Public slides

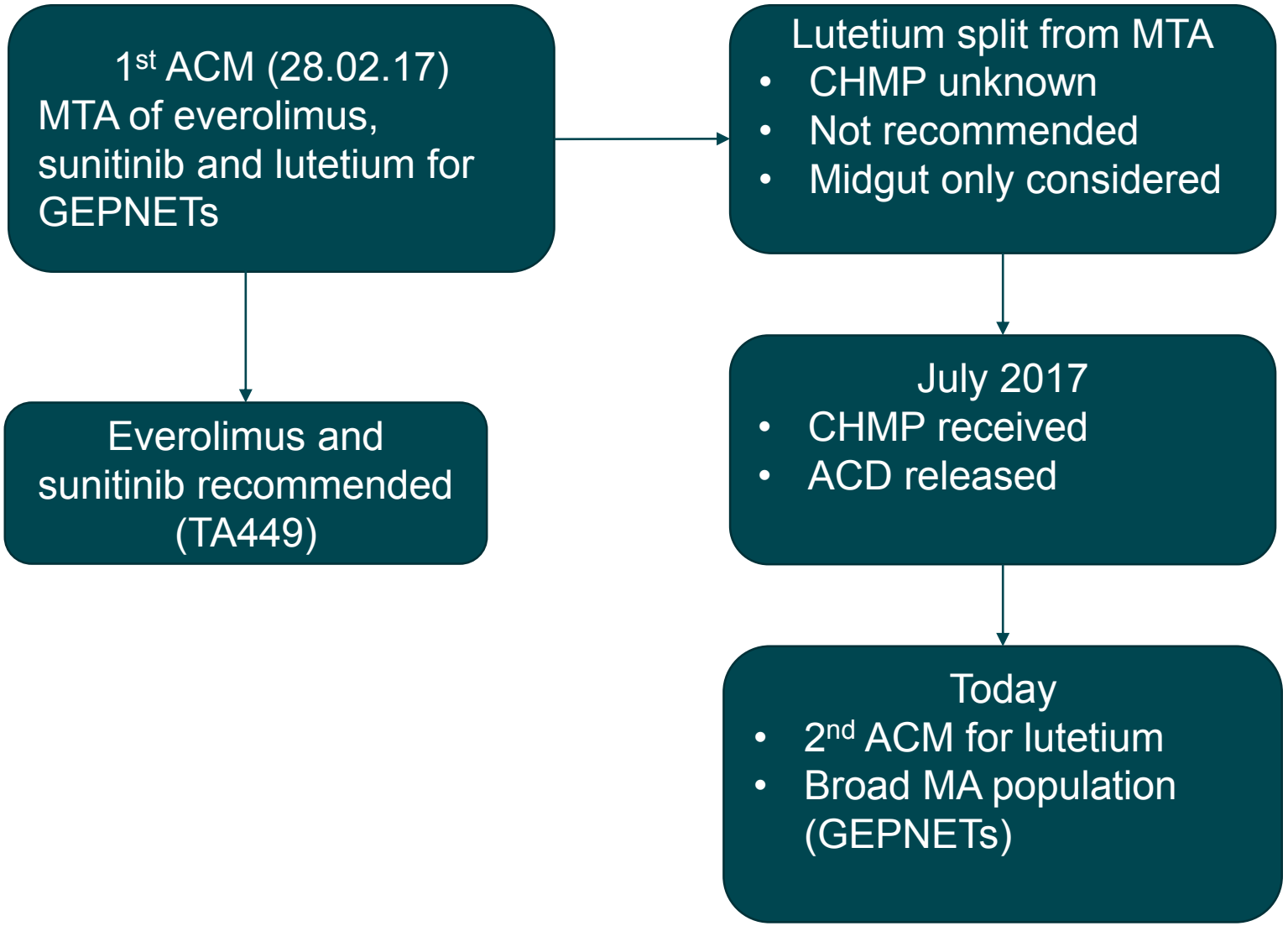
Chair's presentation Lutetium (177lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease

