Public observer slides

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

1st Appraisal Committee meeting

Cost Effectiveness

Committee D

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Key cost effectiveness issues

- Lack of utility data for everolimus from RADIANT-3 in the P-NETs population
- Assumption of equal efficacy between everolimus and sunitinib
- Limited comparability between RADIANT-4 and NETTER-1 patient populations in GI-NETs population
- The most plausible results for P-NETs, GI and Lung NETs, GI only, Lung only and Midgut NETS?
- End of life

Company models

Novartis

- 3-state model – stable disease, disease progression, death
- P-NETs (everolimus with BSC vs sunitinib with BSC)
  - Equal efficacy (PFS and OS) assumed for everolimus and sunitinib (based on ITC results incorporating RADIANT-3 and A6181111 data)
  - Everolimus dominated sunitinib at list prices for both
    - QALY differences in stable disease driven by differences in toxicity and adverse events
- GI and Lungs (everolimus with BSC vs BSC alone)
  - Data from RADIANT-4 trial
  - ICER of £43,642 for everolimus (at list price) vs BSC

Company models

AAA

- P- NETs (everolimus, 177Lu-DOTATATE, sunitinib)
  - MTC using data from NETTER-1, RADIANT-3, A618111
  - 177Lu-DOTATATE dominated sunitinib
  - ICER of £9,847 for 177Lu-DOTATATE vs everolimus
- GI-NETs (everolimus vs 177Lu -DOTATATE)
  - MTC: Octreotide 60mg assumed equivalent to placebo plus octreotide 30mg
  - ICER of £19,816 for 177Lu-DOTATATE vs everolimus

