Public observer slides

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

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee D

Lead team: Dr Ian Davidson, Gillian Ells and Pam Rees

ERG: Peninsula Technology Assessment Group

NICE technical team: Stuart Wood and Nwamaka Umeweni

28 February 2017

Key clinical issues

- How are NETs treated in clinical practice?
- Have the appropriate comparisons been made for each tumour location?
- Can the results from pivotal trials be generalised to current clinical practice?
- What conclusions can be drawn from the network meta-analyses
- Are everolimus and sunitinib clinically equivalent?

Neuroendocrine tumours (NETs)

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

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

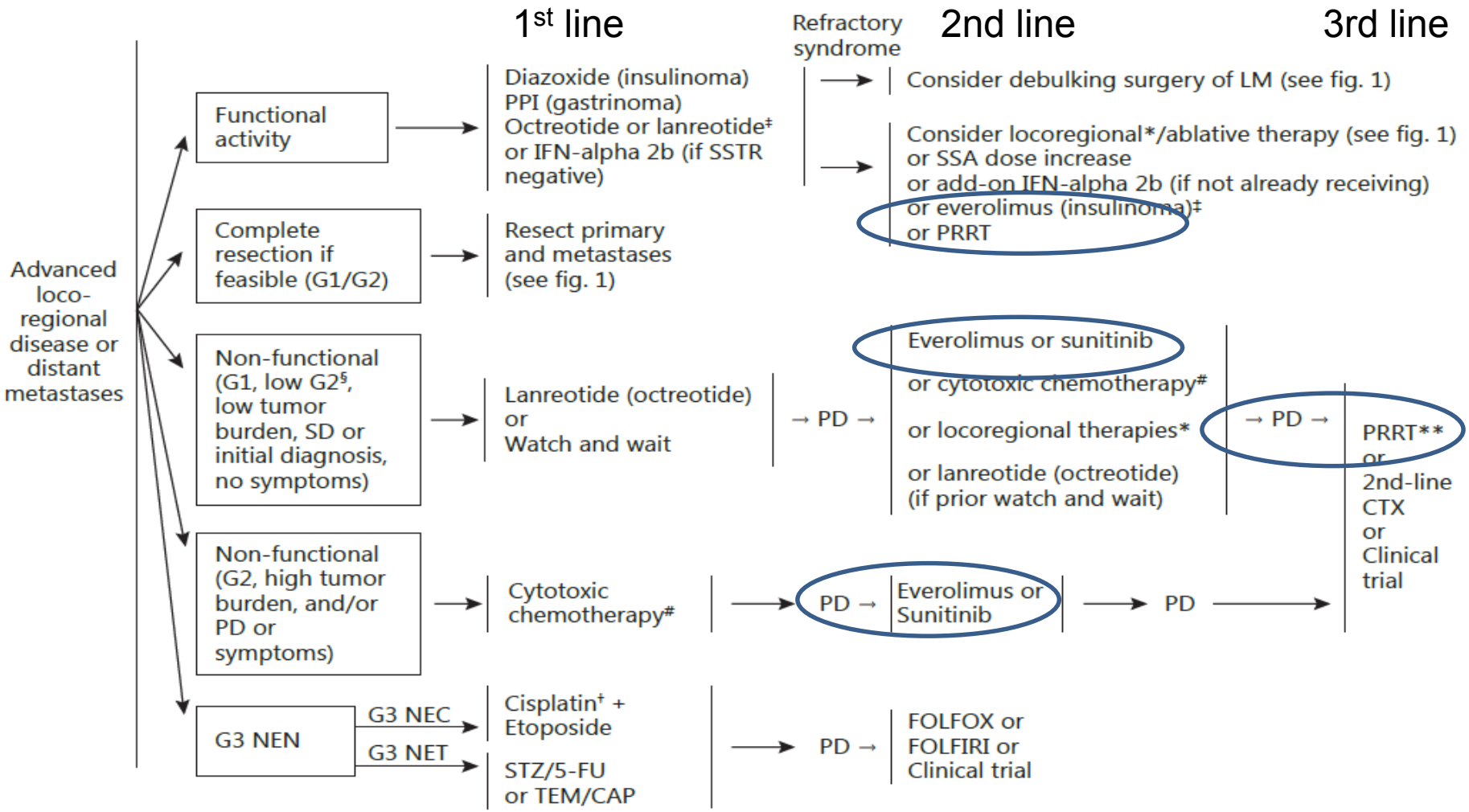
- Ki-67 proliferative index (Ki-67 index) is also used as a prognostic measure for grading parameters for NETs

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

Neuroendocrine tumours
(Management)