2nd Appraisal Committee meeting

Committee D

11 April 2018

History of Appraisal

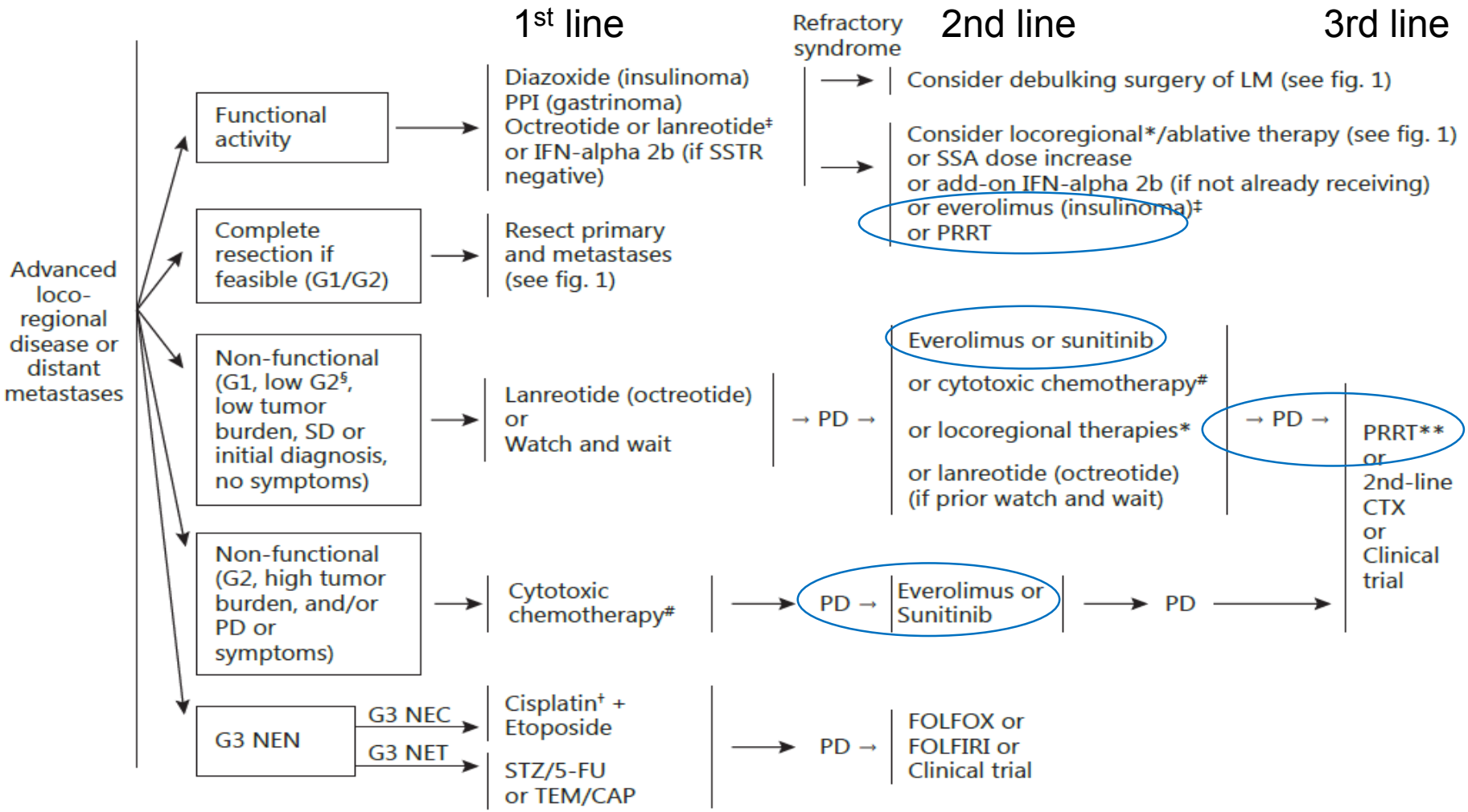


Details of the technology

Technology	Lutetium (177lu) oxodotreotide (Lutathera, AAA*)
Marketing authorisation	Treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults
Administration & dose	Intravenous infusion (IV) • Single cycle: 4 infusions of 7.4 GBq • Recommended interval between 2 infusions is 8 weeks (± about 1 week)
Mechanism of action	A Peptide Receptor Radionuclide Therapy (PRRT), which targets neuroendocrine tumours with radiolabelled somatostatin (SSA) peptides
Acquisition cost	£71,500.00

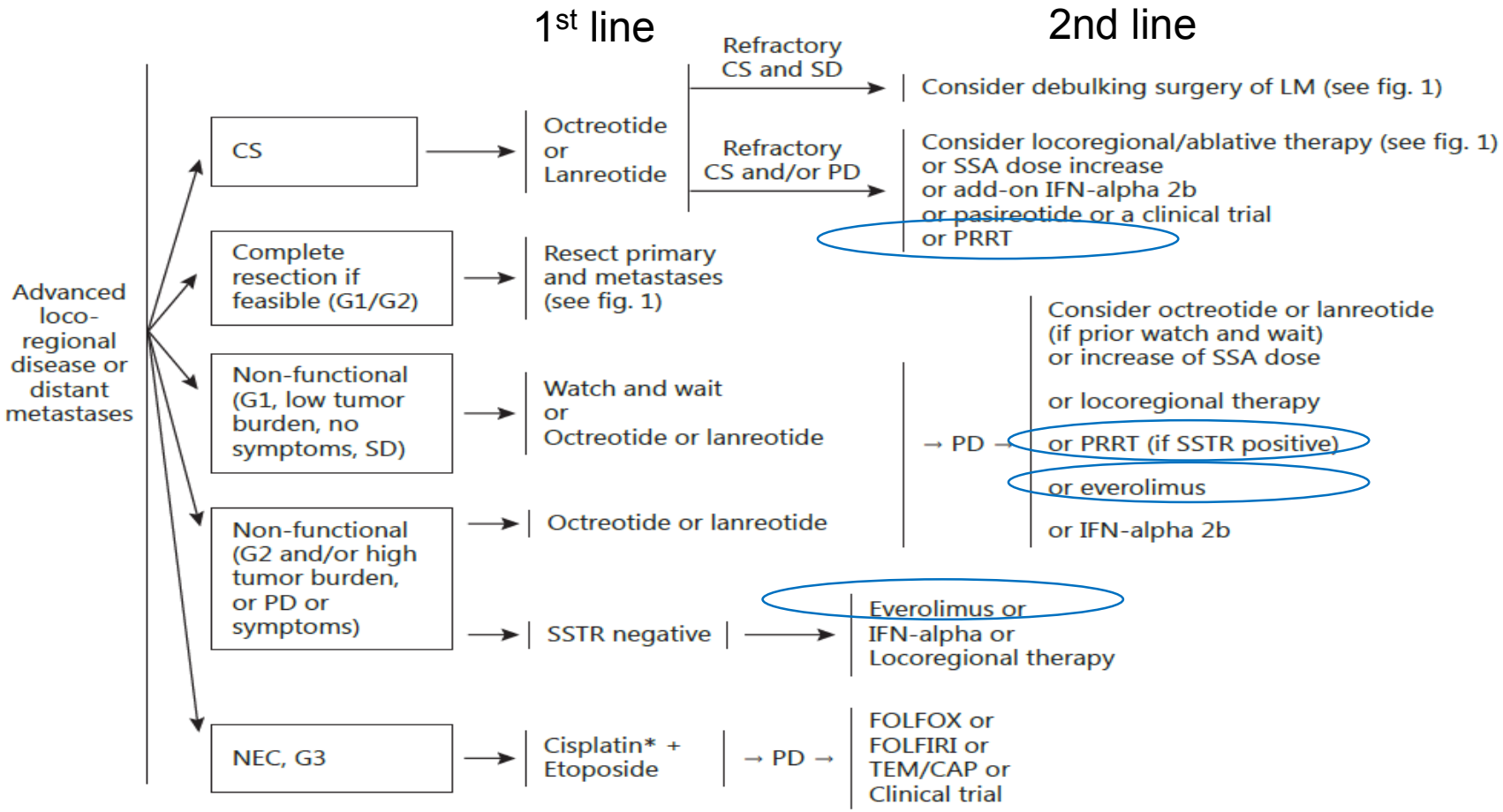
*AAA – Advanced Accelerated Applications

