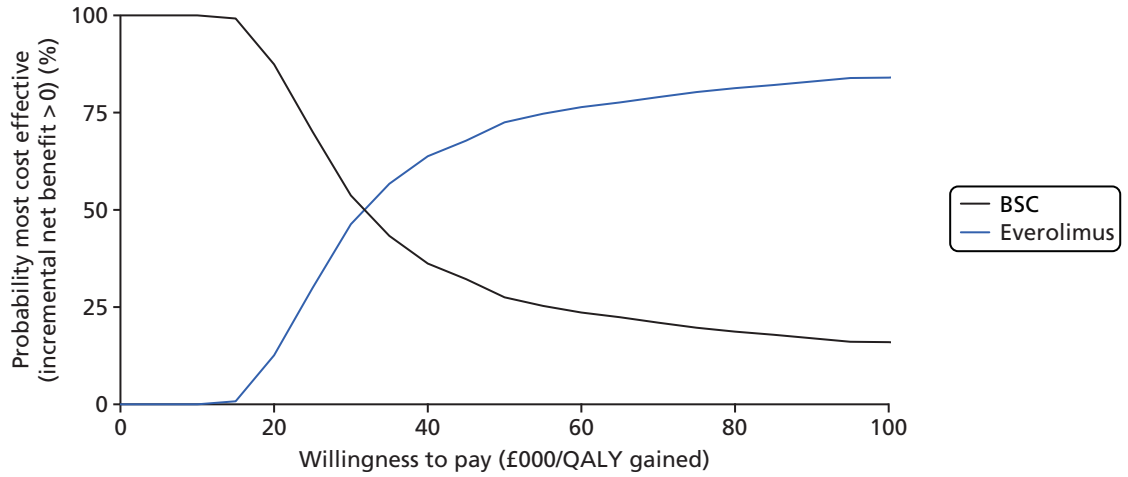

FIGURE 59 Cost-effectiveness acceptability curves for treatments in lung NETs.

Appendix 18 Sensitivity analyses

Probabilistic sensitivity analyses

Pancreatic neuroendocrine tumours

The probabilistic analysis suggests that the ICER for sunitinic compared with everolimus is statistically significantly below the £20,000 incremental cost per QALY gained threshold (*Figure 60*).

In contrast, the ICER for everolimus plus BSC compared with BSC alone was > £20,000 and the data may be consistent with it being > £30,000 (*Figure 61*).

The sampling uncertainty in the data are consistent with sunitinib having an ICER that ranges from slightly > £30,000 to < £20,000 (*Figure 62*).

In line with the results illustrated in the previous figures, the probability that everolimus treatment for pNETs is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY gained is 0% and 0.6% respectively (*Figure 63*).

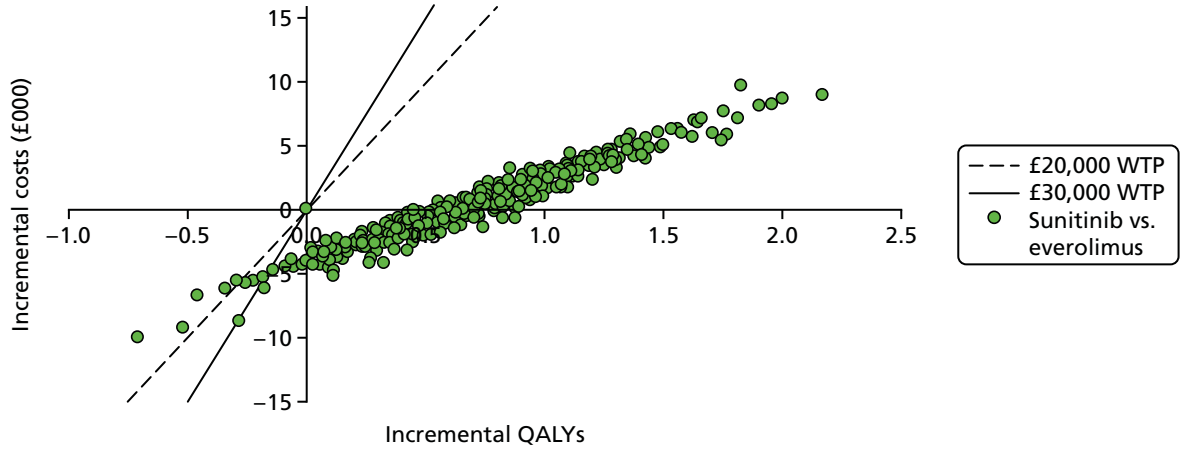

FIGURE 60 Cost-effectiveness plane: comparison of targeted treatments in pNETs. WTP, willingness to pay.

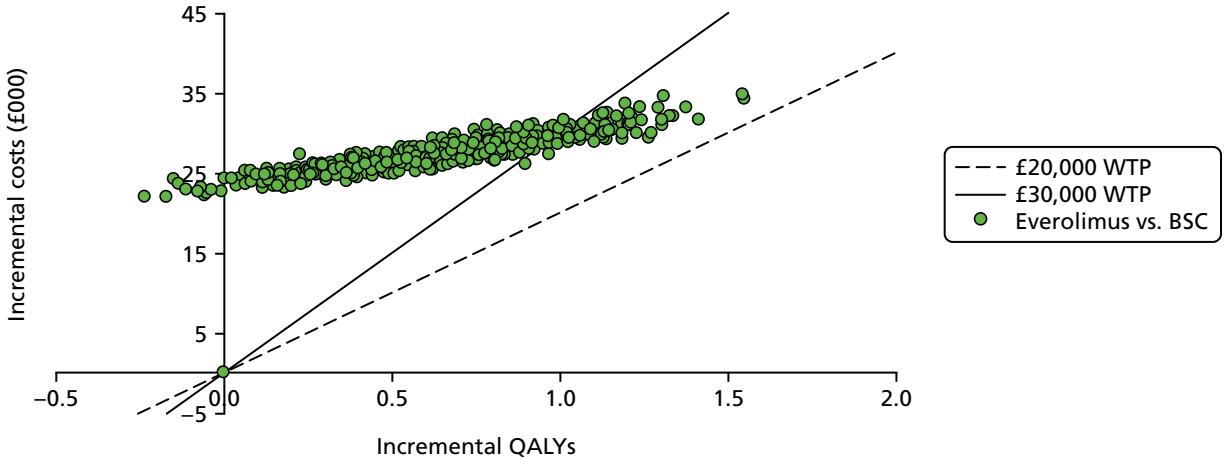

FIGURE 61 Cost-effectiveness plane: everolimus vs. BSC in pNETs. WTP, willingness to pay.

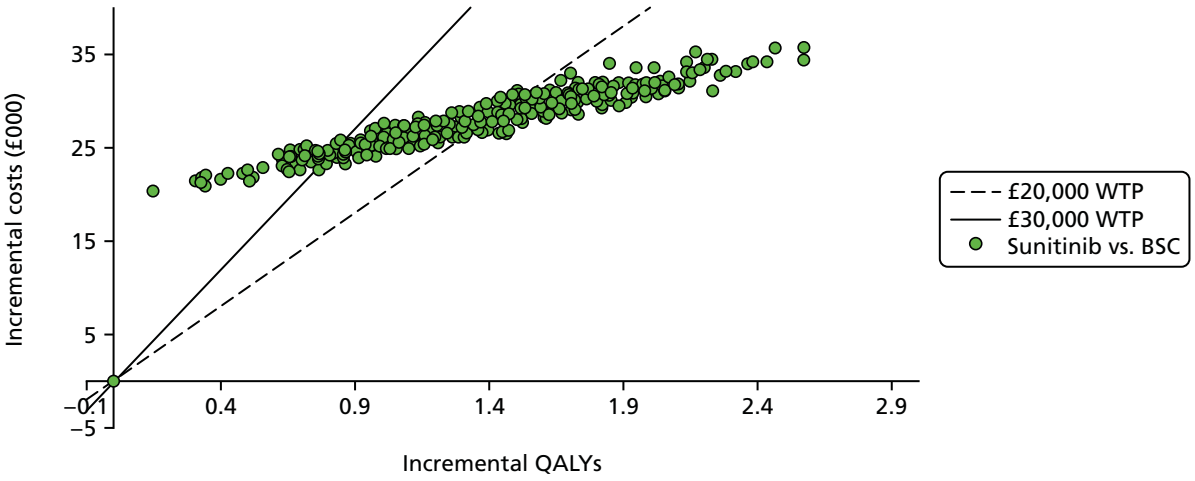

FIGURE 62 Cost-effectiveness plane: sunitinib vs. BSC in pNETs. WTP, willingness to pay.