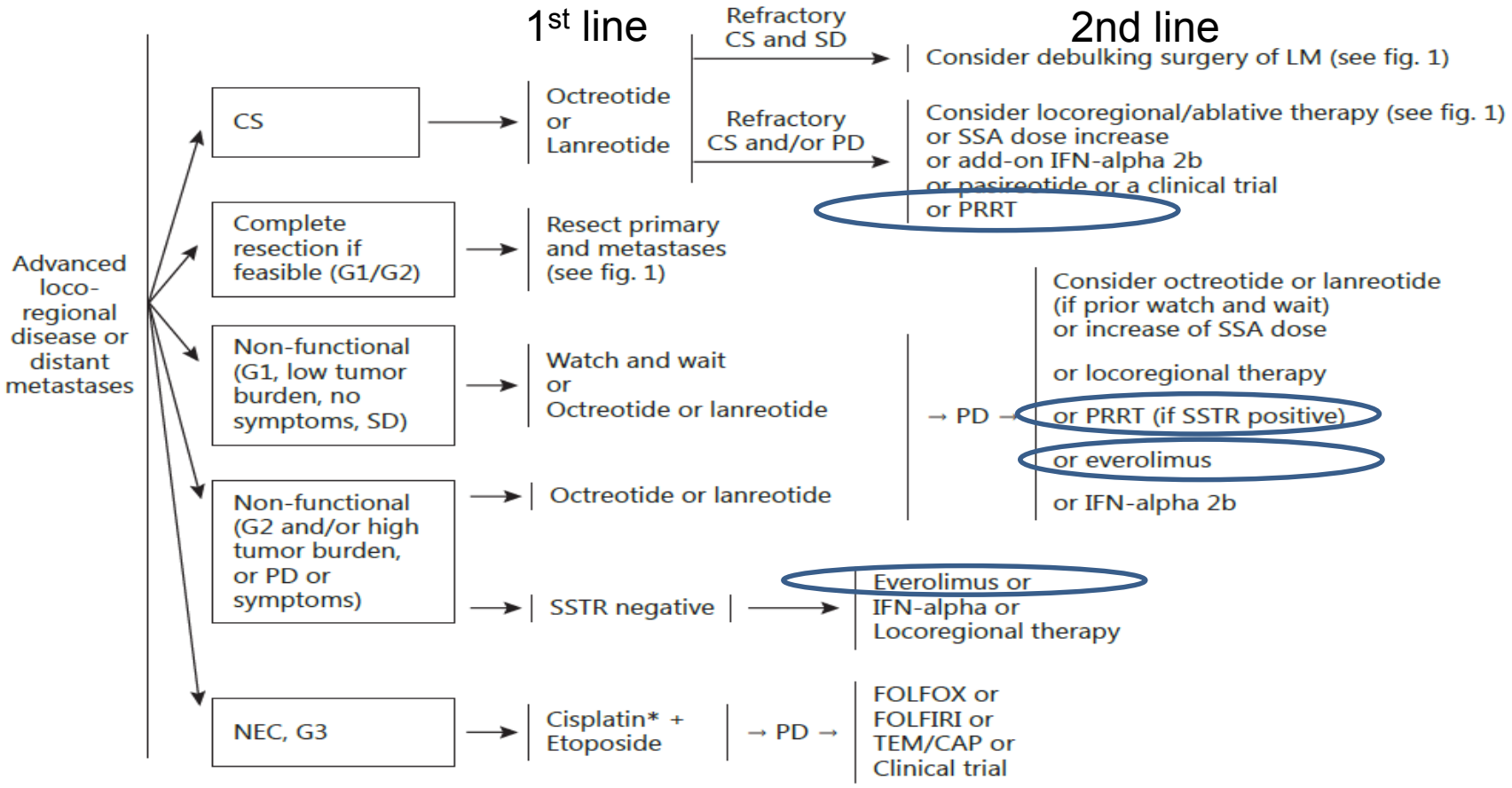
- No NICE guidance on neuroendocrine tumours
- Surgery is the only curative treatment
- Options for treating progressed neuroendocrine tumours include:
  - Somatostatin analogues (for symptomatic control e.g. octreotide, lanreotide)
  - Chemotherapy regimens (using combinations of streptozocin, 5-fluorouracil, doxorubicin, temozolomide and capecitabine)
  - Radionuclides (e.g. lutetium-177 – previously on the CDF)
  - Everolimus (previously on the CDF)
  - Sunitinib (currently on the CDF)
- Limited data for lung NETs
  - ENETS guidelines recommends everolimus for progressive lung NETs

Treatment pathway: Pancreatic NETs



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

Treatment pathway: GI NETs



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

Source: Pavel *et al.* 2016

Source: Novartis submission, figure 3.1, page 29

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

Patient perspectives

NET Patient Foundation

- Challenging tumours to diagnose and treat
- Around 3,000 new diagnoses each year in UK, but many remain undiagnosed
- Historically, treatments often improved symptoms but not always overall survival
- New treatments have improved progression-free survival, but also increased toxicity
- High unmet need in patients with lung NETs, and patients with GI NETs who have progressed following current therapy
- No NICE guidance
- Patients in England have seen their options increasingly restricted over the past two years
- PRRT and the Cancer Drug Fund

Patient perspectives (2)

NET Patient Foundation

- 'No clear pathway' of care for patient with NETs
- Lack of clarity and certainty impact on HRQoL & wellbeing
- Results from First Global NET survey:
  - 60% patients reported NETS negatively impacted emotional health
  - 52% experience significant stress & anxiety levels
  - 39% feel confused about the management of their disease
  - Of the 22% who were not working/unemployed due to medical disability, 82% had stopped working as a result of their NET
- Patients experience of Lu177 DOTATATE has been positive with significant improvement to length of life and quality of life

Clinical perspectives (1)

British Institute of Radiology and British Nuclear Medicine Society

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

Clinical perspectives (2)