Pfizer

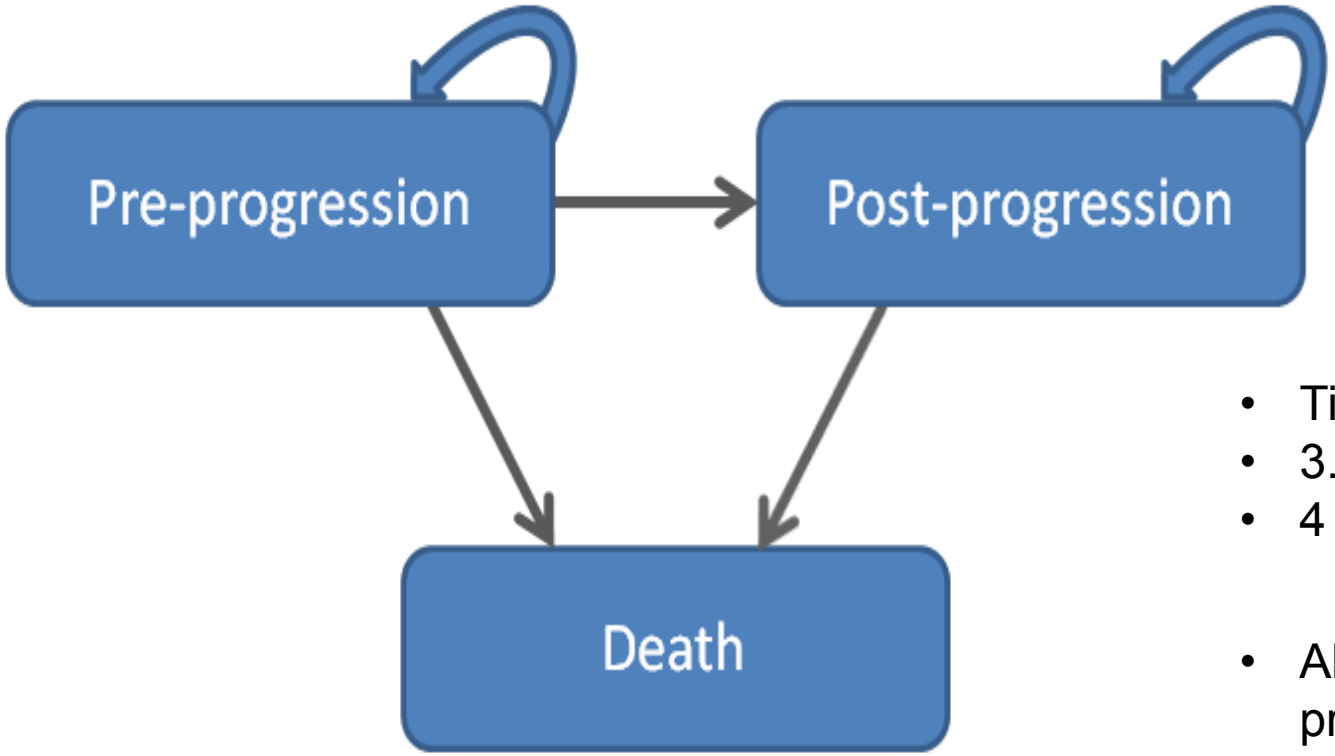
- No model submitted

AG's critique of company models

Novartis P-NET model	Novartis GI/Lung model	AAA P-NET/GI NET model
Did not meet NICE reference case, excluded BSC as a comparator	Major limitation is omission of 177Lu-DOTATATE as a relevant active comparator	P-NETs not included in NETTER-1
Bucher ITC used outdated evidence	Relies on quality of RADIANT-4	No comparison made to BSC
Effectiveness and safety evidence was combined in the model inadequately	Not clear how robust the estimated costs of subsequent treatment are	Uncertainty that 60mg octreotide is equivalent to placebo and placebo+ octreotide 30mg
Equal OS/PFS efficacy based on wide CI	No adjustment despite 10 people crossing over	RADIANT-2 incorrectly included in the GI-NETs
HRQOL based on vignettes	Lack of resource data	Usage of 177Lu underestimated
Assumption of same treatment duration incorrect	Estimation of the costs of subsequent treatments were not correct	No consideration of treatment switching in RADIANT-2, 3 or A6181111
High levels of uncertainty related to clinical effectiveness	Some data well-reported (AE's/treatment duration)	Everolimus and sunitinib were given until progression (incorrect)

AG model structure

Structure of PenTAG cost-effectiveness model



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

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

Source: Assessment report, figure 40, page 223

AG model description

	Model	AG notes
Structure	• Patients receive active treatment until disease progression/earlier treatment discontinuation (SAE) as observed in the RCTs • Patients treated with BSC after progression	-
Population	• Progressed unresectable or metastatic neuroendocrine tumours from 5 different patient populations according to tumour location: • P-NETs/GI+Lung NETs/GI only NETs/ Lung only NETs/GI (midgut) NETs	• Choice determined by the available clinical effectiveness RCT data • No subgroups considered as no evidence could be found
Interventions /comparators	• Everolimus • Sunitinib • 177Lu-DOTATATE • BSC	• All included in the scope • Chemotherapy/ interferon alpha: No evidence found – not included
Source: Assessment report, section 7.1 – 7.4, pages 220 - 225		

AG model comparisons and sources of data

Tumour location	Treatment	Treatment or Comparator	Type of data	Source of data
P-NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-3
	Everolimus	Sunitinib	Indirect comparison	RADIANT-3, A6181111
	Sunitinib	BSC	Head-to-head RCT	A6181111
GI and lung NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4
Lung NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4
GI NETs	Everolimus	BSC	Head-to-head RCT	RADIANT-4
GI (midgut) NETs	Everolimus	177Lu-DOTATATE	Indirect comparison	RADIANT-4, NETTER-1
	177Lu-DOTATATE	BSC	Head-to-head RCT	NETTER-1

Source: Assessment report, table 116, page 225

Model parameters

	Data source and estimate
Mean age	• PenTAG assumed that all patients are 60 at start of treatment • This was the average age of the trials identified
Background mortality	• Not modelled in the base case but scenario analyses are provided • PFS/OS curves were expected to account for it • Background mortality rises as the cohort ages • Novartis: no inclusion of background mortality

Adverse events	• P-NETs
	  • Estimated from AG ITC using related Grade 3/4 AEs of ≥2% incidence in any active treatment arm
	• GI/Lung NETs
	  • Novartis model probabilities used (as they were taken from individual patient level data)
	• GI (midgut) NETs
	  • Both arms - grade 3/4 AEs rates for the everolimus and placebo arm reported in a ASCO conference poster by RADIANT-4 investigators

Source: Assessment report, sections 7.1.5.1, 7.1.5.2 and 7.1.5.3.3

Base case survival curves – P-NETS

Baseline trial: RADIANT-3

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

Source: Assessment report, section 7.1.5.3

Base case survival curves – GI and Lung

Baseline trial: RADIANT-4

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

Base case survival curves – GI only

Baseline trial: RADIANT-4

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

Source: Assessment report, section 7.1.5.3

HRQoL

Utilities in pancreatic NETs - Interventions: Everolimus, Sunitinib; Comparator: BSC only