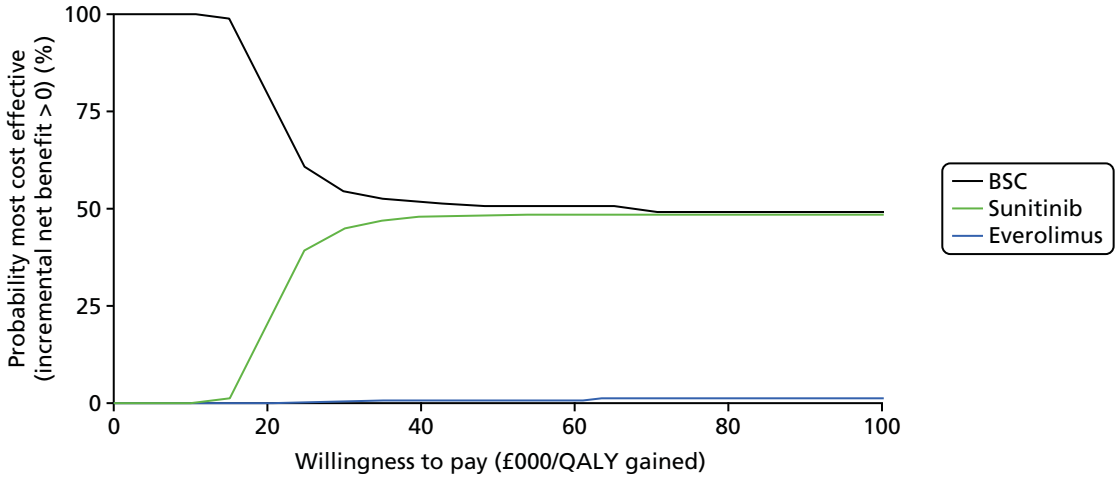

FIGURE 63 Cost-effectiveness acceptability curves of treatments in pNETs.

The probability of sunitinib being the most cost-effective treatment for pNETs at a willingness-to-pay threshold of £20,000 per QALY is 21.2%; at £30,000 per QALY, sunitinib is the most cost-effective treatment, with a probability of 44.8% (see *Figure 63*).

Gastrointestinal and lung neuroendocrine tumours

The model parameter data are consistent with everolimus having an ICER of > £30,000 per QALY gained (*Figure 64*).

The probability that everolimus for GI and lung NETs is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY gained is 0.9% and 10.5% respectively (*Figure 65*).

Gastrointestinal (midgut) neuroendocrine tumours

The model parameter data are consistent with everolimus having an ICER of > £30,000 per QALY gained (*Figure 66*).

The probability that everolimus for GI (midgut) NETs is the most cost-effective treatment at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY gained is 0.1% and 2.5% respectively (*Figure 67*).

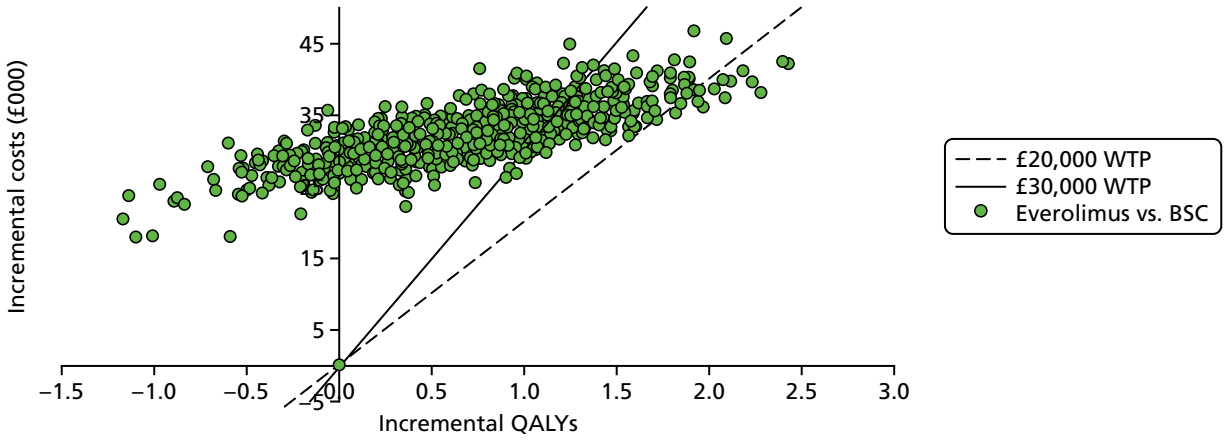

FIGURE 64 Cost-effectiveness plane: everolimus vs. BSC in GI/lung NETs. WTP, willingness to pay.

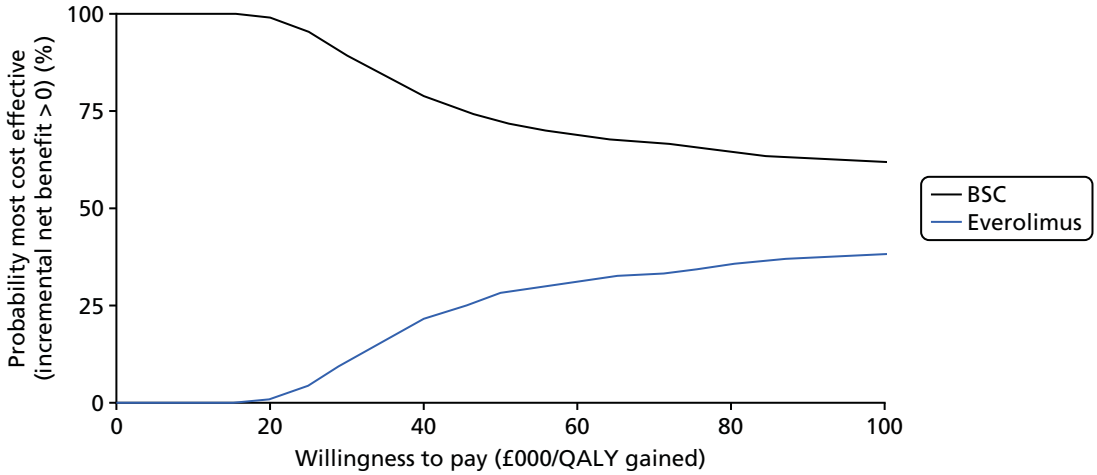

FIGURE 65 Cost-effectiveness acceptability curves of treatments in GI/lung NETs.

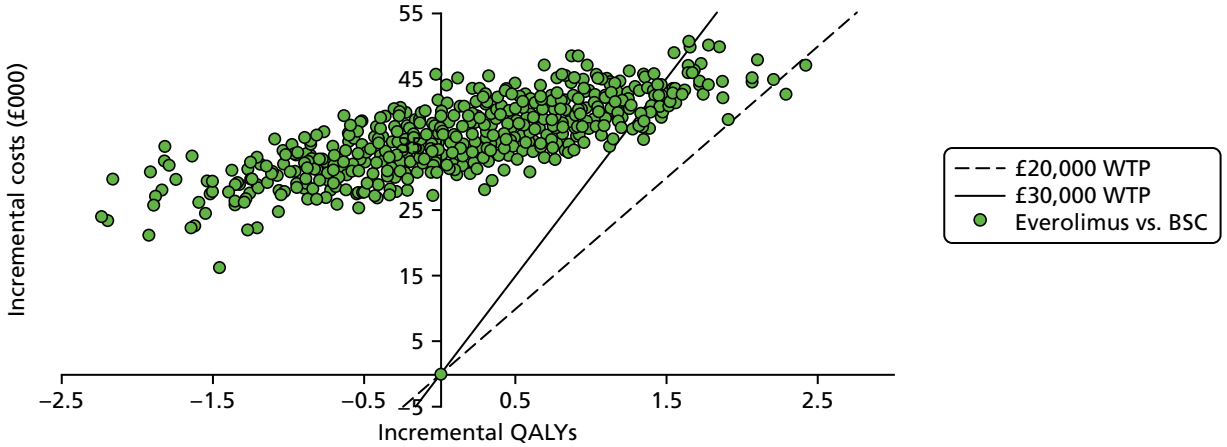

FIGURE 66 Cost-effectiveness plane: everolimus vs. BSC in GI (midgut) NETs. WTP, willingness to pay.

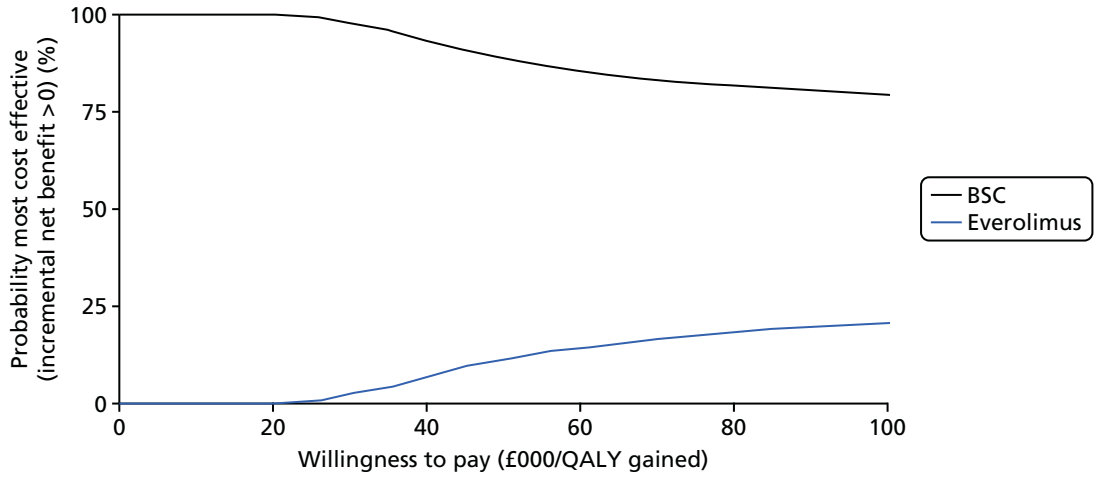

FIGURE 67 Cost-effectiveness acceptability curves of treatments in GI (midgut) NETs.