Royal College of Physicians

- Management of NETs requires a multi-disciplinary treatment approach
- Limiting to patients with advanced disease and well-differentiated is appropriate
- Disease progression, treatment choice depends on site of tumour
- In P-NETs, everolimus and sunitinib are a clinically effective treatment option giving patients extra lines of therapy
  - Treatment continues until progression
- In intestinal NETs, treatment options beyond SSA's are limited
- 177-Lu DOTATATE allows the use of targeted radiotherapy, likely to be effective in all NETs
- No recognised optimal sequence of therapies
- Targeted therapies have the same level of activity regardless of prior chemotherapy use
- Clinicians are familiar with everolimus and sunitinib and management of toxicity
  - Adverse events are manageable
- NICE positive guidance would allow the UK to remain as one of the leading countries in NET patient-centred care

DETAILS OF THE TECHNOLOGIES

	Lutetium-177 DOTATATE (Lutathera, AAA)	Everolimus (Afinitor, Novartis)	Sunitinib (Sutent, Pfizer)
MA	[redacted]	• unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease • unresectable or metastatic, well-differentiated (grade 1 or grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease	• unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults
Admin.	Intravenous Infusion (IV)	Oral	Oral
Costs	[redacted] • A single cycle comprising four administrations of 7.4 GBq. The recommended interval between two infusions is eight weeks (± 1 week).	• The list price for everolimus is £2,673.00 for 30 x 10 mg everolimus tablets • A confidential PAS is available and details are presented in a confidential appendix	• Pack of 28, 12.5 mg capsules £784.70. • Pack of 29, 25 mg capsules £1,569.40. • Pack of 28, 50 mg capsules £3,138.80.

DECISION PROBLEM

Final scope issued by NICE		AG comments
Pop	People with progressed unresectable or metastatic neuroendocrine tumours (according to the specific locations covered by the existing and anticipated marketing authorisations of the interventions)	The AG population is consistent with the NICE scope
Int	• Everolimus (GI, Pancreatic or Lung NETS) • Lutetium-177 DOTATATE (GI or Pancreatic NETs) • Sunitinib (Pancreatic NETs)	The AG included all of these interventions
Comp	• the technologies listed above will be compared with each other where appropriate • interferon alpha • chemotherapy regimens • best supportive care	The AG consulted with clinicians and were told that interferon alpha was not commonly used within UK clinical practice. Therefore, it was not included
Out	• overall survival • progression-free survival • response rates • symptom control • adverse effects of treatment • health-related quality of life	The AG considered and included all of these outcome measures

Pancreatic NETs: Clinical Trials

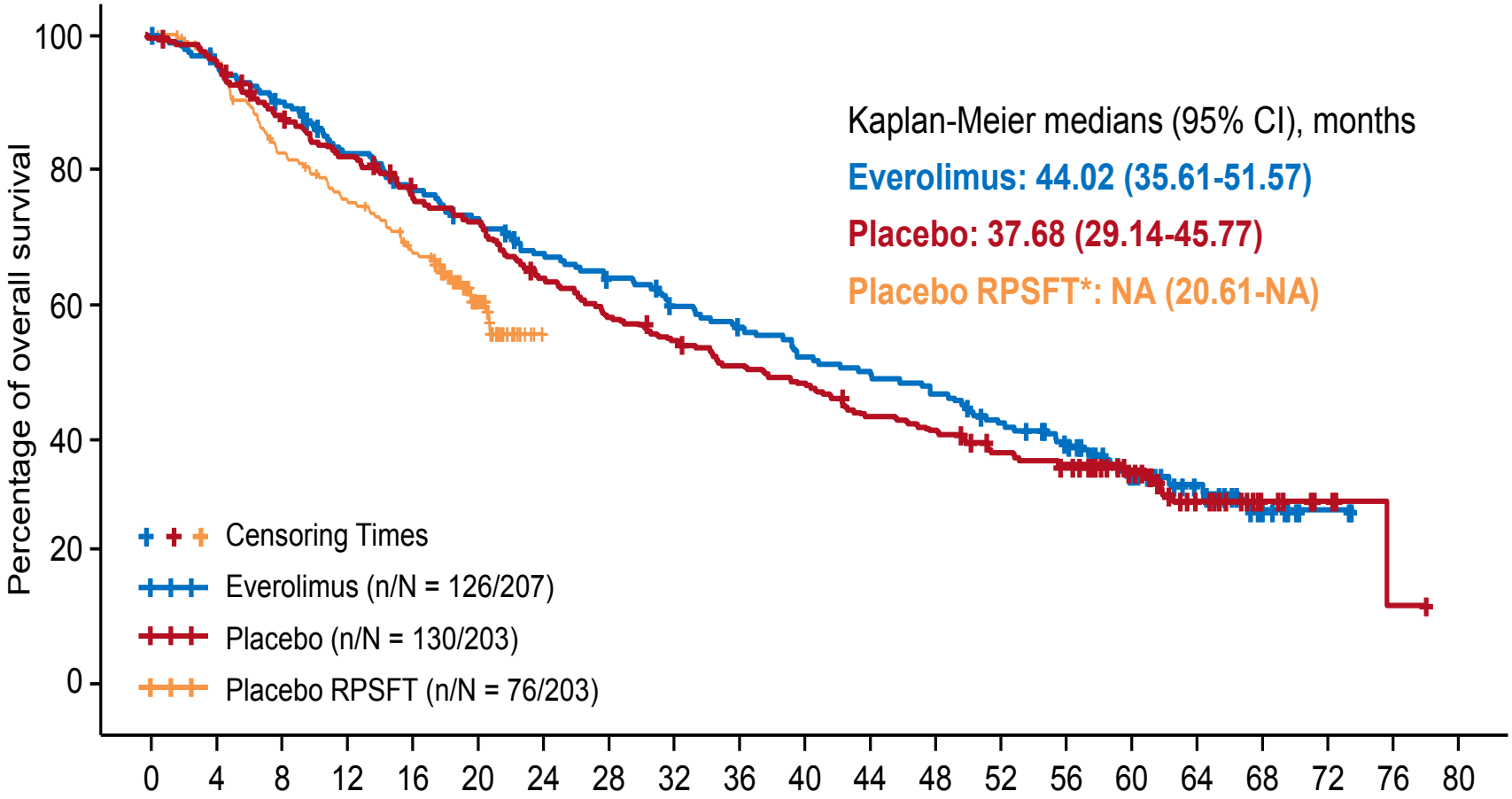
Trial	RADIANT-3 – everolimus plus BSC Vs. placebo plus BSC	A6181111 – sunitinib plus BSC Vs. placebo plus BSC
Design	• Double-blind, randomised, placebo-controlled phase III	
Population	• Patients with advanced, progressive, low- or intermediate-grade P-NETs	• Patients with progressive well-differentiated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