	Pre-progression			Post-progression		
Treatment	Everolimus + BSC	Sunitinib + BSC	Placebo	Everolimus	Sunitinib	Placebo
N	N/A	86	85	N/A	86	85
Mean utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source	Assumed equal to Sunitinib +BSC	Analysis by the AG from IPD from A6181111	Analysis by the AG from IPD from A6181111	Assumed same as sunitinib +BSC	Analysis by the AG from IPD from A6181111	Analysis by the AG from IPD from A6181111

Source: Assessment report, table 126, page 256

HRQoL (2)

Utilities in gastrointestinal NETs - Interventions: Everolimus, 177Lu-DOTATATE						
	Pre-progression			Post-progression		
Treatment	Everolimus + BSC	Placebo + BSC	177Lu-DOTATATE	Everolimus + BSC	Placebo + BSC	177Lu-DOTATATE
N	837	281	227	238	143	111
Mean utility	**0.767**	**0.807**	**0.77**	**0.725**	**0.725**	**0.725**
Source	Treatment arm analysis using IPD from RADIANT-4 (Novartis, 2016)		Erasmus study (AAA Ltd., 2016)	Pooled analysis of individual patient data from RADIANT-4 (Novartis, 2016)		Assumed the same as everolimus (RADIANT-4)

Resources and costs

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

AG's base case results (using list prices)
P-NETs & GI+Lung NETs

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

Source: Assessment report, table 149, page 269

GI+Lung NETs	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	6.21	4.82	1.39
QALYs (mean, discounted)	3.74	3.05	0.69
Total costs (mean, discounted)	£47,334	£16,526	£30,809
ICER (Cost / QALY)			**£44,557**

Source: Assessment report, table 151, page 271

- Probabilistic ICER's were similar to the base case results

AG's base case results (using list prices)
GI only and Lung only NETs

GI only NETs	Everolimus	BSC	Everolimus vs. BSC
Life years (mean, undiscounted)	7.50	7.05	0.44
QALYs (mean, discounted)	4.37	4.19	0.17
Total costs (mean, discounted)	£55,842	£21,119	£34,723
ICER (Cost / QALY)			**£199,233**

Source: Assessment report, table 151, page 271

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

Source: Addendum to Assessment report, table 151

- Probabilistic ICER's were similar to the base case results

AG's base case results – GI (midgut) NETs

	Everolimus	177Lu-DOTATATE	BSC	Everolimus vs. BSC	177Lu-DOTATATE vs. everolimus	177Lu-DOTATATE vs. BSC
Life years (mean, un-discounted)	5.75	6.66	4.90	0.85	0.91	1.76
QALYs (mean, discounted)	3.57	4.19	3.11	0.45	0.63	1.08
Total costs (mean, discounted)	£52,018	£83,667	£16,628	£35,390	£31,649	£67,039
ICER (Cost /QALY)				**£78,330**	**£50,499**	**£62,158**

Source: Assessment report, table 155, page 272

Scenario analyses (1)

PFS data using local investigator assessment (not central independent review)	• minor impact on the ICER in both P-NETs and GI+Lung NETs
OS data from ITT analysis (not RPSFT-adjusted)	• ICER's 3 times higher than the base case for sunitinib vs placebo (P-NETs)
Alternative set of utility values (p.275 of AG report)	• small ICER reductions in P-NETs for everolimus and sunitinib when compared with BSC • small ICER increases in GI/GI and Lung • 177-Lu DOTATATE ICER decreased by 7% when compared with BSC
Alternative set of OS and PFS curves	• minimal impact on ICER for sunitinib vs BSC in P-NETs • 33% ICER reduction for everolimus vs BSC • everolimus in GI/NETs became less effective than BSC

Scenario analyses (2)

Background mortality adjustments - OS/PFS curves	• limited effect on results in P-NETs and GI+Lung NETs • ICER for everolimus, from £200,000 to £78,330 in GI-NETs • Adjustment made to 177Lu-DOTATATE as in the base case this was not applied due to immature data • reduces the ICER from £62,158 to £43,348
1st cycle costs of subsequent treatment	• minor impact for all tumour locations
0% discount - costs/benefits	• minor impact for all tumour locations
Analysis limited to PFS	• increase of sunitinib ICER by 75% in P-NETs • increase in everolimus ICER by 26% in P-NETs • higher ICER in GI compared to GI+Lung (suggesting not as cost effective) • 177Lu-DOTATATE ICER is less than half that of everolimus (suggesting PRRT may have better long term outcomes)

Deterministic (one-way) sensitivity analyses

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

- Parameters varied by 20%, except for utility differences between stable disease and progressive disease, which were varied by 40%
- The parameters with the most impact are reported in the table above
- Changes to other parameters did not have as much impact as those above