Deterministic sensitivity analyses

We varied parameters to either side of their point estimates by 20%, except for utility differences between stable disease and progressive disease, which were varied by 40%.

Pancreatic neuroendocrine tumours

In pNETs the OS HR 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 68*). Other influential parameters include RDI and treatment duration. The utility of progressive disease and stable disease are much less influential and are ranked fourth on the list of most influential parameters in the model, with a larger influence on the ICER for sunitinib (*Figure 69*).

Gastrointestinal and lung neuroendocrine tumours

Similar results to those for pNETs were found for GI and lung NETs, with variations around the point estimate of the OS HR of ±20% yielding an increase of 300% or a decrease of about 50% in the ICER for everolimus; RDI and mean treatment duration had smaller but significant effects (*Figure 70*).

Gastrointestinal (midgut) neuroendocrine tumours

The OS HR 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 a dominated value (shown in *Figure 71* as a missing bar to the right-hand side of the point estimate). Unlike for treatments in other locations, the ICER for everolimus in GI (midgut) NETs was sensitive to the variation in the PFS HR. This, however, is partly an artefact of how OS was populated in the model; whereas for other locations OS data were available, for GI (midgut) NETs we did not have OS data available and thus had to rely on imputation based on PFS differences compared with the placebo plus BSC arm in RADIANT-4.[35] As a consequence, part of the effect of PFS depicted in *Figure 71* is an indirect effect through OS.

The cost-effectiveness of 177Lu-DOTATATE is almost equally sensitive to the OS and PFS HRs, with utilities the third most influential parameter (*Figure 72*).

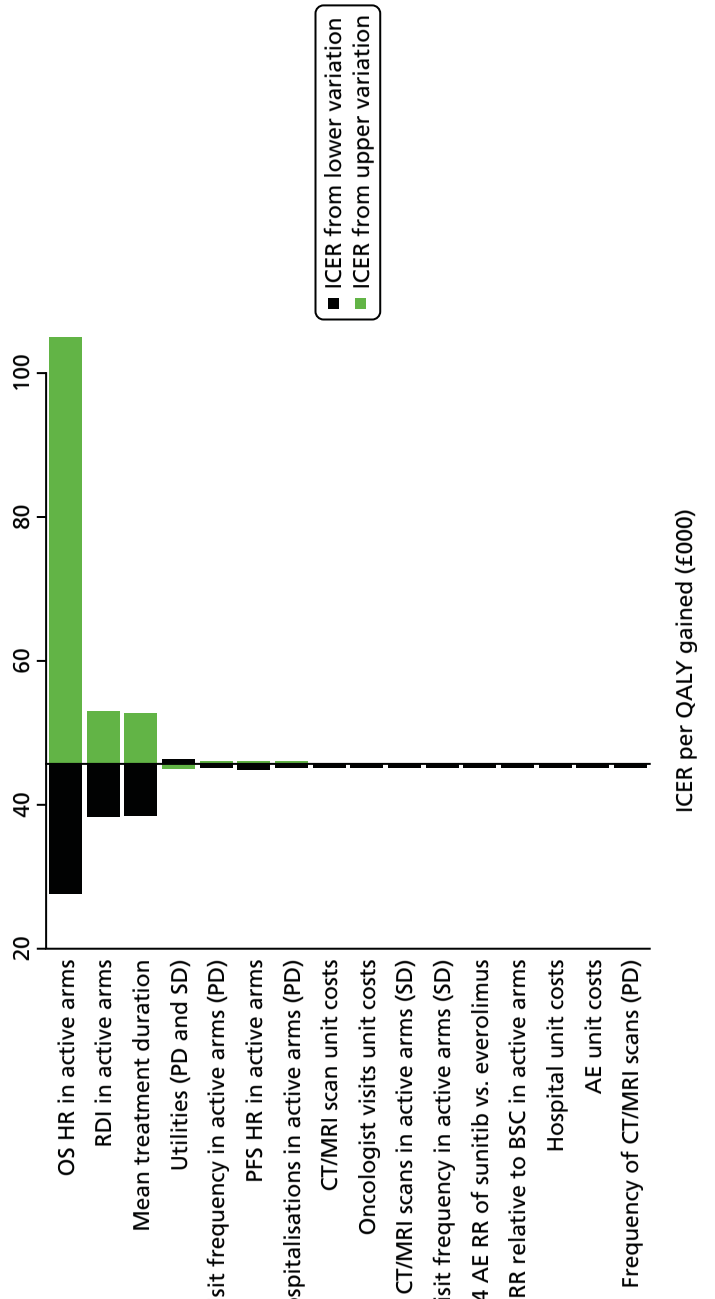

FIGURE 68 Tornado analysis of everolimus treatment in pNETs. PD, progressive disease; SD, stable disease.

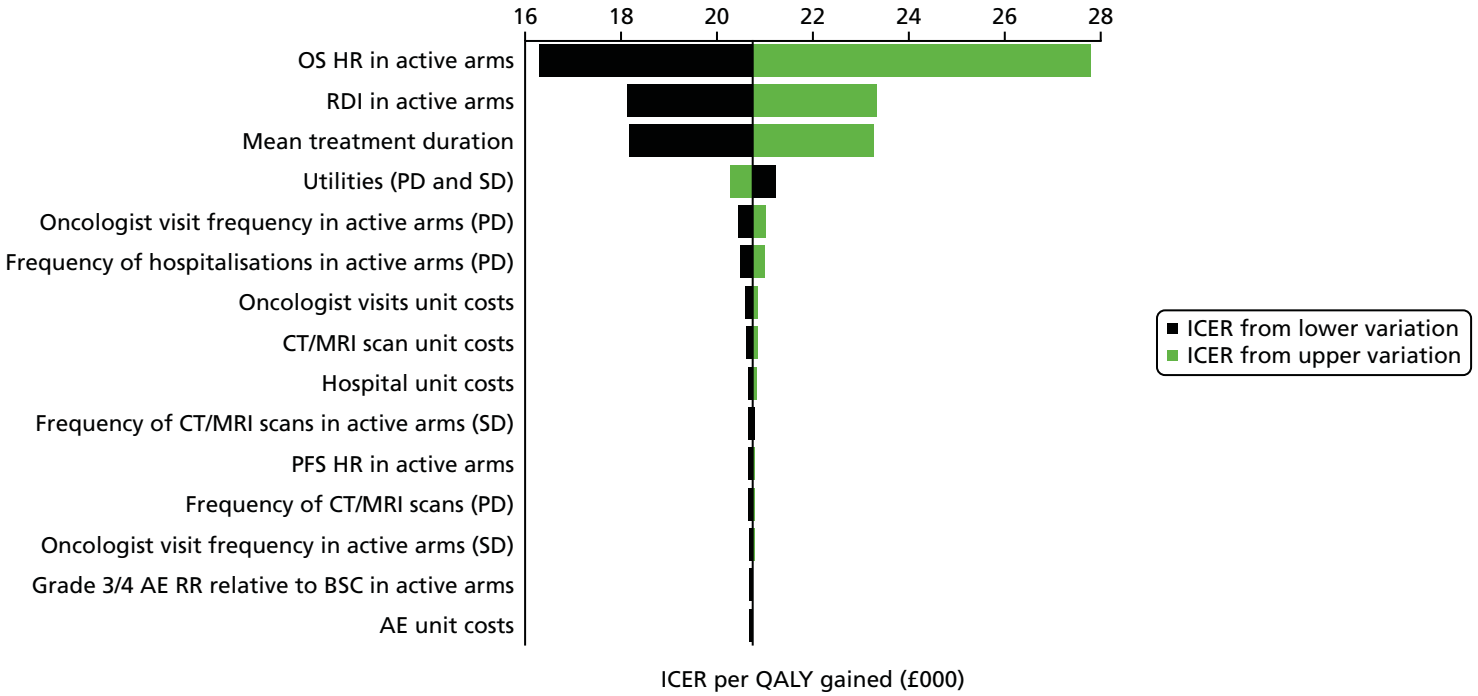

FIGURE 69 Tornado analysis of sunitinib treatment in pNETs. PD, progressive disease; SD, stable disease.