RADIANT-3 Results

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

Outcomes	Local assessment		Adjudicated central review	
Progression-free survival (PFS)				
	Everolimus + BSC (n=207)	Placebo + BSC (n=203)	Everolimus + BSC (n=207)	Placebo + BSC (n=203)
PFS, median, months HR (95% CI)	**11.0** (8.4 – 13.9)	**4.6** (3.1 – 5.4)	**11.4**	**5.4**
	0.35 (0.27–0.45)		**0.34** (0.26 – 0.44)	
Overall survival (OS) with adjustment for cross-over (Final OS analysis, March 2014, open label phase)				
OS, median, months HR (95% CI)	**44.02**	**37.68**	-	
	0.60 (0.09–3.95)			
Tumour response rates (n%)				
Partial response	**10** (4.8)	**4** (2.0)	• Results from the central reviews were similar to those reported for the local review • Compared with placebo, everolimus was associated with a superior response profile according to RECIST	
Stable disease	**151** (72.9)	**103** (50.7)		
Progressed disease	**29** (14.0)	**85** (41.9)		

RADIANT-3 Overall Survival



No. of patients still at risk

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

Source: Novartis submission, figure 4.7, page 45

RADIANT-3 subgroup analyses

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

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

Sources: Assessment report, tables 29 – 30, page 96

A6181111 Results (1)
Pfizer submission, section 4.7, pages 42 - 50

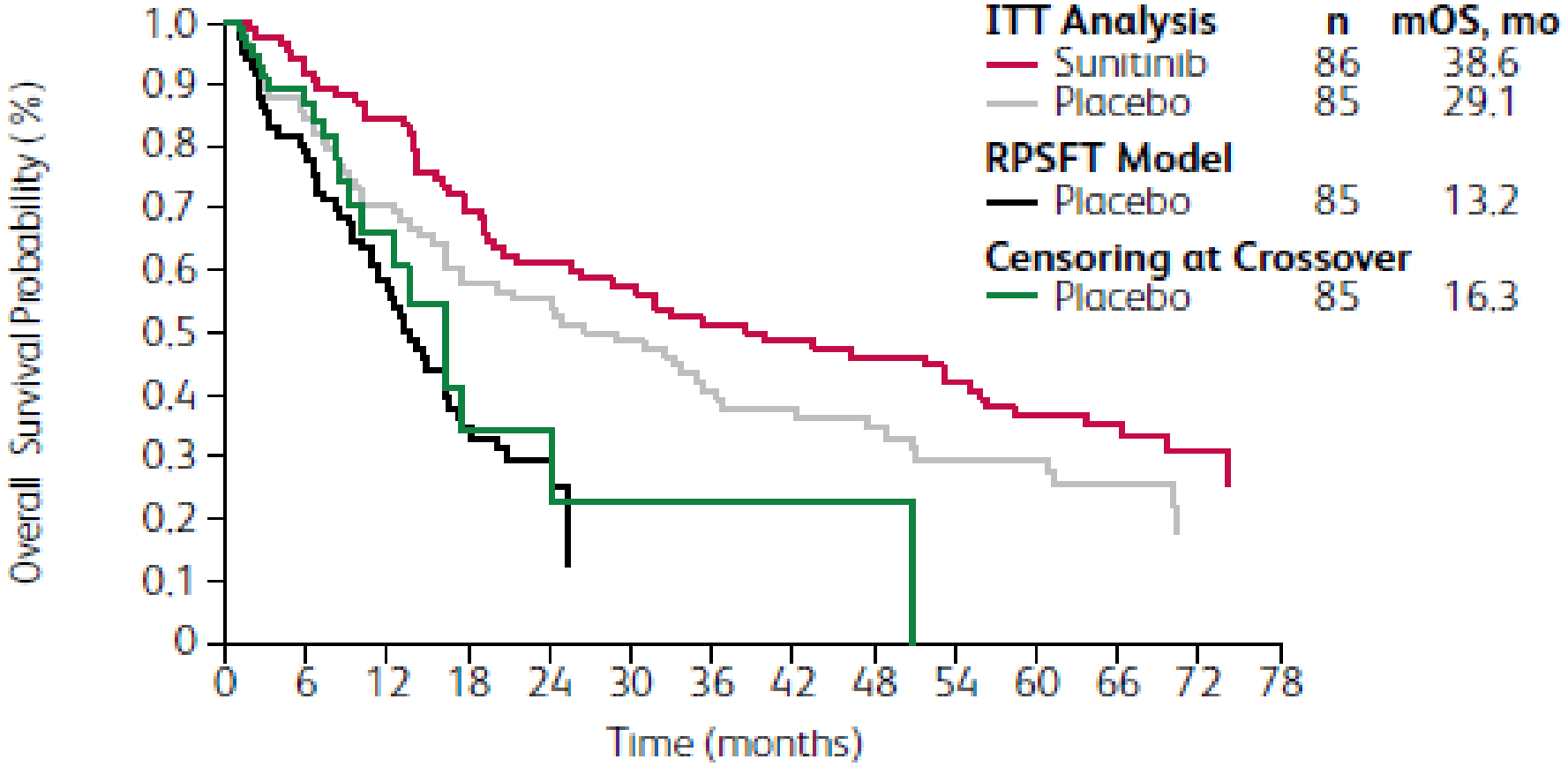
Outcomes	Investigator assessment		Independent review	
	Sunitinib (n=86)	Placebo (n=85)	Sunitinib (n=86)	Placebo (n=85)
Progression-free survival				
PFS, median, months	**11.4** (7.4 – 19.8)	**5.5** (3.6 – 7.4)	**12.6** (11.1 - 20.6)	**5.8** (3.8 - 7.2)
HR (95% CI)	**0.418** (CI: 0.263, 0.662)		**0.315**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