Treatment pathway: P-NETs



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

Treatment pathway: GI-NETs



Abbreviations: 5-FU: 5-fluorouracil, CAP: capecitabine, CS: carcinoid syndrome, CTX: chemotherapy, FOLFIRI: folinic acid, 5-FU, irinotecan, FOLFOX: folinic acid, 5-FU, oxaliplatin, IFN: interferon, LM: liver metastases, NEN: neuroendocrine neoplasm, PD: progressive disease, PRRT: peptide receptor radionuclide therapy, SD: stable disease, SSA: somatostatin analogue, SSTR: somatostatin receptor, STZ: streptozotocin, TEM: temozolomide.
Source: Pavel *et al.* 2016

ACD: preliminary recommendation

Lu-177 dotatate is not recommended, within its marketing authorisation, for treating unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults

ACD committee conclusions (1)

Clinical need	• Recognised need for treatment for NETs at different sites
Relevant comparators	• P-NETs: sunitinib, everolimus and BSC • Midgut GI NETs: everolimus and BSC

NETTER-1 trial	• Lutetium vs. Octreotide LAR 60mg
	  • Population: midgut GI NETs only
	  • PFS – 0.21 (95% CI 0.13 to 0.33)
	  • OS – 0.40 (95% CI 0.21 to 0.77)
	  • Median OS: not reached in both treatment arms at time of data analysis
	Recommendations should be guided by evidence from the trial – focus on midgut only

Company's mixed treatment comparison (MTC)	• MTC: Lutetium vs. everolimus vs. sunitinib for advanced pancreatic NETs → ***Inappropriate and uninformative*** • NETTER-1 only included people with midgut GI NETs

ACD committee conclusions (2)

Indirect treatment comparison (ITC)	**AG's ITC (preferred by committee):**
	• Lutetium (NETTER-1) vs. everolimus (midgut subgroup from RADIANT-4) vs. BSC for midgut GI NETs:
	  • PFS - 0.37 (95% CI 0.19 to 0.69)
	  • OS benefit unclear due to immature data
	Uncertainties:
	• Population in RADIANT-4 and NETTER-1 not fully comparable
	  • RADIANT-4: people with non-functional tumours
	  • NETTER-1: people with functional or non-functional, somatostatin receptor-positive tumours
	• Octreotide LAR from NETTER-1 assumed to be equivalent to BSC from RADIANT-4
	• Company's ITC included RADIANT-2 and the whole GI group from RADIANT-4, which introduced further uncertainty – ***not accepted***

CE model	• Preferred AG's model which included BSC as a comparator • All relevant costs included in the model
Results	• ICERs for lutetium (list price) vs. everolimus (with PAS) and BSC = > £30k/QALY
EoL	• Not met for mid-gut GI NETs – life expectancy: • Extrapolated mean survival was 58.8 months for BSC and 69 months for everolimus

ACD consultation responses

- Consultee comments from:
  - Advanced Accelerator Applications – including new evidence
  - NCRI-ACP-RCP-RCR
  - NET Patient Foundation
  - British Nuclear Medicine Society (BNMS)
- 8 Web comments
- Expert comments from:
  - 1 Patient expert

ACD consultation responses
(*Advanced Accelerator Applications)*

1. NICE has failed to consider full MA and evidence for lutetium

- Only midgut population considered despite broader licence (GEP-NET) and the opinion of clinical experts

ACD: *"The clinical experts explained that in their experience, they do not expect much difference in the efficacy of Lu-177 dotatate across the different tumour sites."*

  - Midgut NETs are representative of the GEP-NET population by being the most common type and are frequently metastatic and progressive at diagnosis (other subpopulations are too small for clinical trials)
  - ERASMUS trial, which partly informed the MA has not been considered
    - Population consists of GEP-NETs, including foregut, midgut and hindgut, bronchial and pancreatic
    - NICE has previously recommended treatments using single arm trials

ACD consultation responses
(*Advanced Accelerator Applications)*

2. NICE has acted unfairly in its appraisal of Lutetium

- Lack of clarity and major discrepancies between the ACD and the AG model
- AG model provided late in process
- AG analysis not consistent with NICE methods and is perverse:
  - Important evidence submitted (ERASMUS trial), have not been considered and no justification provided
  - Full details of the structural assumptions underpinning AG model 2 have not been provided
  - Lutetium relegated to scenario analysis in the AG's report
  - NICE methods guide - describes methods that AGs should follow for their economic evaluations – not provided by AG

3. Lutetium is a cost-effective use of NHS resources

- Concerned about errors that bias against lutetium in AG's CE model and the lack of transparency in amendments made
- Impossible to reconcile ACD conclusions with AG model figures:
  - In testing the reliability of the AG's CE model, lutetium was shown to be cost-effective between £20,000 to £30,000 vs. everolimus

ACD consultation responses
(*Advanced Accelerator Applications)*

4. The AG analysis of overall survival is fundamentally flawed

- The assumption that all patients die immediately upon disease progression is clinically implausible and unfair as it has not been assumed when compared with other treatments including everolimus and BSC
  - This approach contravenes NICE's recommended methods for modelling an appropriate time horizon and dealing with uncertainties
  - Interim and updated analysis from NETTER-1 results show that patients having lutetium live well beyond disease progression

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

- AG's rationale for using control arm of RADIANT-4 is unclear
  - Only 10% of patients who progress with NETs receive somastatin analogues (SSA) as part of their treatment. It should be much higher as validated by clinical expert → total cost of BSC is under-calculated
- Clinical practice is more aligned with NETTER-1
  - All patients who progress with NETs are treated with an escalated dose of octreotide (30-60mg)

ACD consultation responses
(*NCRI-ACP-RCP-RCR, BNMS, NET Patient Foundation, patient expert)*

- Disappointed that treatment shown to have robust clinical effectiveness is not approved for routine use – would like to see further negotiation to ensure availability
- Clear unmet need – no targeted treatment for well differentiated, low-moderate, SSTR+, functional midgut NETs after disease progression
- It would have been beneficial for an expert on PRRT to attend the meeting
- 1st product in 20 years showing improvement in PFS and quality of life in progressive neuroendocrine tumours
- PRRT compared with high-dose octreotide LAR shows significant improvement in PFS and OS - rarely seen and a step change
- Trial evidence confirms high-dose octreotide is a valid/effective comparator, although unlikely to be used in clinical practice
- 177-Lu much less toxic than other chemotherapy-based regimens
- Subgroup most likely to benefit and best value for money could be identified by somatostatin receptor status using variety of techniques
- Inequality – 'UK' and 'England' used interchangeably. Currently people in England do not have access to this treatment whilst other UK countries do