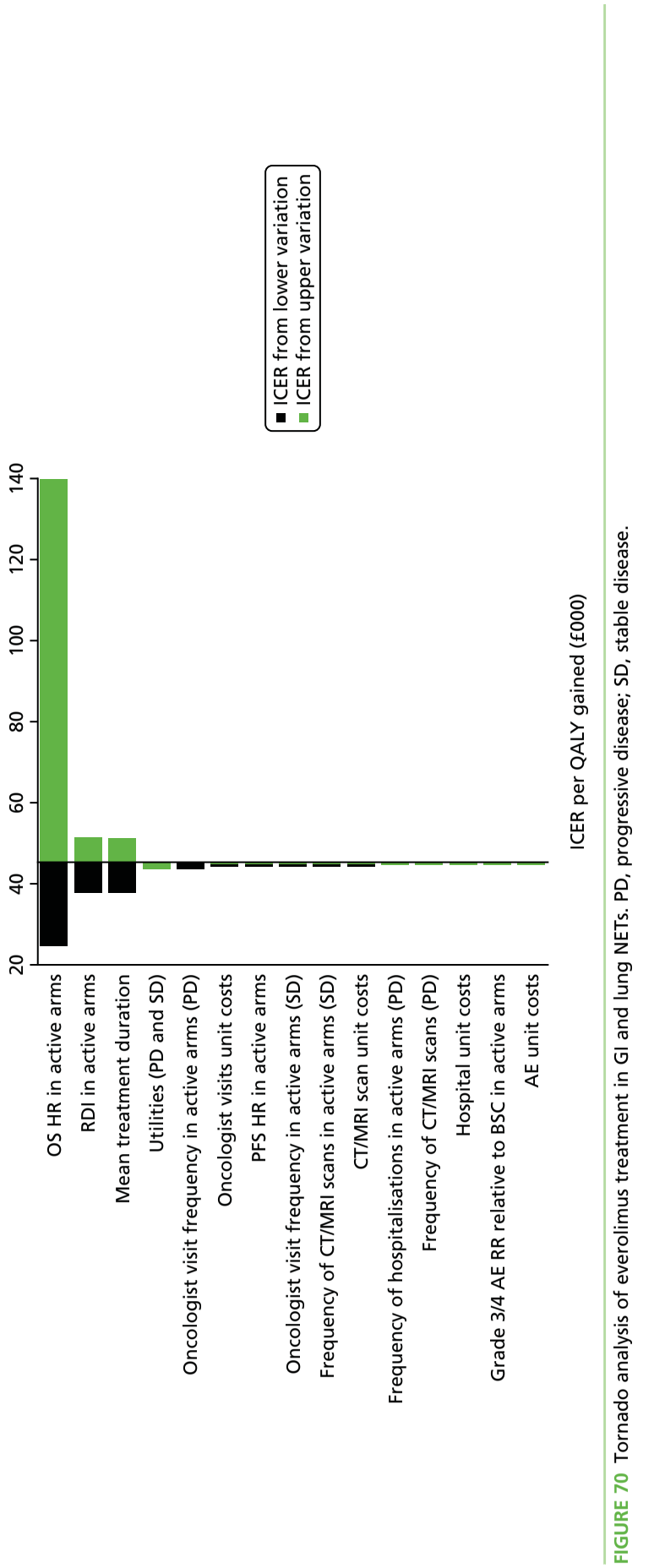

FIGURE 70 Tornado analysis of everolimus treatment in GI and lung NETs. PD, progressive disease; SD, stable disease.

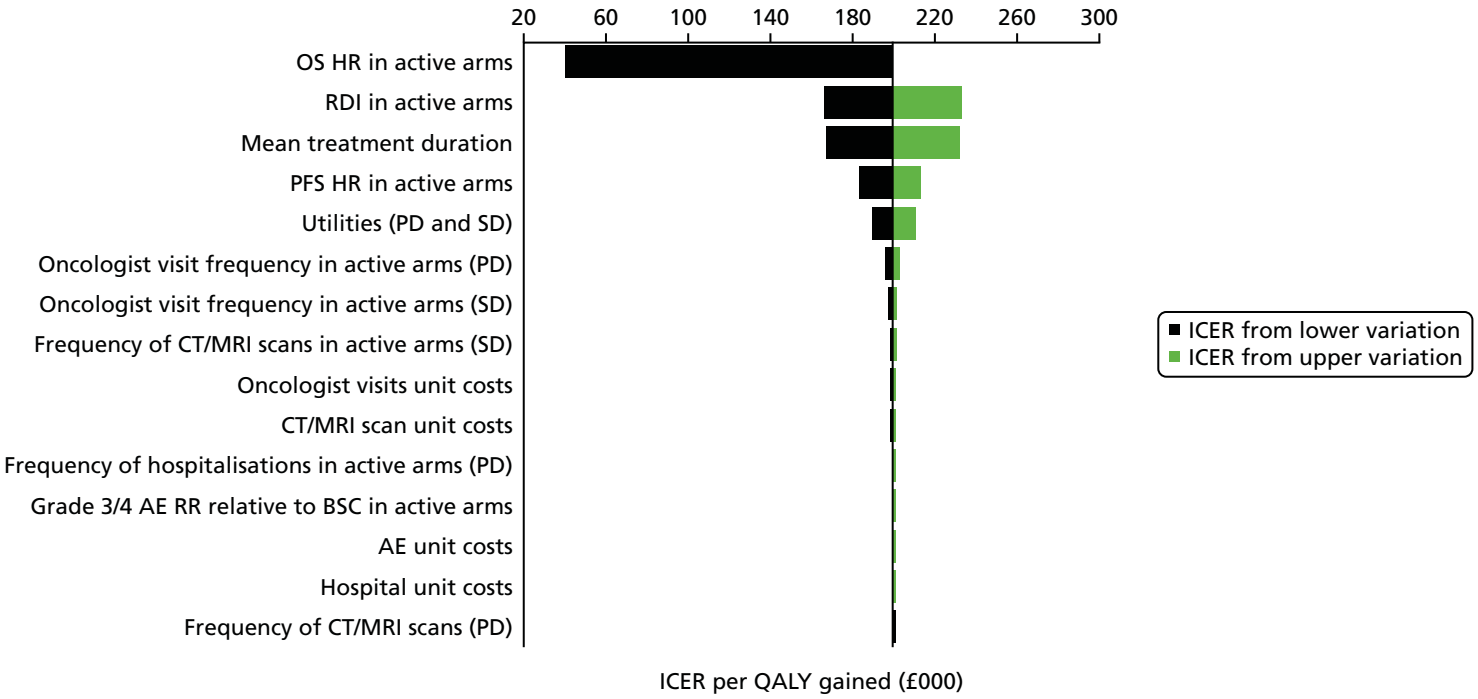

FIGURE 71 Tornado analysis of everolimus treatment in GI (midgut) NETs. PD, progressive disease; SD, stable disease.