A6181111 Results (2)
Pfizer submission, section 4.7, pages 42 - 50

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

A6181111 Overall Survival

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



Source: Pfizer submission, figure 6 (page 48)

A6181111 subgroup analyses

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

GI and Lung NETs: Clinical Trials

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

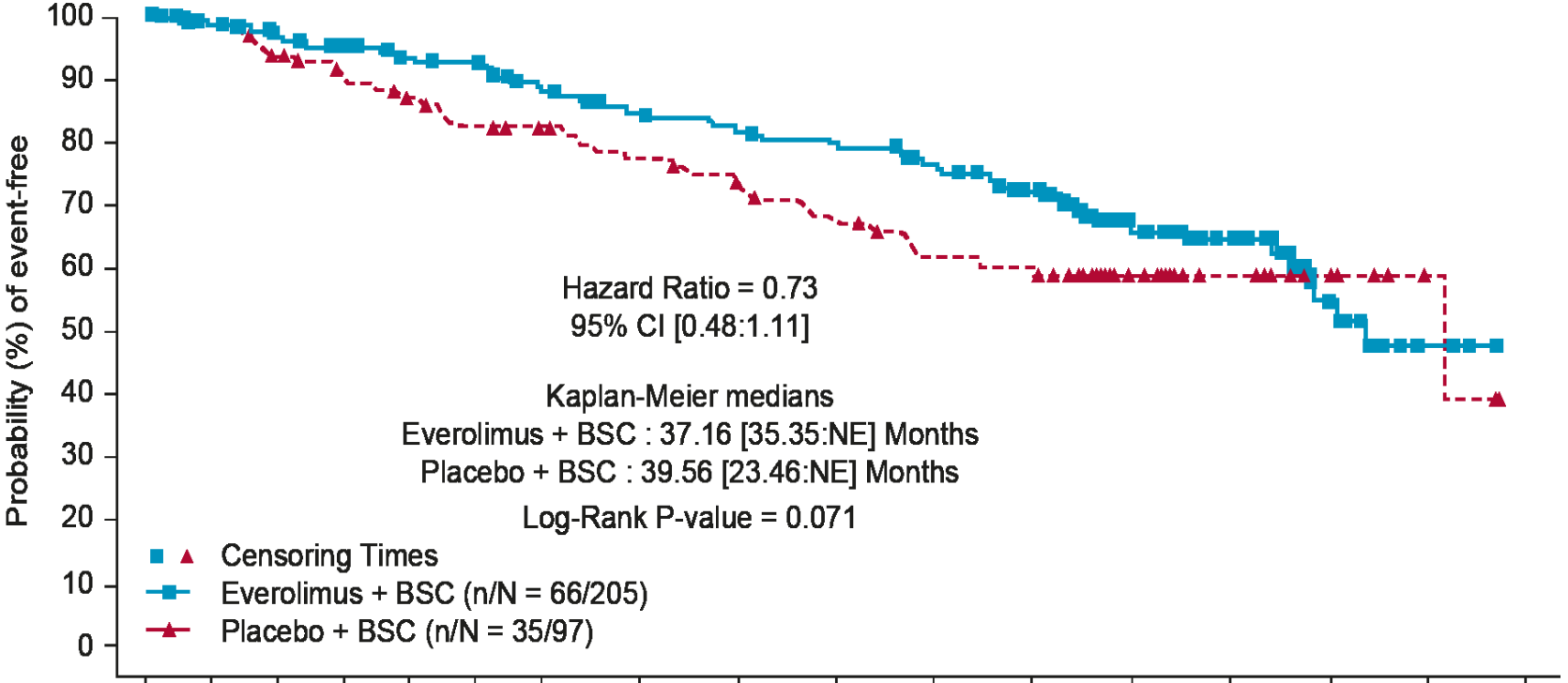
RADIANT-4 results: GI and Lung NETs combined
Novartis submission, tables 5.4 and 5.5 (pages 66 – 74)