ACD consultation responses
(*NCRI-ACP-RCP-RCR, BNMS, NET Patient Foundation, patient expert)*

- The scope of the appraisal was confusing with various different tumour locations covered
- Unclear what BSC actually entails – clarity would be appreciated
- Have all costs been considered? – for example, costs of not being treated
- Uncertainties surrounding administration costs, need to be addressed
  - Overnight admission is possible due to few centres and geographical issues
- Costing doesn't account highly specialised nature of molecular radiotherapy
  - As low dose radioactivity is present, important to consider that treatment will be individualised
- Concerns over a "post code lottery" (no centres experienced in using lutetium in East Midlands, Yorkshire, the North East and South West)
- Best screening test for PRRT with lutetium - Ga-68 DOTATOC PET
  - Not currently funded by NHS England
  - Only available in a few centres in the England
  - Centres may find it difficult to scan patients under the provisions of NHS England phase II PET/CT contract roll out

ACD consultation responses
(*Web comments)*

- Disappointed not recommended as it was removed from CDF due to lack of data – that is now available through NETTER-1
- 177-Lu dotatate has become standard of care, superior to SSA's (which have low response rate) after progression
- Licensed indication is for more sites of disease than evidence base
- Likely to be effective in other NET subgroups, evidence base may not be robust enough
- PFS benefit seen in NETTER-1 – rarely seen in oncology
- Median OS survival not reached – can be seen as positive, shows people are not dying
- Use of octreotide as comparator is correct – dosage
- NETTER-1/RADIANT-4 comparison not appropriate, heterogeneous studies
- UK leading country within ENETS with 10 European Centres of Excellence
  - Without 177-Lu dotatate (standard in Europe) status of UK centres affected

Company's new evidence

- Updated data provided for NETTER-1 (June 2016 data-cut) and ERASMUS
- Revised NMA using updated data from NETTER-1
- Matched adjusted indirect treatment comparison (MAIC) on P-NETs and GI-NETs using data from ERASMUS
- Revised base case and scenario analyses

Company's new evidence
(NETTER-1: June 2016 data-cut)

Outcomes	Independent IRC	
	Lutetium + Octreotide LAR (30 mg) (n=116)	**Octreotide LAR (60 mg) (n=113)**
PFS, median, months	28.35 (28.35 – N/R)	8.54 (5.81 – 11.0)
HR (95% CI)	**0.21 (0.14 - 0.33)**	
ORR (all patients)	14.7%	4.0%
OS, median, months	Not reached	27.37 (23.13 – N/R)
HR (95% CI)	**0.54 (0.33 – 0.86)**	
RPSFT-adjusted OS, median, months	Not reached	27.4 (20.9 – NE)
HR (95% CI)	**0.488 (0.3 – 0.795)**	

Sources: Company additional evidence submission (8th December), pages 9 and 48; N/R= Not reached; NE= Not evaluable

Company's new evidence
(ERASMUS: Phase I/II single arm trial)

Tumour subtype	PFS, median, months (95% CI)	OS, median, months (95% CI)
***GEP-NET (n=360)**	28.5 (24.8 to 31.4)	61.2 (54.8 to 67.4)
Pancreatic (n=133)	30.3 (24.3 to 36.3)	66.4 (57.2 to 80.9)
Foregut† (n=12)	43.9 (10.9 to NR)	NR
Midgut (n=183)	28.5 (23.9 to 33.3)	54.9 (47.5 to 63.2)
Hindgut (n=13)	29.4 (18.9 to 35.0)	NR

Notes:

- * includes foregut, midgut and hindgut; † foregut NETs other than bronchial and pancreatic; ND= Not determined; NR= Not reached

Company's MAIC for P-NETs
(ERASMUS data)

- MAIC using data from ERASMUS P-NETs Dutch population only (for Lutetium), RADIANT-3 and A6181111
- ERASMUS P-NETs Dutch population was matched to each of arm of A6181111 (sunitinib and BSC) and RADIANT-3 (everolimus and BSC), separately (post matching effective sample sizes n= 31, 36, 17, 18, respectively)
- Covariates for matching: Age, ECOG performance status, proportion previously treated with chemotherapy and proportions previously treated with radiotherapy (chosen on the basis of their significant effect on OS and PFS; $p<0.20$)

Comparator	HR PFS [95% CI]	HR OS [95% CI]
Lutetium versus. Sunitinib (A6181111)	0.47 [0.25, 0.88]	0.50 [0.29, 0.84]
Lutetium versus. BSC (A6181111)	0.12 [0.07, 0.21]	0.33 [0.20, 0.56]
Lutetium versus. Everolimus (RADIANT-3)	0.52 [0.34, 0.79]	0.61 [0.39, 0.98]
Lutetium versus. BSC (RADIANT-3)	0.21 [0.13, 0.32]	0.56 [0.36, 0.90]

Company's MAIC for GI-NETs
(ERASMUS data)

- MAIC using data from ERASMUS Dutch population (for Lutetium) and RADIANT-4 (Everolimus vs BSC)
- Only able to conduct a MAIC for PFS (OS data for the GI-subgroup from RADIANT-4 was not available)
- Covariates for matching: Age, sex, ECOG performance status and proportion previously treated with chemotherapy

Comparator	Hazard ratio PFS [95% CI]
Lutetium vs. Everolimus	0.72 [0.51, 1.04]
Lutetium vs. BSC	0.68 [0.43, 1.07]

Company's revised NMA for GI-NETs
(NETTER-1 data)

- Included updated data for lutetium from NETTER-1 vs. everolimus from RADIANT-4
- Removed RADIANT-2, which included people with functioning tumours
- Assumptions made:
  - Control arm of RADIANT-4 (placebo + BSC) equivalent to the control arm of NETTER-1 (octreotide LAR 60mg)
  - Population from RADIANT-4 (non-functioning GI and Lung NETs) equivalent to the population from NETTER-1 (functioning and non-functioning mid-gut only NETs)

Comparator	PFS* HR (95% CI)	OS** HR (95% CI)
Lutetium vs. Everolimus	2.69 (0.07, 93.28)	1.20 (0.03, 43.73)
Lutetium vs. Octreotide LAR	4.80 (0.37, 59.00)	1.86 (0.15, 24.46)