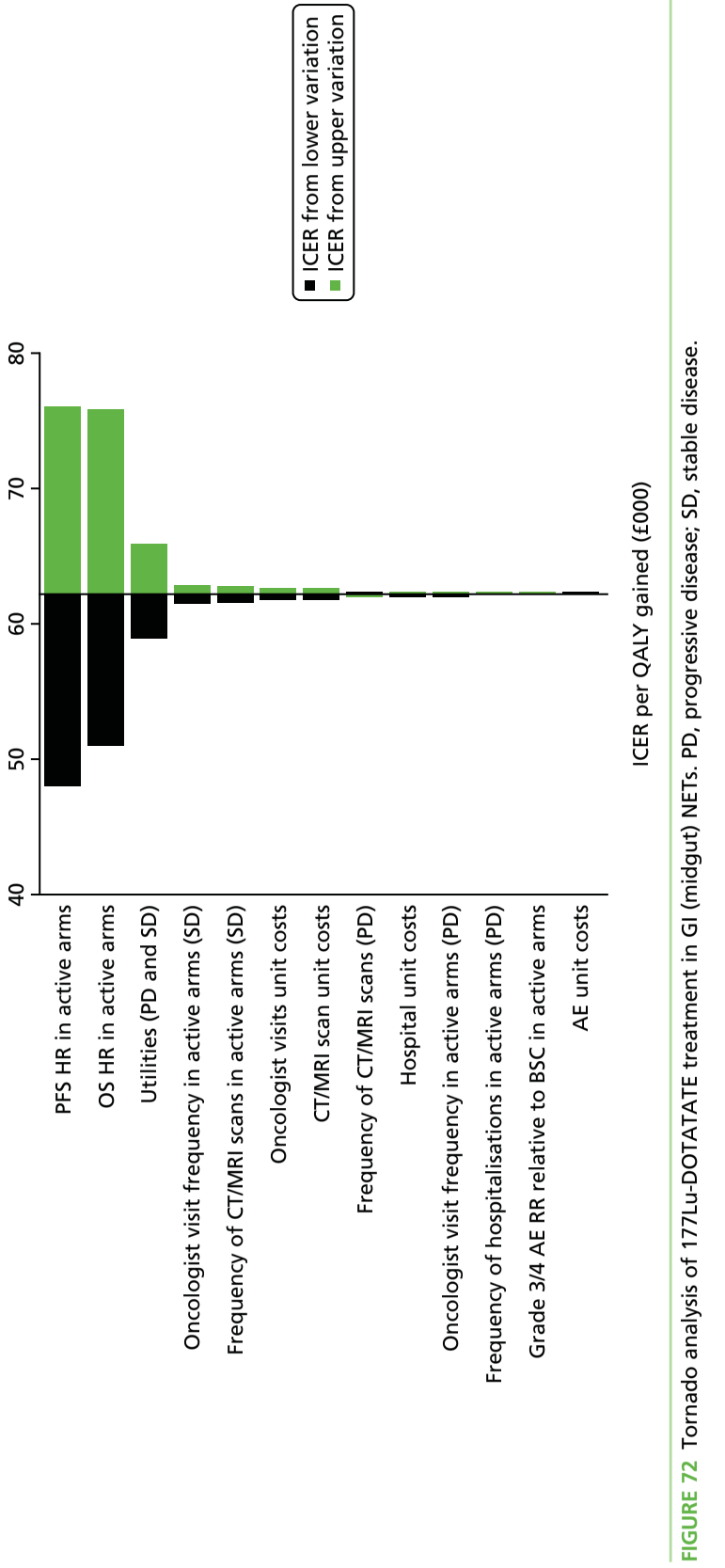

FIGURE 72 Tornado analysis of 177Lu-DOTATATE treatment in GI (midgut) NETs. PD, progressive disease; SD, stable disease.

Appendix 19 Addendum 2

Gastrointestinal neuroendocrine tumours

The comparison between treatment with everolimus and treatment with BSC for the whole GI NETs patient subpopulation in RADIANT-4[35] yielded an ICER of £26,383 (*Table 126*). Treatment of these patients with everolimus results in better survival (8.25 years vs. 5.19 for BSC). Likewise, the treatment costs in the everolimus arm are higher; this is driven by the drug acquisition costs in the preprogression health state (*Table 127*).

It must be noted that these analyses were derived using:

- mean treatment durations from exponential extrapolations of the median everolimus treatment duration (40 weeks) reported for the GI subgroup provided by Novartis on 11 November 2016 in response to a data request by the AG
- exponential curves fitted to individual patient data derived from OS Kaplan–Meier curves and number of patients at risk data provided by Novartis for the GI subgroup of RADIANT-4[35] in response to the assessment report produced by the AG [data cut-off 30 November 2015, resulting in a HR of 0.65 (95% CI 0.37 to 1.13); the GI HR of 0.57 (95% CI 0.28 to 1.16) was provided by Novartis on 11 November 2016 in response to a data request by the AG]
- exponential curves fitted to individual patient data derived from PFS Kaplan–Meier curves for the GI subgroup reported in the ASCO poster by Singh *et al.*[73] (data cut-off date 28 November 2014; from PFS curves for midgut and non-midgut subgroups in RADIANT-4,[35] resulting in a HR of 0.54 (95% CI 0.36 to 0.82); the GI HR of 0.56 (95% CI 0.37 to 0.84) was provided by Novartis on 11 November 2016, in response to a data request by the AG)
- all other parameters were assumed to be the same as for the GI/lung patient population in RADIANT-4.[35]

Alternative set of utility values

With alternative utility values, sunitinib has an ICER of £19,411 in patients with pNETs and everolimus has an ICER of £28,063 in the overall GI NETs population. All other evaluated treatments have ICER values of > £30,000 (*Table 128*).

Analysis limited to progression-free survival

Limiting the analytical horizon to the time of disease progression results in 177Lu-DOTATATE having the lowest ICER (£30,115) of all of the evaluated treatments and tumour locations (*Table 129*).

TABLE 126 Peninsula Technology Assessment Group 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 per QALY) (£)			26,383

Note
Estimated assuming background mortality.

TABLE 127 Peninsula Technology Assessment Group 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	4779	2202	2577
AEs	171	34	137
Total (pre progression)	34,940	2644	32,296
Post-progression			
Drug acquisition	5621	2663	2958
Drug administration	27	10	17
Medical management	11,533	8296	3237
End-of-life care	3377	3692	–315
Total (post progression)	20,558	14,661	5897
Total	55,499	17,305	38,193
ICER (cost per QALY)			26,383

TABLE 128 Peninsula Technology Assessment Group scenario analysis results using 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

TABLE 129 Peninsula Technology Assessment Group scenario analysis results limiting the 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

Background mortality adjustments to overall survival and progression-free survival curves

After background mortality adjustment only sunitinib treatment in pNETs had an ICER of < £30,000. Everolimus treatment in the overall GI NETs population had an ICER of £31,353 (*Table 130*).

First-cycle costs and disease monitoring

When the costs of subsequent treatments are included, sunitinib had an ICER of £20,624 in pNETs and everolimus had an ICER of £27,834 in the overall GI NETs population (*Table 131*).

TABLE 130 Peninsula Technology Assessment Group scenario analysis results adjusting for 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

TABLE 131 Peninsula Technology Assessment Group scenario analysis results adjusting for first-cycle costs of subsequent treatments

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
GI	Everolimus	BSC	27,834

Everolimus had an ICER of £27,669 in the overall GI NETs population when the cost of disease monitoring that Novartis used in its model submitted to NICE was adopted (*Table 132*).

Scenario analysis using a 0% discount rate

When no discounting is applied to costs and benefits the ICER for everolimus in the overall GI NETs population is £20,184 (*Table 133*).

Probabilistic sensitivity analyses

The model parameter data are consistent with everolimus having an ICER that is > £30,000 in the overall GI NETs population (*Figure 73*).

TABLE 132 Peninsula Technology Assessment Group scenario analysis results adjusting for first-cycle costs of 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

TABLE 133 Peninsula Technology Assessment Group 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

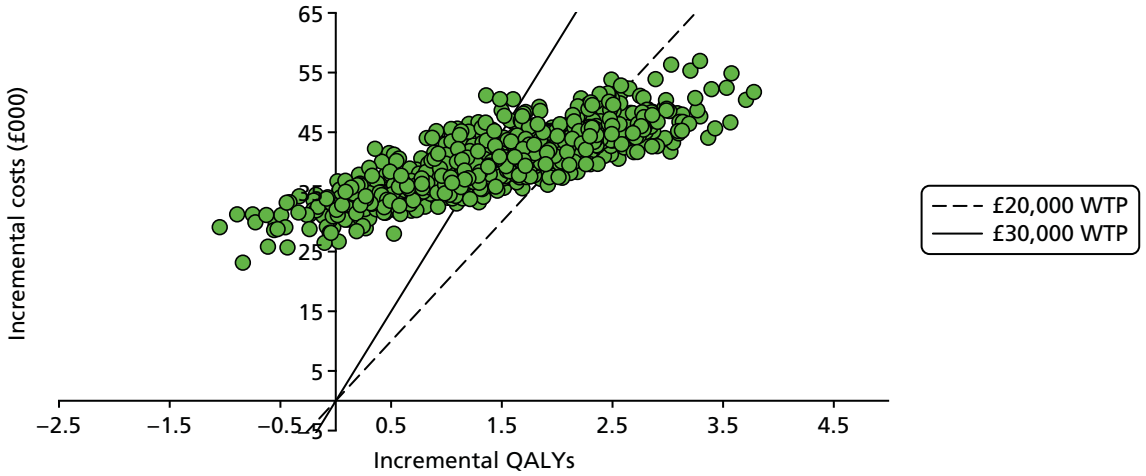

FIGURE 73 Cost-effectiveness plane: treatments for the overall GI NETs population. WTP, willingness to pay.

For GI NETs, the probabilistic mean ICER is £27,582. The probability that everolimus is the most cost-effective treatment for GI NETs at the willingness-to-pay thresholds of £20,000 per QALY and £30,000 per QALY gained is 18.3% and 55.5%, respectively (*Figure 74*).