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

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

RADIANT-4 Overall survival: GI and Lung NETs

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



No. of patients still at risk

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

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

Source: Novartis submission, figure 5.12, page 73

RADIANT-4 results: GI NETs only
Assessment report, tables 47- 49 (page 110)

Progression-free survival (PFS) - central review		
	Everolimus + BSC (n=118)	Placebo + BSC (n=57)
PFS, median, months	**13.1** (9.2, 17.3)	**5.4** (3.6, 9.3)
HR (95% CI)	**0.56** (0.37, 0.84)	
Overall survival (OS)		
OS, median, months	[redacted]	[redacted]
HR (95% CI)	[redacted]	
Tumour response rates (n %)		
Stable disease (SD)	[redacted]	[redacted]
Progressed disease (PD)	[redacted]	[redacted]

RADIANT-4 results: Lung NETs only
Assessment report, tables 52 - 54 (page 112)

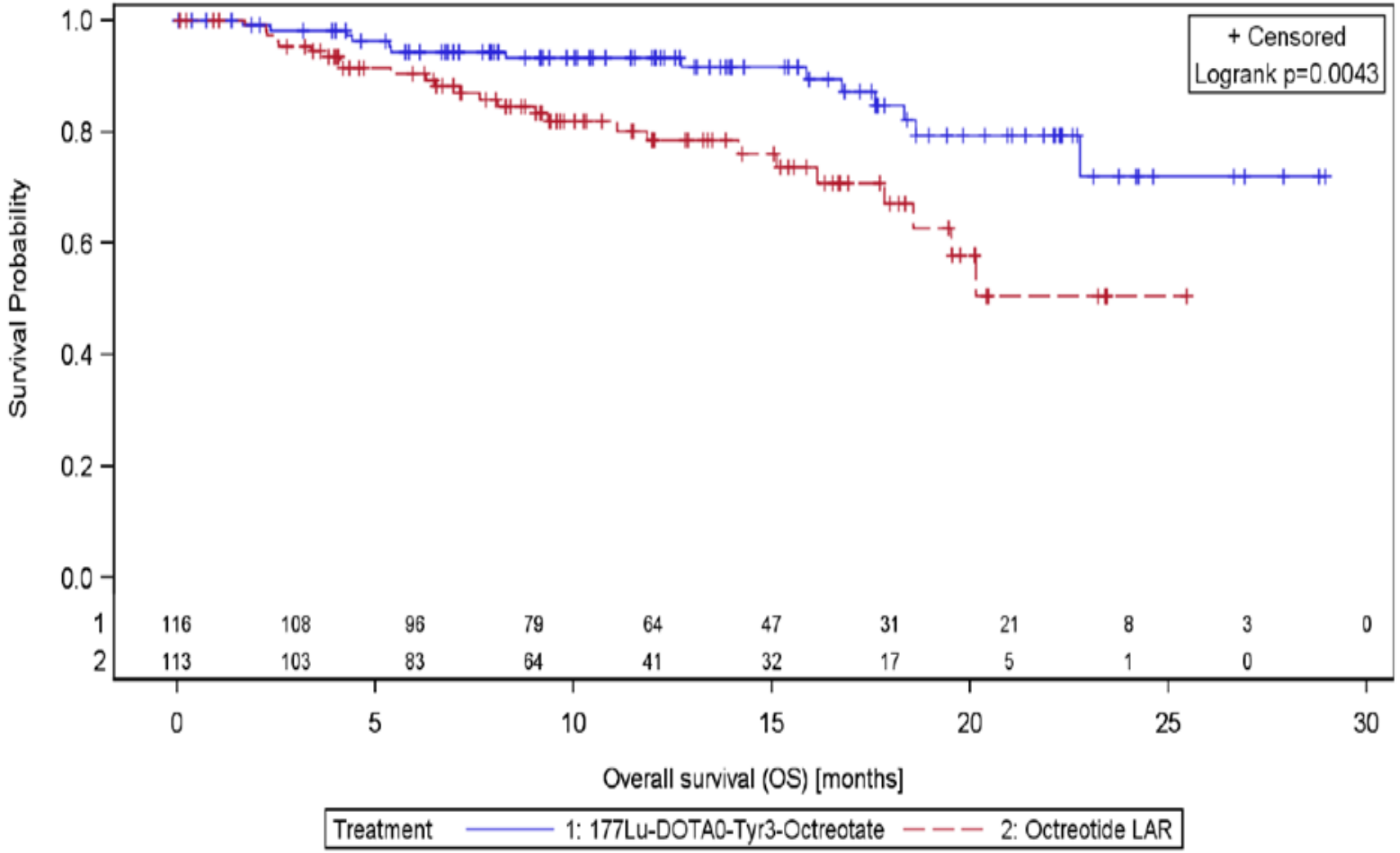
Progression-free survival (PFS)		
	Everolimus + BSC (n=63)	Placebo + BSC (n=27)
PFS, median, months	**42** (CI not recorded)	**18** (CI not recorded)
HR (95% CI)	**0.50** (0.28-0.88)	
Overall survival (OS)	[redacted]	[redacted]
OS, median, months	[redacted]	
HR (95% CI)		
Tumour response rates (n %)	[redacted]	[redacted]
Partial response (PR)	[redacted]	[redacted]
Stable disease (SD)	[redacted]	[redacted]
Progressed disease (PD)		