End of life – P-NETs

Criterion	AG comments/conclusions
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	RADIANT-3 Population Placebo+BSC – mean 18.3 months (95% CI 17.2, 19.4) Parametric/extrapolated - 41.6 months (95% CI 33.9, 53.6) A6181111 Population Placebo+BSC – mean 14.5 months (95% CI 12.6, 16.3) Parametric/extrapolated - 20.5 months (95% CI 16.4, 27.4)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Everolimus vs BSC RADIANT-3 – treatment effect of 1.6 months Parametric/extrapolated – 14.7 months Sunitinib vs BSC A6181111 – treatment effect of 5.9 months Parametric/extrapolated - 38.5 months

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

End of life – GI and Lung NETs

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

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

Innovation

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

Equalities issues

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

Consultation comments on Assessment Report (1)

- NICE received 6 responses during consultation:
  - Pfizer
  - Novartis
  - AAA
  - Healthcare Improvement Scotland
  - NET Patient Foundation
  - Royal College of Physicians

Consultation comments on Assessment Report (2)

- Pfizer
  - AG report provides a balanced account given the available trial data for sunitinib
  - Despite AG concerns, the OS findings from the matched-adjusted indirect comparison (MAIC) analyses are generalizable to the patient population
  - Issues around generalisability were explored using sensitivity analyses

Consultation comments on Assessment Report (3)

- Novartis
  - Agree with the AG – comparison of 177Lu-DOTATATE to everolimus or sunitinib in P-NETs is inappropriate
  - Comparison with 177Lu-DOTATATE in GI-NETs population is inappropriate
  - Comparison to BSC is inappropriate due to the current pathway
  - Despite AG concerns regarding the wide CI's, ITC suggest little difference in treatment effect between everolimus and sunitinib
  - OS results taking into account crossover adjustment using RPSFT should be interpreted with caution due to nature of method
  - Treatment duration would be the same between everolimus and sunitinib
  - EoL conclusions are inconsistent and inaccurate (flawed methodology for life expectancy)
  - Question the models used for PFS and OS
  - Based on flawed assumptions the AG cost effectiveness results are incorrect

Consultation comments on Assessment Report (4)

- AAA
  - Report has been poorly structured and there are a number of errors/misrepresentations
  - NETTER-1 has been falsely described as a poorly designed study – pointed out it is NEJM peer reviewed study
  - AG has failed to take into account the full anticipated MA
  - Concern that the AG has misunderstood the role of SSA's in the treatment pathway and subsequently the economic analyses is fundamentally flawed
    - Underestimated SSA use within BSC (impact on CE results – brings ICER down in comparison to 177Lu-DOTATATE)
  - Number of other errors in the economic analyses related to drug acquisition costs and exactly what BSC consists of
  - Treatments in pre and post progression state are incorrect
  - Modelling choices used by the AG are focused purely on the fit of the data and ignored biological/clinical plausibility

Consultation comments on Assessment Report (5)

- Healthcare Improvement Scotland & Royal College of Physicians
  - No specialist neuroendocrine tumour clinician recognised as a key opinion leader in the UK involved
  - Treatments should be considered as alternatives not rivals
  - Sunitinib and everolimus are not interchangeable (due to differing toxicity profiles)
  - Interventions generally make patients feel better with manageable side effects and improve the quality of life allowing them to functioning more normally
  - Majority of patients with progressed disease will be dead within 2 years
  - PRRT offers an additional (not rival) treatment option

Consultation comments on Assessment Report (6)

- NET Patient Foundation
  - No specialist neuroendocrine tumour clinician recognised as a key opinion leader in the UK involved
  - Despite changes to the scope, still remains a lack of understanding around the disease area
    - Not all NETs develop slowly over a number of years
    - No uniform rate – hence grading system
  - Definitions of ‘response’ and ‘disease progression’ needed
  - Treatment based on a number of factors
  - Difficult to see how 177Lu-DOTATATE can be compared with everolimus and sunitinib (due to different patient populations/ location/functionality)
  - Acceptance that trials used are flawed, however, unclear as to why trials including placebo as a comparator arm are considered superior
  - Due to uncertainty and limited information, CDF inclusion should be considered

Key cost effectiveness issues

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

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

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

- There is limited comparability between RADIANT-4 and NETTER-1 patient populations
  - Differences in patient population means the results of ITC must be interpreted with caution
  - OS data from both trials are immature with more than 50% of patients still alive in at least one arm - modelling is highly uncertain
- The most plausible results for the different locations
- Do any of the treatments being appraised meet the end of life criteria?
- Can the treatments be considered innovative?
- Any equalities issues?