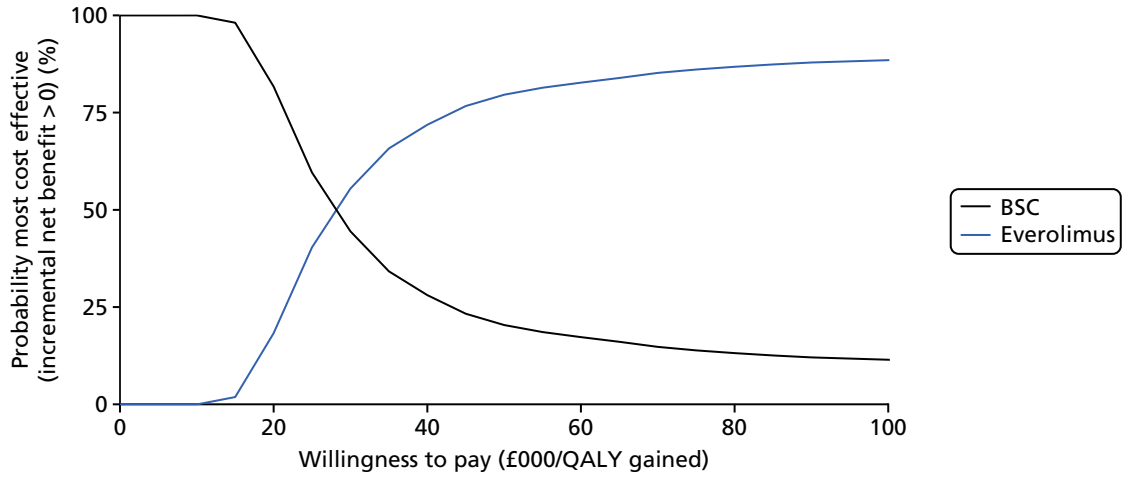

FIGURE 74 Cost-effectiveness acceptability curve: treatments for overall GI NETs.

Appendix 20 Background tables

TABLE 134 Tumour–node–metastasis staging criteria for NETs of the digestive tract and pancreas according to the UICC *TNM Classification of Malignant Tumours*, Seventh Edition[7]

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

SMA, superior mesenteric artery.

TABLE 135 Tumour–node–metastasis staging criteria for NETs of the stomach, appendix and pancreas according to the ENETS grading schemes[5,6]

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

SMA, superior mesenteric artery.

Appendix 21 Adverse events: indirect comparison

TABLE 136 Adverse event data obtained from MAIC by the AG

	RADIANT-3[34] (everolimus, *N* = 204; placebo, *N* = 203)						A6181111[81] (sunitinib, *N* = 83; placebo, *N* = 82)						OR		
	n		%		Odds		*n*		%		Odds				
AE	Everolimus	Placebo	Everolimus	Placebo	Everolimus	Placebo	Sunitinib	Placebo	Sunitinib	Placebo	Sunitinib	Placebo	Everolimus vs. placebo	Sunitinib vs. placebo	Bucher IC
Neutropenia	0	0	0.25	0.25	0.002	0.002	10	0	12.70	0.60	0.145	0.006	1.00	23.61	23.723
Hypertension	0	0	0.25	0.25	0.002	0.002	8	0	10.20	0.60	0.114	0.006	1.00	18.60	18.689
PPE syndrome	0	0	0.25	0.25	0.002	0.002	5	0	6.60	0.60	0.071	0.006	1.00	11.57	11.625
Leukopenia	0	0	0.25	0.25	0.002	0.002	5	0	6.60	0.60	0.071	0.006	1.00	11.57	11.625
Diarrhoea	7	1[a]	3.43	0.49	0.036	0.005	4	1	4.80	1.20	0.051	0.012	7.18	4.10	0.571
Stomatitis	14[b]	0	7.11	0.25	0.077	0.002	3	0	4.20	0.60	0.044	0.006	30.99	7.18	0.232
Thrombocytopenia	8	0	4.17	0.25	0.043	0.002	3	0	4.20	0.60	0.044	0.006	17.61	7.18	0.408
Anaemia	12[c]	0	6.13	0.25	0.065	0.002	0	0	0.60	0.60	0.006	0.006	26.44	0.99	0.037
Hyperglycaemia	11[d]	4[e]	5.39	1.97	0.057	0.02	0	0	0.60	0.60	0.006	0.006	2.84	0.99	0.348
Fatigue	5[f]	1	2.45	0.49	0.025	0.005	4[g]	3[h]	4.80	3.70	0.051	0.038	5.08	1.33	0.263
Infections	5	1	2.45	0.49	0.025	0.005	0	0	0.60	0.60	0.006	0.006	5.08	0.99	0.195
Pneumonitis	5	0	2.70	0.25	0.028	0.002	0	0	0.60	0.60	0.006	0.006	11.22	0.99	0.088
Nausea	5[i]	0	2.70	0.25	0.028	0.002	1[j]	0	1.80	0.60	0.018	0.006	11.22	3.00	0.267
Sum	72	7	35.30	3.45	0.545	0.036	43[k]	4[l]	51.80	4.90	1.075	0.051	15.27	20.96	1.372[m]

IC, indirect comparison; *N*, total number of participants; *n*, number of events; PPE, palmar–plantar erythrodysaesthesia.

a Latest figure is 0.[73]
b Latest figure is 15.[73]
c Latest figure is 10.[73]
d Latest figure is 12.[73]
e Latest figure is 5.[73]
f Latest figure is 3.[73]
g Updated with data from Pfizer submission;[140] Novartis submission used a figure of 0.[33]
h Updated with data from Pfizer submission;[140] Novartis submission used a figure of 0.[33]
i Latest figure is 2.[73]
j Updated with data from Pfizer submission;[140] Novartis submission used a figure of 0.[33]
k Updated with data from Pfizer submission;[140] Novartis submission used a figure of 38.[33]
l Updated with data from Pfizer submission;[140] Novartis submission used a figure of 1.[33]
m Updated with data from Pfizer submission;[140] Novartis submission used a figure of 4.479.[33]

Appendix 22 Mapping FACT-G to the EuroQol-5 Dimensions

Linearised version of the best-fitting mapping algorithm of Longworth *et al.*[134]

The best-fitting mapping algorithm for the FACT-G estimated by Longworth *et al.*[134] (*Table 137*) maps the domain scores of that tool into each dimension of the EQ-5D-3L by fitting a multinomial logit model to response data for each dimension separately.

The EQ-5D index score equation (Dolan[235]) is:

$$\begin{aligned}\text{EQ-5D index} = 1 &- 0.081 \times D1 - 0.069 \times Mob_m - 0.314 \times Mob_s - 0.104 \times Selfcare_m - 0.214 \\ &\times Selfcare_s - 0.036 \times Usualact_m - 0.094 \times Usualact_s - 0.123 \times Pain_m - 0.386 \\ &\times Pain_s - 0.071 \times Anx_m - 0.236 \times Anx_s - 0.269 \times D2,\end{aligned} \tag{6}$$

where $D1 = 1$ if the person had any problems in any dimension and zero otherwise, and $D2 = 1$ if he had any severe problems in any dimension and zero otherwise; Mob is a binary indicator of reporting problems in the mobility dimension; Selfcare is a binary indicator of problems in self-care; Usualact is a binary indicator of problems with usual activities; Pain a binary indicator of problems in pain/discomfort; and Anx is an indicator of problems in anxiety/depression. Separate indicators are used for moderate and severe problems, denoted by the subscripts *m* and *s* respectively.

The mapping algorithm substitutes the binary indicators with the corresponding predicted probabilities of reporting the problem in question. As in the EQ-5D-3L, there are two levels of a problem that a person can choose as the response, the polytomous 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 *D*1) and of reporting any severe problems across all dimensions, these could be obtained by running separate regression analyses for dichotomous variables or by assuming that the probability 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) is simply equal to:

$$\widehat{D2} = 1 - (1 - \widehat{Mob_s}) * (1 - \widehat{Selfcare_s}) * (1 - \widehat{Usualact_s}) * (1 - \widehat{Pain_s}) * (1 - \widehat{Anxiety_s}), \tag{7}$$

where the hat symbols denote predicted probabilities of reporting the problem described by the respective variable. The value of $\widehat{D1}$ is similarly obtained, except that the expressions within brackets in *Equation 7* now include the predicted probability of reporting moderate problems:

$$\begin{aligned}\widehat{D1} = 1 &- (1 - \widehat{Mob_s} - \widehat{Mob_m}) * (1 - \widehat{Selfcare_s} - \widehat{Selfcare_m}) * (1 - \widehat{Usualact_s} - \widehat{Usualact_m}) \\ &* (1 - \widehat{Pain_s} - Pain_m) * (1 - \widehat{Anxiety_s} - \widehat{Anxiety_m}).\end{aligned} \tag{8}$$

The Longworth *et al.*[134] response mapping algorithm (p. 220) is then used to estimate the predicted probabilities of D1 and D2 and the 10 probabilities of reporting problem levels for the EQ-5D dimensions on the right-hand side of *Equations 7* and *8*. In the case of $\widehat{Mob_m}$ this is obtained by:

$$\begin{aligned}&\widehat{Mob_{mj}} = P_{m2j}(PW_j, EW_j, FW_j) \equiv \\ &P(D_{mj} = 2 | PW_j, EW_j, FW_j) \\ &\quad = \frac{\exp(\alpha_2 + \beta_{m2} PW_j + \gamma_{m2} EW_j + \delta_{m2} FW_j)}{1 + \exp(\alpha_2 + \beta_{m2} PW_j + \gamma_{m2} EW_j + \delta_{m2} FW_j) + \exp(\alpha_3 + \beta_{m3} PW_j + \gamma_{m3} EW_j + \delta_{m3} FW_j)},\end{aligned} \tag{9}$$