NETTER-1 Results
AAA submission, tables 13 and 14, page 50 –53

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

NETTER-1 Overall Survival

OS interim analysis, full analysis set



Source: AAA submission, figure 10, page 52

Health-related quality of life (HRQoL)

- **Everolimus**
  - **RADIANT-3**
    - Not collected
  - **RADIANT-4**
    - Everolimus had longer median time to definitive deterioration in HRQoL using FACT-G but not statistically significant
- **177-Lu DOTATATE**
  - **NETTER-1**
    - Treatment with 177Lu-DOTATATE does not negatively affect the patient's HRQoL compared with octreotide LAR when using EORTC QLQ-30
- **Sunitinib**
  - **A6181111**
    - No statistically significant difference between the sunitinib and placebo groups at any time when using EORTC QLQ-30

Adverse events (1)

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

Adverse events (2)

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

AG's comments on clinical trials

RADIANT-3, RADIANT-4 and A6181111

- All 3 trials double blind - low risk of bias in all
- Populations for the 3 trials all in line with the licensed indication for each treatment and with final scope
- Limited information for current prevalence of NETs to assess generalisability
- The applicability of the results in the UK setting was unclear
- High levels of crossover in RADIANT-3 and A6181111 (73% and 69%)

Company network meta-analyses (P-NETs)

Novartis and Pfizer

- **Novartis (everolimus vs sunitinib)**
  - Bucher indirect comparison using data from RADIANT-3 and A6181111
  - PFS local investigator assessment – **HR 0.83** (0.49, 1.42)
  - PFS blinded independent review committee - **HR 1.08** (0.59, 1.99)
  - OS ITT analysis – **HR 1.32** (0.81, 2.16)
  - OS RPSFT-adjusted analysis – **HR 1.40** (0.17, 11.72)
- **Pfizer (sunitinib vs everolimus)**
  - MAIC using patient-level data from A6181111 and aggregate data from RADIANT-3

Company network meta-analyses
AAA

P-NETs

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

GI NETs

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

AG'S comments on company network meta-analyses (1)

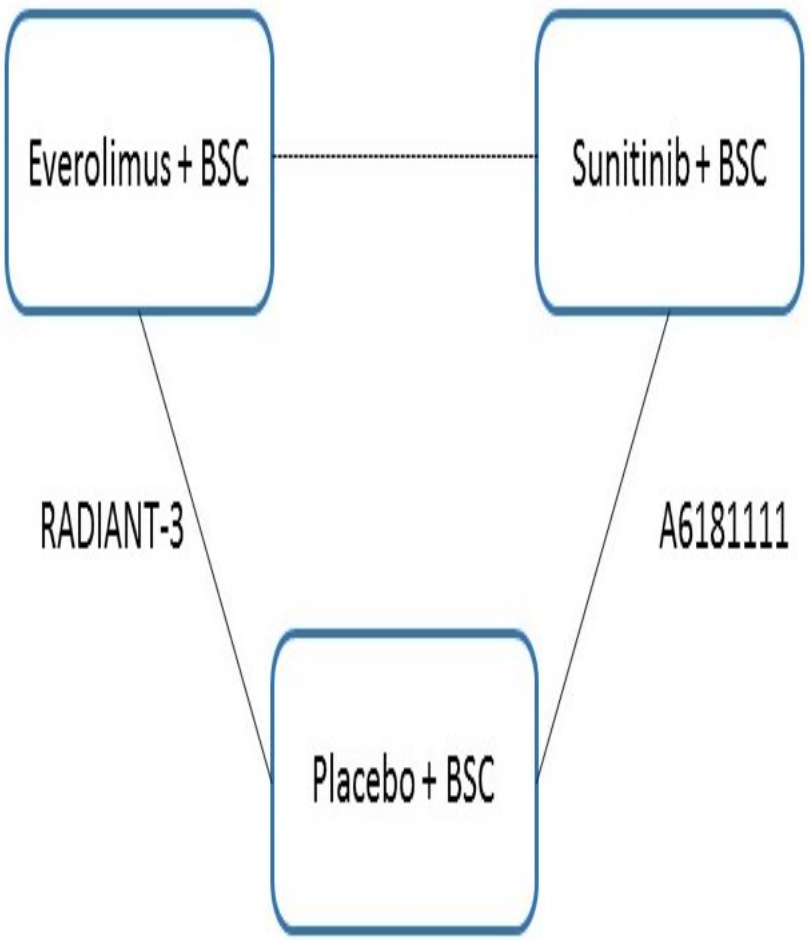
- **Novartis submission (Bucher indirect comparison using data from RADIANT-3 and A6181111)**
  - Inconsistent results for PFS between central and local review
  - Wide confidence intervals for all results - uncertainties
  - Different results when using crossover unadjusted and adjusted results
  - Response rates results with wide confidence intervals suggesting little difference between the two treatments
  - Unclear why Bucher was used over MAIC. However, similar results and Bucher has more mature data
- **Pfizer submission (MAIC using patient-level data from A6181111 and aggregate data from RADIANT-3)**
  - MAIC here could not adjust for differences in study design across trials
  - RADIANT-3 and A6181111 populations were similar (some differences)
  - Balanced baseline characteristics in RADIANT-3/Imbalanced baseline characteristics in A6181111
  - Small sample size (which after matching halved in size)