*PFS: Mid-gut NETs (NETTER-1) vs. GI NETs (RADIANT-4)
**OS: Mid-gut NETs (NETTER-1) vs. GI and Lung NETs (RADIANT-4)

Company's revised economic model (P-NETs)

- Comparisons:
  - Lutetium vs. Octreotide LAR (BSC)
  - Lutetium vs. Everolimus (list price)
  - Lutetium vs. Sunitinib
- The revised economic model incorporates:
  - updated data from the ERASMUS study
  - data on relative effectiveness from the MAIC analysis
  - relative dose intensity for lutetium (86.4%), everolimus (79.4%) and sunitinib (91.3%) in the base case analysis
- Parametric model used for PFS and OS:
  - Weibull model used because it made more reasonable assumption of progression and survival, although the log-normal in most cases had the best fit to NETTER-1 and ERASMUS data

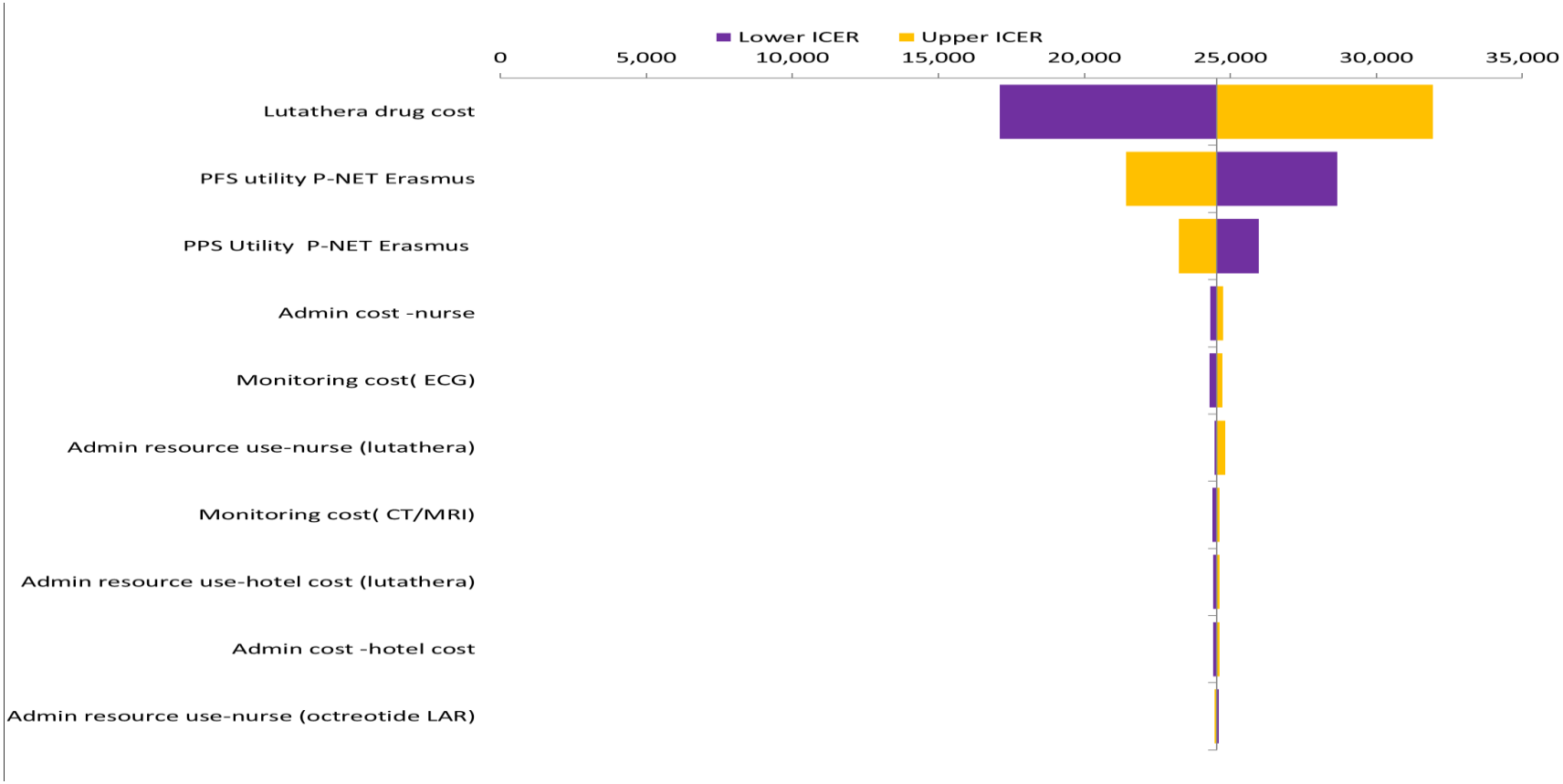
Company's revised base case results (P-NETs – deterministic)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutetium compared to everolimus (RADIANT-3)						
Lutetium	£109,805	6.10	4.81	£38,831	1.58	**£24,526**
Everolimus	£70,974	4.11	3.23			
Lutetium compared to BSC (octreotide LAR 60mg) (RADIANT-3)						
Lutetium	£111,416	6.21	4.90	£51,658	1.78	**£29,091**
BSC	£59,759	3.94	3.12			
Lutetium compared to sunitinib (A6181111)						
Lutetium	£114,763	7.16	5.65	£33,460	2.17	**£15,433**
Sunitinib	£81,303	4.47	3.48			
Lutetium compared to BSC (octreotide LAR 60mg) (A6181111)						
Lutetium	£119,837	7.13	5.63	£67,081	2.94	**£22,854**
BSC	£52,756	3.39	2.69			

Company's revised base case results (P-NETs – Probabilistic)

Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutetium compared to everolimus (RADIANT-3)						
Lutetium	£109,771	6.12	4.83	£38,660	1.60	**£24,236**
Everolimus	£71,111	4.11	3.23			
Lutetiumcompared to BSC (octreotide LAR 60mg) (RADIANT-3)						
Lutetium	£111,653	6.23	4.92	£51,733	1.79	**£28,940**
BSC	£59,920	3.95	3.13			
Lutetium compared to sunitinib (A6181111)						
Lutetium	£114,460	7.16	5.65	£32,483	2.15	**£15,091**
Sunitinib	£81,976	4.49	3.50			
Lutetium compared to BSC (octreotide LAR 60mg) (A6181111)						
Lutetium	£118,815	7.07	5.59	£65,942	2.70	**£22,809**
BSC	£52,872	3.40	2.70			