TABLE 137 The best-fitting mapping algorithm of Longworth *et al.*[134]

	Mobility		Self-care		Usual activities		Pain		Anxiety/depression	
Summary statistics and model performance test	Some problems	Extreme problems	Some problems	Extreme problems	Some problems	Extreme problems	Some problems	Extreme problems	Some problems	Extreme problems
Physical	–0.111 (0.023)***	NA	–0.100 (0.024)***	–0.244 (–2.191)	–0.237 (0.044)***	–0.285 (0.056)***	–0.206 (0.030)***	–0.319 (0.051)***		
Emotional									–0.331 (0.036)***	–0.607 –5.147
Functional	–0.074 (0.020)***	NA	–0.104 (0.027)***	–0.307 (–6.663)	–0.124 (0.030)***	–0.266 (0.053)***	–0.057 (0.023)*	0.01 (0.053)	–0.047 (0.021)*	–0.197 (1.465)
Constant	3.089 (0.418)***	NA	1.633 (0.427)***	2.017 (60.731)	7.737 (0.895)***	8.239 (1.210)***	5.499 (0.574)***	3.51 (1.045)**	6.773 (0.660)***	8.839 (47.729)
Log-likelihood	–310.22		–189.70		–338.3		–346.92		–302.08	
Pseudo R^2	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.
NA, not applicable as there is no one who had extreme problems with mobility.
Note
Values in parentheses are the standard errors of regression coefficients.

where P_{m2j} is the probability of a person *j* reporting 'moderate problems' for the EQ-5D dimension *m* (mobility) and the Greek symbols represent coefficients estimated by Longworth *et al.*[134] 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 *Equations 7* and *8* 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 *Equations 7* and *8*, which are then used to derive EQ-5D utilities using *Equation 6*, are obtained by first substituting the FACT-G scores for each person in *Equation 9* 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 map FACT-G data into EQ-5D utilities using *Equation 6*.

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 *Equation 9* and the other nine multinomial equations for obtaining the required predicted response probabilities because their non-linear form means that the resulting predictions will have systematic errors. To solve this issue it is proposed that each of *Equation 9* and the other nine 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 RADIANT-4,[35] Thus, the linearised predictor of the probability of response in *Equation 9* is:

$$\widehat{Mob}_{mJ} \approx P_{m2}(PW_o, EW_o, FW_o) + \frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} * (PW - PW_o) \quad (10)$$
$$+ \frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} * (EW - EW_o) + \frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} * (FW - FW_o),$$

where $P_{m2}(PW_o,EW_o,FW_o)$ represents *Equation 9* evaluated at the midpoint value between the mean scores of the FACT-G domains *PW*, *EW* and *FW* for observations in the stable disease and disease progression states. (Here, the issue of missing data or information lost to follow-up is ignored but is a pertinent issue to address in further research). The derivatives of the P_{m2} function are also evaluated at the midpoint and have the following expressions:

$$\frac{\partial P_{m2}(PW_o, EW_o, FW_o)}{\partial PW} = \beta_{m2} * P_{m2}\left(1 - P_{m2}\left(P_{m2} + \frac{\beta_{m3}}{\beta_{m2}} * P_{m3}\right)\right) \quad (11)$$

Similar expressions are used for the other derivatives in *Equation 10* and in the corresponding equations for other EQ-5D dimensions and levels. Note that *Equation 10* and the corresponding equations for other dimensions and levels are linear in the FACT-G domain 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 $\overline{PW}$, $\overline{EW}$ *and* $\overline{FW}$.

Finally, substituting expressions such as *Equation 10* (after substituting *Equation 11* into *Equation 10*) for all arguments in *Equation 6* 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 for $\overline{PW}$, $\overline{EW}$ *and* $\overline{FW}$. for the two phases, reported in Singh *et al.*,[73] to reproduce their reported mapped utilities, which used the original best-fitting response mapping non-linear Longworth *et al.*[134] algorithm with unpublished individual patient data. *Table 138* presents the two sets of these estimates.

TABLE 138 Comparison of utilities obtained from the mapping of FACT-G mean domain scores using the linearised best-fitting algorithm of Longworth *et al.*[134] and the utilities obtained by Yao *et al.*[35] based on mapping individual patient data using the same algorithm

		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		
	Statistics	Pre progression	Post progression	Pre progression	Post progression	
Young mapping algorithm ($n = 1499$)	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	
	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	
	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed	
	Confidential information has been removed	Confidential information has been removed		Confidential information has been removed		Confidential information has been removed

Confidential information has been removed.

Appendix 23 Comparison of the Assessment Group results with the company results

Our model results can be compared with those of the companies in three areas:

1. everolimus, sunitinib and BSC in pNETs
2. everolimus and BSC in GI and lung NETs
3. everolimus, 177Lu-DOTATATE and BSC in GI (midgut) NETs.

In all analyses, drug list prices, not PAS prices, were assumed. Life-years were not discounted.

Everolimus, sunitinib and best supportive care in pancreatic neuroendocrine tumours

A compilatation of the main results for pNETs is presented in *Table 139*.

- *Life-years*. The estimation of expected life-years in our model and the models of Novartis[33] and AAA[31] 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 vs. 4.62 years). AAA's OS estimate was significantly larger for sunitinib (8.19 years for sunitinib and 4.62 years for everolimus). The differences arise because of the adoption of three different methodological approaches, including differences in the parametric distribution selected for PFS/OS extrapolation. AAA did not adjust for treatment crossover in its MTC; Novartis used an assumption of no difference in OS from the outset; and we used publicly available survival curves with statistical adjustment for treatment crossover for each trial in our MTC.
- *QALYs*. After adjusting for quality of life, our own and Novartis's QALY estimates for everolimus remained similar [(confidential information has been removed) and 2.73], but AAA's estimate of time with stable disease was higher, resulting in a higher estimate of total QALYs (3.25). Our estimate of QALYs with sunitinib was higher than that for everolimus, because of longer PFS and OS. Novartis estimated fewer QALYs with sunitinib than everolimus in spite of equal PFS and OS, because of differences in disutility from SAEs. From a MTC of the most up-to-date evidence submitted to NICE (see *Appendix 21*), 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 its inclusion of other drug treatments under disease monitoring and management. The same methodological difference is behind the differences in component costing 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 overcosting of the acquisition of the active drug, because of the company's assumption that treatment would continue until disease progression.
- *Incremental analysis compared with BSC*. Given that neither Novartis nor AAA included a BSC strategy, it is not possible to compare our ICERs for everolimus compared with BSC and sunitinib compared with BSC with company estimates.

TABLE 139 Peninsula Technology Assessment Group results vs. the company base-case results in pNETs

	Everolimus			Sunitinib			BSC
Outcome	PenTAG	Novartis[33]	AAA[31]	PenTAG	Novartis[33]	AAA[31]	PenTAG
Pre progression							
Drug acquisition (£)[a]	25,547	21,782	Confidential information has been removed	22,216	21,994	59,557	2003
Drug administration (£)	1104	[b]	Confidential information has been removed	1308	[b]	0	510
Disease monitoring and management (£)	776	5343	Confidential information has been removed	952	5242	2290	184
SAE management (£)	132	678	Confidential information has been removed	89	2101	91	15
Post progression							
Drug acquisition (£)	6363	2216	Confidential information has been removed	8368	2216	56,667	4939
Drug administration (£)	1706	[b]	Confidential information has been removed	2187	[b]	965	1422
Disease monitoring and management (£)	3798	7206	Confidential information has been removed	5032	7206	5138	3447
SAE management (£)	0	0	Confidential information has been removed	0	0	205	0
Death							
End-of-life care (£)	3747	3836	Confidential information has been removed	3565	3836	0	3889
Total costs pre-progression (£)	27,559	27,802	Confidential information has been removed	24,566	29,337	61,939	2712
Total costs post-progression (£)	11,867	9422	Confidential information has been removed	15,587	9422	62,976	9808
Total costs (£)	43,173	41,061	Confidential information has been removed	43,718	42,596	124,914	16,409

TABLE 139 Peninsula Technology Assessment Group results vs. the company base-case results in pNETs (*continued*)

	Everolimus			Sunitinib			BSC
Outcome	PenTAG	Novartis[33]	AAA[31]	PenTAG	Novartis[33]	AAA[31]	PenTAG
Life-years pre progression[c]	1.28	1.18	Confidential information has been removed	1.60	1.18	2.22	0.57
Life-years post progression[c]	3.41	3.44	Confidential information has been removed	4.79	3.44	5.98	2.89
Total life-years[c]	4.69	4.62	Confidential information has been removed	6.39	4.62	8.19	3.46
QALYs pre progression	Confidential information has been removed	0.89	Confidential information has been removed	Confidential information has been removed	0.87	1.60	0.38
QALYs post progression	Confidential information has been removed	1.84	Confidential information has been removed	Confidential information has been removed	1.84	3.74	1.53
Total QALYs	Confidential information has been removed	2.73	Confidential information has been removed	Confidential information has been removed	2.71	5.34	1.91

a 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.
b Drug administration costs were not presented separately but were included within the cost of drug acquisition.
c Undiscounted life-years.