AG'S comments on company network meta-analyses (2)

- **AAA P-NETs submission (Mixed treatment comparison using data from NETTER-1, RADIANT-3 and A6181111)**
  - No justification that octreotide LAR 60mg is equivalent to placebo, placebo + octreotide (30mg) and placebo + BSC
  - NETTER-1 should be excluded: no patients with P-NETs
  - No consideration of treatment switching for the trials included
  - Wide confidence intervals suggesting uncertainty
  - Models used not reported in the submission and so no comparison of any differences in point estimates
- **AAA GI-NETs submission (Indirect treatment comparison comparing results from NETTER-1 and RADIANT-4)**
  - No justification that octreotide LAR 60mg is equivalent to placebo, placebo+octreotide (30mg) and placebo+BSC
  - RADIANT-2 should be excluded: population all have functioning tumours (outside MA for everolimus for GI-NETs)
  - For GI NETs populations for OS differ across the studies
  - No consideration of treatment switching for the trials included
  - Wide confidence intervals suggesting uncertainty

Everolimus Vs Sunitinib (P-NETs)

Assessment Group



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

Source: Assessment report, figure 17 (page 98)

ITC – PFS results (P-NETs)

AG Report

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

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

ITC – OS results (P-NETs)
AG Report

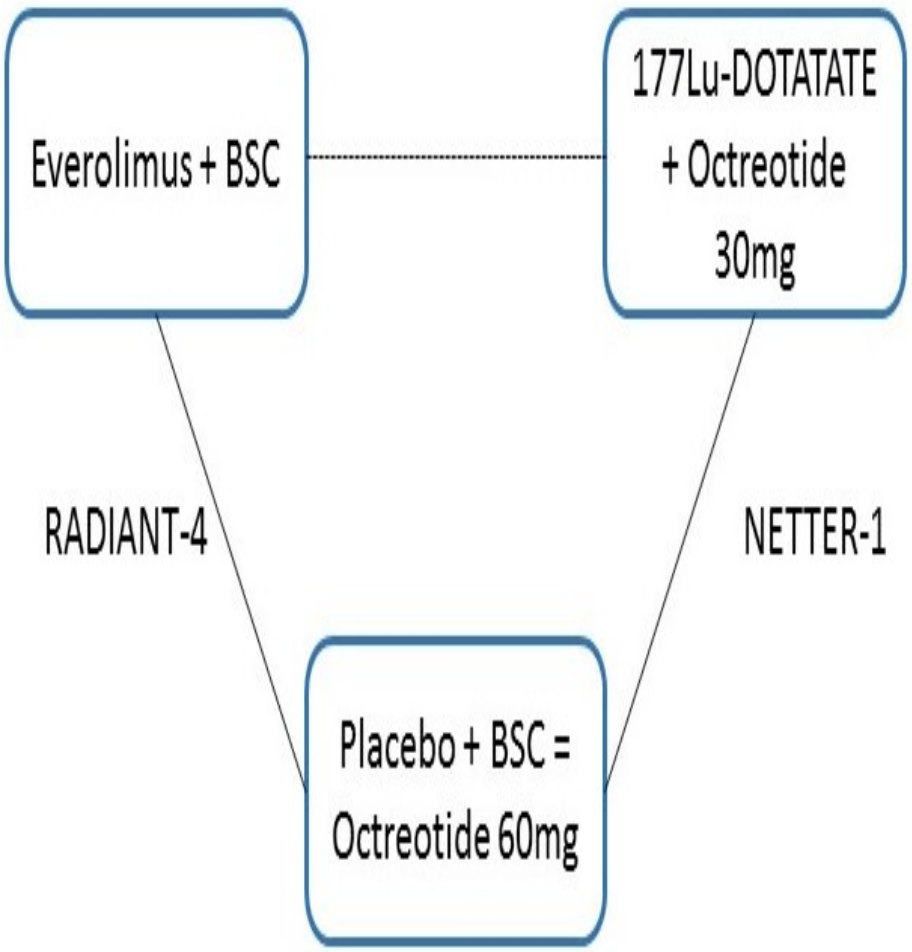
HRs (95%CI) for death P-NETs based on final follow-up data (crossover unadjusted)			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus + BSC	Placebo + BSC	RADIANT-3	[redacted]
Sunitinib + BSC	Placebo + BSC	A6181111	[redacted]
Everolimus + BSC	Sunitinib + BSC	Calculated by AG	[redacted]

HRs (95%CI) for death P-NETs (crossover adjusted RPSFT)			
Intervention	**Comparator**	**Data source**	**HR (95% CI)**
Everolimus + BSC	Placebo + BSC	RADIANT-3	[redacted]
Sunitinib + BSC	Placebo + BSC	A6181111	[redacted]
Everolimus + BSC	Sunitinib + BSC	Calculated by AG	[redacted]

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

Lutetium-177 Vs everolimus (GI-NETs)

Assessment Group



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

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

ITC – PFS & OS results (GI-NETs)

AG Report

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

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

Key clinical issues (1)

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

  Have the appropriate comparisons been made for each tumour locations?

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

Key clinical issues (2)

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