Company's revised P-NETs base case analysis tornado diagram (Lutetium vs. Everolimus)



The key drivers of the model results were similar when lutetium was compared with sunitinib and BSC, with drug acquisition cost being the key driver, followed by PFS and PPS utility

Company's revised economic model (GI-NETs)

- Comparisons:
  - Base case analysis: Lutetium vs. BSC – (using NMA)
  - Scenario analysis: Lutetium vs. Everolimus – (using NMA)
  - Scenario analysis: Lutetium vs. Everolimus and BSC - (using MAIC)
  - The revised economic model incorporates:
    - updated data from NETTER-1 in the base case analysis
    - relative dose intensity for everolimus (79.4%) in the base case analysis
    - data from a scenario analysis of NETTER-1 where treatment cross-over (22.8%) was accounted for
    - data from the revised MTC in a scenario analysis
    - data on relative effectiveness from the MAIC analysis
- Parametric model used for PFS and OS:
  - Weibull model used because it made more reasonable assumption of progression and survival, although the log-normal in most cases had the best fit to NETTER-1 and ERASMUS data

Company's revised base case
(GI-NETs)

Deterministic						
Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutetium	£86,370	4.53	3.46	£37,080	1.27	**£29,196**
Octreotide LAR	£49,289	2.90	2.19			
Probabilistic						
Lutetium	£88,118	4.82	3.68	£35,627	1.33	**£26,826**
Octreotide LAR	£52,491	3.12	2.36			

Company's Scenario analyses
(GI-NETs)

- **Scenario analysis including relative dose intensity of 84.4% from ERASMUS**

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

- **Scenario analysis of NETTER-1 where treatment cross-over (22.8% from control arm to Lutetium) was accounted for using RPSFT method**

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

- **Scenario analysis of Lutetium compared to Everolimus using NMA data**

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

Company's scenario analysis
(GI-NETs – MAIC analyses)

- **Lutetium vs. Everolimus**

Deterministic results						
Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutetium	£93,181	4.97	3.82	£18,424	0.83	**£22,227**
Everolimus	£74,757	4.00	2.99			
Probabilistic results						
Lutetium	£93,221.27	4.98	3.83	£18,006.88	0.82	**£21,976**
Everolimus	£75,215.38	4.02	3.01			

- **Lutetium vs. BSC (Octreotide LAR 60mg)**

Deterministic results						
Therapy	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. QALYs	ICER
Lutetium	£91,874.77	5.12	3.94	£18,486.90	0.89	**£20,741**
BSC	£73,387.87	4.00	3.05			
Probabilistic results						
Lutetium	£91,910.64	5.14	3.95	£17,167.72	0.86	**£19,983**
BSC	£74,742.92	4.05	3.09			

AG critique of company's new clinical evidence (1)

Evidence sources:

- New data provided by the company is not systematically identified
- The updated data for NETTER-1 and ERASMUS is unpublished
- The focus on just one non-RCT (ERASMUS) is unjustified since there are a further 7 non-RCT studies published with relevant data
  - None of the other treatments (Sunitinib or Everolimus) have had their non-RCT evidence reviewed → bias?
- ERASMUS trial:
  - Included primarily Dutch patients
  - Very small number of patients included in the trial
  - Very limited data surrounding the baseline population characteristics

AG critique of company's new clinical evidence (2)

Indirect comparisons (MAIC using ERASMUS):

- **On P-NETs only**
  - ERASMUS is a non-RCT; RADIANT-3 and A618111 are both RCTs
  - Inclusion criteria between the 3 trials differed
  - Not a closed network – pairwise analyses not strictly comparable – reference population varied across the comparative analyses
- **On GI-NETs only**
  - Lack of OS outcome data → the life expectancy at the time of disease progression was therefore assumed to be the same across treatments – appropriate?
- **Both P-NETs and GI-NETs**
  - Only included Dutch patients from ERASMUS → very small effective sample sizes after matching covariates → unreliable estimates
  - The approach to selecting covariates inappropriate due to small sample size and failed to adjust for the more important covariates such as tumour functionality, measures for grade and stage of disease
  - Relative treatment effects were modelled after imposing the assumption of proportional hazards – not justified with any statistical testing

AG critique of company's new clinical evidence (3)

Network meta-analyses: GI-NETs

- No justification that octreotide LAR 60mg is equivalent to placebo + BSC
- Population in RADIANT-4 not comparable with population in NETTER-1:
  - non-functioning GI and Lung NETs vs. both functioning and non-functioning, somatostatin receptor positive mid-gut only NETs
  - Tumour locations between the 2 trials differed

New adjustment for cross-over in NETTER-1

- Quality of the RPSFT method unclear – no methodological information provided
  - Conducted with or without re-censoring to avoid bias?
- RPSFT estimates are likely to underestimate the effectiveness of lutetium because it was given alongside a lower dose (30mg) of octreotide than that used in the control arm (60mg)

AG's critique on company's revised economic model (P-NETs and GI-NETs) (1)

- Definition of BSC is premised on the design of NETTER-1 – all treated with high dose SSRA (60mg octreotide)
  - significantly different to AG's definition of BSC, which is premised on that observed in RADIANT-3 (P-NETs) and RADIANT-4 (GI-NETs)

Disease and stage	Strategy	Proportion using SSRAs – AG model	Proportion using SSRAs – AAA model
Pancreatic NETs			
Pre-progression	BSC	39.90%(LD)	100.00%(HD)
	Active treatments	37.70%(LD)	0.00%
Post-progression	BSC	2.00%(LD)	100.00%(LD)
	Active treatments	2.02%(LD)	100.00%(LD)
Whole/midgut GI NETs			
Pre-progression	BSC	1.03%(LD)	100.00%(HD)
	Active treatments	1.95%(LD)	0.00%
Post-progression 1st cycle	BSC	22.74%(LD)	100.00%(LD)
	Active treatments	29.80%(LD)	100.00%(LD)
Post-progression Subsequent cycles	BSC	1.03%(LD)	100.00%(LD)
	Active treatments	1.95%(LD)	100.00%(LD)