Everolimus and best supportive care in gastrointestinal and lung neuroendocrine tumours

Overall, there was consistency between the cost-effectiveness results produced by us and those produced by Novartis. A compilation of the main results is presented in *Tables 139* and *140*.

- *Life-years*. For people receiving BSC our own model and Novartis's model[33] found the number of expected life-years to be similar, at 4.82 and 4.77, respectively, with 0.83 and 0.87 years, respectively, of stable disease before progression. For people receiving everolimus we estimated life expectancy as 6.21 years, whereas Novartis estimated a value of 5.79 and we estimated a lower proportion with stable disease (23% vs. 27%). This was caused by our higher estimate of OS and lower estimate of PFS from our parametric extrapolation.
- *QALYs*. For people receiving BSC we estimated a lower quality of life pre and post progression than Novartis, so, despite similar PFS and OS, slightly more QALYs for BSC were estimated by Novartis than by us (3.51 vs. 3.05). Similarly, for people receiving everolimus we found that our higher estimates of PFS and OS were more heavily adjusted for loss of quality of life than those of Novartis, so that our estimate of total QALYs for everolimus was lower than Novartis's (3.74 vs. 4.28). This is because, although Novartis used the same utility values for stable disease and disease progression across arms, we adopted treatment arm-specific utility estimates for stable disease, with the utility estimate likely to be lower for everolimus than for BSC.

- *Costs*. Our estimate of the cost of BSC was significantly less than that of Novartis (£16,526 vs. £25,817 per person) because the estimate of the cost of disease monitoring and management in the Novartis model was twice as high our estimate and also partly because we modelled fewer physician consultations. Our estimate of the cost of everolimus was also lower (£47,334 vs. £59,720). This was again because of our lower rate of resource utilisation for disease monitoring and management.
- *Incremental analysis*. We estimated that the ICER for everolimus compared with BSC was £44,557 per QALY gained. Novartis found an ICER of £43,642 per QALY gained. We estimated that BSC was £30,809 less costly and provided 0.69 fewer QALYs. Novartis found that BSC was £33,903 less costly and provided 0.78 fewer QALYs.

TABLE 140 Peninsula Technology Assessment Group vs. Novartis's base-case findings in GI and lung NETs

	Everolimus		BSC	
Outcome	PenTAG	Novartis	PenTAG	Novartis
Pre progression				
Drug acquisition (£)[a]	26,054	26,881	376	0
Drug administration (£)	147	[b]	2	[b]
Disease monitoring and management (£)	4141	8583	2038	2799
SAE management (£)	171	601	34	87
Post progression				
Drug acquisition (£)	4331	2927	2511	3312
Drug administration (£)	21	[b]	10	[b]
Disease monitoring and management (£)	8886	17,205	7822	15,918
SAE management (£)	0	0	0	0
Death				
End-of-life care (£)	3583	3524	3732	3702
Total costs pre progression (£)	30,513	36,064	2450	2886
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[c]	1.42	1.68	0.83	0.89
Life-years post progression[c]	4.79	5.51	3.99	4.90
Total life-years[c]	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

a 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.
b Drug administration costs were not presented separately but were included with the cost of drug acquisition.
c Undiscounted life-years.

TABLE 141 Incremental analysis of everolimus vs. BSC in GI and lung NETs

Outcome	PenTAG	Novartis
Pre progression		
Drug acquisition (£)[a]	25,679	26,881
Drug administration (£)	144	[b]
Disease monitoring and management (£)	2102	5784
SAE management (£)	137	513
Post progression		
Drug acquisition (£)	1820	–385
Drug administration (£)	11	[b]
Disease monitoring and management (£)	1064	1287
SAE management (£)	0	0
Death		
End-of-life care (£)	–149	–178
Total costs pre progression (£)	28,063	33,178
Total costs post progression (£)	2895	902
Total costs (£)	30,809	33,903
Life-years pre progression[c]	0.59	0.78
Life-years post progression[c]	0.80	0.61
Total life-years[c]	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 per life-year gained (£)	22,213	33,298
Cost per QALY gained (£)	44,557	43,642

a 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.
b Drug administration costs were not presented separately but were included with the cost of drug acquisition.
c Undiscounted life-years.

Everolimus, 177Lu-DOTATATE and best supportive care in gastrointestinal (midgut) neuroendocrine tumours

For GI (midgut) NETs we modelled everolimus, 177Lu-DOTATATE and BSC, whereas AAA[31] modelled only everolimus and 177Lu-DOTATATE. The main results are provided in *Table 142*.

TABLE 142 Peninsula Technology Assessment Group vs. AAA's base-case findings in GI (midgut) NETs

	Everolimus		177Lu-DOTATATE		BSC
	PenTAG	AAA	PenTAG	AAA	PenTAG
Pre progression					
Drug acquisition (£)	31,786	Confidential information has been removed	59,187	59,633	633
Drug administration (£)	178	Confidential information has been removed	3482	1820	4
Disease monitoring and management (£)	5904	Confidential information has been removed	14,051	2702	3437
SAE management (£)	287	Confidential information has been removed	85	304	105
Post progression					
Drug acquisition (£)	3349	Confidential information has been removed	1093	21,235	2117
Drug administration (£)	16	Confidential information has been removed	5	723	8
Disease monitoring and management (£)	6871	Confidential information has been removed	2242	1925	6595
SAE management (£)	0	Confidential information has been removed	0	108	0
Death					
End-of-life care (£)	3627	Confidential information has been removed	3522	–	3728
Total costs pre progression (£)	38,155	Confidential information has been removed	76,805	64,459	4180
Total costs post progression (£)	13,863	Confidential information has been removed	6862	23,991	12,448
Total costs (£)	52,018	Confidential information has been removed	83,667	88,450	16,628
Life-years pre progression[a]	2.07	Confidential information has been removed	5.41	2.66	1.43
Life-years post progression[a]	3.68	Confidential information has been removed	1.25	2.13	3.46
Total life-years[a]	5.75	Confidential information has been removed	6.66	4.79	4.90
QALYs pre progression	1.48	Confidential information has been removed	3.51	1.97	1.10
QALYs post progression	2.09	Confidential information has been removed	0.68	1.31	2.01
Total QALYs	3.57	Confidential information has been removed	4.19	3.29	3.11

a Undiscounted.

Our estimates of survival and costs for people who were treated with everolimus were significantly different from those reported by AAA. In contrast, there was some consistency in the cost results for the 177Lu-DOTATATE strategy produced by the AG and AAA.

- *Life-years*. AAA's[31] estimates of OS for everolimus and 177-Lu-DOTATATE were substantially lower than our own. For 177Lu-DOTATATE the difference in life expectancy (4.79 life-years in AAA's analysis vs. 6.66 life-years in the AG analysis) arose because of the different methods used for OS extrapolation: 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 its 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 model was the model with the best goodness-of-fit statistics. The differences in survival time were most pronounced in the case of life-years post progression following everolimus, with AAA including lung and other non-midgut NETs patients from RADIANT-4[35] in its calculation, and a baseline risk of progression and death for both everolimus and 177Lu-DOATATE equal to that for people treated with 60 mg of octreotide; instead, we used the GI (midgut) subgroup of RADIANT-4[35] as the reference patient population, to which patients treated with 177Lu-DOTATATE were matched by a Bucher-type indirect comparison adjustment method.
- *QALYs*. Our estimates of QALYs for everolimus and 177Lu-DOTATATE were also higher than AAA's estimates (3.57 vs. 1.87 for everolimus; 4.19 vs. 3.29 for 177Lu-DOTATATE), although they were reduced by our lower estimate of utility for both pre and post progression. Therefore, the difference in total QALYs between the models was driven by the difference in life-year estimates. We found that BSC produced fewer QALYs (3.11) than the active treatments.
- *Costs*. Similar to AAA, we found that totals costs for 177Lu-DOTATATE were higher than those for everolimus. 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 costs was for drug acquisition; this is because AAA costed everolimus treatment until progression and did not adjust for RDI. In RADIANT-4[35] the median time to progression was 11 months, compared with a median time on treatment of 9.3 months, and the RDI was 79.4%. Comparing 177Lu-DOTATATE across models there was agreement on the total cost but notable differences in the costs of disease monitoring and management in stable disease, drug acquisition in progressive disease and end-of-life care. This is because AAA did not include the cost of hospital consultations, assumed that 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 overestimates were counterbalancing.
- *Incremental analysis*. As AAA did not include a BSC strategy, there were no company figures with which to compare our estimated additional cost, QALY gains and ICER for 177Lu-DOTATATE versus BSC.

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