- Cost of BSC prior to and post progression in the company model is ~600% and 300% more vs. AG model, respectively

AG's critique on company's revised economic model (P-NETs and GI-NETs) (2)

- Treatment with everolimus and sunitinib was assumed to continue until disease progression, potentially overestimating their use
- Treatment after progression was over-simplified to octreotide in every patient, potentially overestimating the use of octreotide and underestimating the use of other resources post-progression
- The cost of administration of Lutetium was low compared to expert opinion collected by the AG
- The cost burden of SAEs included considerable imprecision due to low unit costing of SAEs and application well beyond the expected mean duration of treatment
- Dose intensity estimate of lutetium is based on NETTER-1 (86.4%) instead of the reference trial of the MAIC, ERASMUS (94.4%- 97.8%), potentially overestimating the cost-effectiveness of lutetium
- Implausible costing assumptions adopted:
  - Use and dosage of SSRAs

AG's revisions to the clinical analyses (1)

Indirect comparisons (MAIC using ERASMUS):

- **P-NETs:**
  - Covariates for matching: Age, **sex**, ECOG performance status, **time from initial diagnosis**, **prior SSA treatment**, and prior radiotherapy and chemotherapy treatment
  - Included all ERASMUS P-NETs patients with covariates for matching (n=156) vs. only Dutch patients (n=62) in AAA's MAIC P-NETs analysis
  - ERASMUS lutetium was matched to:
    - the mean baseline values for the whole RADIANT-3 sample (n=210) to produce 1 set of MAIC results
    - a single reference population (RADIANT-3) to produce results for the complete network in that population

- **Overall GI-NETs:**
  - MAIC of the whole GI-NETs sample in ERASMUS (n=245) vs. the overall GI subpopulation of RADIANT-4 (n=175)
    - Uses published information (PFS) and information from Novartis (OS)
  - Covariates for matching: Age, sex, ECOG performance status, prior SSA treatment, prior radiotherapy and chemotherapy treatment, and the proportion of mid-gut NETs

AG's revisions to the clinical analyses (2)

- **GI mid-gut NETs only:**
  - ERASMUS GI mid-gut (n=108) was matched to the overall GI-NETs in RADIANT-4 (n=175) (no baseline characteristics information available for the GI midgut subgroup in RADIANT-4)
    - Note: 117/ 175 (66.8%) patients in the overall GI subpopulation in RADIANT-4 had mid-gut NETs
  - Covariates for matching: Age, sex, ECOG performance status, prior SSA treatment, and prior radiotherapy and chemotherapy treatment

Network meta-analysis for OS for GI-NETs using NETTER-1:

- Included the new RPFST-adjusted results for treatment crossover provided by the company

AG revisions to the economic analyses

- **Cost of lutetium**
  - National average cost of an elective inpatient excess bed day used instead of the national average cost of a non-elective inpatient short stay to reduce potential double counting
- **Dose intensity of lutetium**
  - Derived from usage in ERASMUS, the reference trial of the MAIC
- **Adjustment in the GI survival analysis for background mortality**
  - Applied because of the short follow-up period in the supporting indirect comparison of progression and mortality
  - The point of adjustment was matched to the point at which the last in-trial event was recorded

Survival curves: Indirect comparison in P-NETs and GI-NETs
Baseline trial: ERASMUS

Outcome	Treatment arm	Parametric model used
P-NETs		
PFS	• Lutetium plus BSC • Sunitinib plus BSC • Everolimus plus BSC • BSC only	PFS base case: Weibull model
		PFS sensitivity analysis: Lognormal
OS		OS base case: Exponential model
		OS sensitivity analysis: Lognormal
GI-NETs		
PFS	• Lutetium plus BSC • Everolimus plus BSC • BSC only	PFS base case: Exponential model
		PFS sensitivity analysis: Lognormal
OS		OS base case: Exponential model
		OS sensitivity analysis: Lognormal

AG's revised NMA using Bucher - OS for GI-NETs (using NETTER-1)

- Based on updated data from NETTER-1 and previous OS data from RADIANT-4 that includes GI NETs only (data request from Novartis – not available to AAA)
- Two HRs for NETTER-1 used:
  - HR estimated by the Kaplan Meier method
  - HR estimated by the RPSFT method

Intervention	Comparator	Data source	HR (95%CI)
HRs (95% CIs) for OS in GI NETs			
Everolimus+BSC	Placebo+BSC	RADIANT-4 (from AG data request to Novartis)	[redacted]
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1, using Kaplan Meier Method	0.54 (0.33, 0.86) unstratified 0.54 (0.33, 0.87) stratified
177Lu-DOTATATE + octreotide 30mg	Octreotide 60mg	NETTER-1 using RPSFT method	0.50 (0.31, 0.80) unstratified 0.49 (0.30, 0.80) stratified
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG using NETTER1 Kaplan Meier Method	0.95 (0.40, 2.23) unstratified 0.95 (0.40, 2.24) stratified
177Lu-DOTATATE + octreotide 30mg	Everolimus +BSC	Calculated by AG using NETTER1 RPSFT method	0.88 (0.37, 2.06) unstratified 0.86 (0.36, 2.04) stratified

AG's revised base case ICERs: P-NETs (MAIC)

Deterministic discounted QALY and cost means

Interventions:

- P-NETs populations of ERASMUS (Lutetium) vs. RADIANT-3 (Everolimus) vs. A6181111 (Sunitinib)

	Lutetium vs. BSC	Lutetium vs. Everolimus	Lutetium vs. Sunitinib
Incremental life years gained	5.353	4.125	2.428
Incremental QALYs gained	2.343	1.752	1.018
Incremental Costs (£)	70,174	43,289	42,743
ICER (Cost/QLY) – lifetime horizon	**£29,956**	**£24,714**	**£41,967**

AG's revised base case ICERs: GI-NETs (MAIC)

Deterministic discounted QALY and cost means

Interventions:

- ERASMUS whole GI-NETs population (Lutetium) vs. overall GI-NETs subpopulation of RADIANT-4 (Everolimus)

	Lutetium vs. BSC	Lutetium vs. Everolimus
Incremental life years gained	3.007	1.096
Incremental QALYs gained	1.549	0.576
Incremental Costs (£)	72,607	36,758
ICER (Cost/QLY) – lifetime horizon	**£46,870**	**£63,792**

AG's revised base case ICERs: GI Midgut NETs (MAIC)

Deterministic discounted QALY and cost means

Interventions:

- ERASMUS midgut-NETs population (Lutetium) vs. overall GI-NETs population in RADIANT-4 (Everolimus)

	Lutetium vs. BSC	Lutetium vs. Everolimus
Incremental life years gained	2.722	1.923
Incremental QALYs gained	1.399	0.992
Incremental Costs (£)	73,704	40,102
ICER (Cost/QLY) – lifetime horizon	**£52,690**	**£40,423**

PSA of base case model

Probabilistic discounted QALY and cost means

	P-NETs			Whole GI-NETs		Midgut NETs	
	Lutetium versus:			Lutetium versus:		Lutetium versus:	
	BSC	Everolimus	Sunitinib	BSC	Everolimus	BSC	Everolimus
PSA ICER	29,434	24,300	40,428	48,692	65,317	53,416	40,589
Deterministic ICER	29,956	24,714	41,967	46,870	63,792	52,690	40,423

Scenario analyses: P-NETs

Deterministic discounted means

Scenarios	ICER Lutetium versus:		
	BSC	Everolimus	Sunitinib
Base case ICER (£)	***29,956***	***24,714***	***41,967***
Assuming 100% dose intensity in pre-progression for all treatments	31,610	24,919	44,157
Using the dose intensity observed in NETTER-1, adjusted for attrition death on treatment (93.3% vs. 94.4% in ERASMUS)	26,425	24,004	40,747
Including the cost of supportive therapies (chemoembolization, radiotherapy, chemotherapy) bundled into first cycle of treatment post-progression	29,840	24,621	41,809
Parametric curve choice for PFS: using accelerated failure time distributions (everolimus – loglogistic; lutetium and BSC – lognormal; sunitinib - unchanged)	32,683	28,558	48,204
Parametric curve choice for OS: using accelerated failure time distributions (everolimus and lutetium – lognormal; BSC and sunitinib – unchanged)	35,829	45,617	72,383
Using naïve BSC RAD-3 and BSC A618111 trial results (i.e. without cross-over adjustment)	35,108	24,714	34,105
Locally assessed outcomes instead of Central review	29,444	24,702	43,286

Scenario analyses: whole GI-NETs (1)
Deterministic discounted means

Scenarios	ICER Lutetium versus:	
	BSC	Everolimus
Base case ICER (£)	***46,870***	***63,792***
Assuming 100% dose intensity in pre-progression for all treatments	56,973	42,475
Using the dose intensity observed in NETTER-1, adjusted for attrition death on treatment (90.8% vs. 94.6% in ERASMUS)	47,112	64,443
Mean duration of treatment with everolimus increased from 13.3 months to 16.3 months (based on estimate from mid-gut population)	56,973	53,330
Increased resources for disease monitoring	48,314	65,120
Including the cost of supportive therapies (chemoembolization, radiotherapy, chemotherapy) bundled into first cycle of treatment post-progression	47,477	61,719
Alternative sources of utility estimates	48,674	62,043
Removing adjustment for background mortality in PFS and OS event rate	46,524	297,048
Parametric curve choice for PFS – using accelerated failure time distributions (lutetium - lognormal instead of Weibull)	50,061	71,765

Scenario analyses: whole GI-NETs (2)

Deterministic discounted means

Scenarios	ICER Lutetium versus:	
	BSC	Everolimus
Base case ICER (£)	***46,870***	***63,792***
Parametric curve choice for OS – using accelerated failure time distributions (lutetium - lognormal instead of Exponential)	56,797	126,046
Alternative definition of BSC 1: no supportive therapies in stable disease except SSRAs; high dose 60mg octreotide in 40% patients	42,216	63,792
Alternative definition of BSC 2: no supportive therapies in stable disease except SSRAs; high dose 60mg octreotide in 100% patients	34,888	63,792
Estimates prevalence and dose of octreotide based on expert clinical opinion: octreotide 30mg in 90% of patients in pre-progression, reducing to 85% post-progression	45,126	37,745
Increase in the proportion of patients administered lutetium as day case (from 10% to 65%)	46,747	63,461

End of life estimates (AG model)

Criteria	BSC	Everolimus	Sunitinib
P-NETs			
Extrapolated survival (months)	41.6	56.3	76.7
Extrapolated survival benefit for lutetium (months)	64.2	49.5	29.1
Whole GI-NETs			
Extrapolated survival (months)	58.8	81.7	-
Extrapolated survival benefit for lutetium (months)	36.1	13.2	-
Midgut-NETs			
Extrapolated survival (months)	52.5	62.1	-
Extrapolated survival benefit for lutetium (months)	32.7	23.1	-

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- **Everolimus (RADIANT-3) and sunitinib (A6181111) for P-NETs met the life expectancy criterion**
  - extrapolated survival of BSC: 41.6 (from RADIANT-3) and 20.5 months (from A6181111)
  - Clinical experts stated they would expect survival to be closer to 20.5 months – committee agreed
- **Everolimus for GI-NETs did not meet the life expectancy criterion**
  - extrapolated survival of BSC: 51.4 months
  - Clinical experts stated that life expectancy was around 5 to 6 years (similar for midgut)

Issues for consideration

- ERASMUS study data
  - Do the results of ERASMUS allow for a wider consideration of all tumour subgroups?
  - Are lung NETs included in the MA for lutetium?
- Lutetium was previously on the CDF after sunitinib for PNETs
  - should sequential use be considered?
- Use of SSAs in the NHS – (timing of treatment, dosage, disease stage, functional status etc.)
- What conclusions can be drawn from the company's and assessment group's indirect comparisons and which are the most appropriate (company vs. AG)?
  - robustness of the MAICs for the P-NETs and GI-NETs tumour location?
  - the appropriateness of the NMA for midgut GI-NETs using data from NETTER-1 and RADIANT-4
- Robustness of company's and assessment group's model for decision making - assumption on SSA uptake, admin cost for lutetium as a radiopharmaceutical
- Does lutetium meet the end of life criteria?
- Committee's preferred analyses and most plausible ICERs