Chair's presentation

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

3rd Appraisal Committee meeting

Committee D

12 June 2018

Issue for consideration

- Which analysis best reflects the use of somatostatin analogues (SSAs) in the NHS, in terms of;
  - Proportion of patients having SSAs
  - Octreotide dose

History of the appraisal

ACM 1 Feb 2017

- Everolimus and sunitinib **recommended (TA449)**
- Lutetium **not recommended**
  - split from MTA – no CHMP
  - CHMP July 2017 – ACD released

ACM 2 April 2018

- Lutetium **recommended** for pancreatic NETs, but **not recommended** for GI NETs
- Issues relating to the use of SSAs identified during 2nd ACD development
  - Clinical experts contacted to clarify the issues
  - ACD **not released**

Today

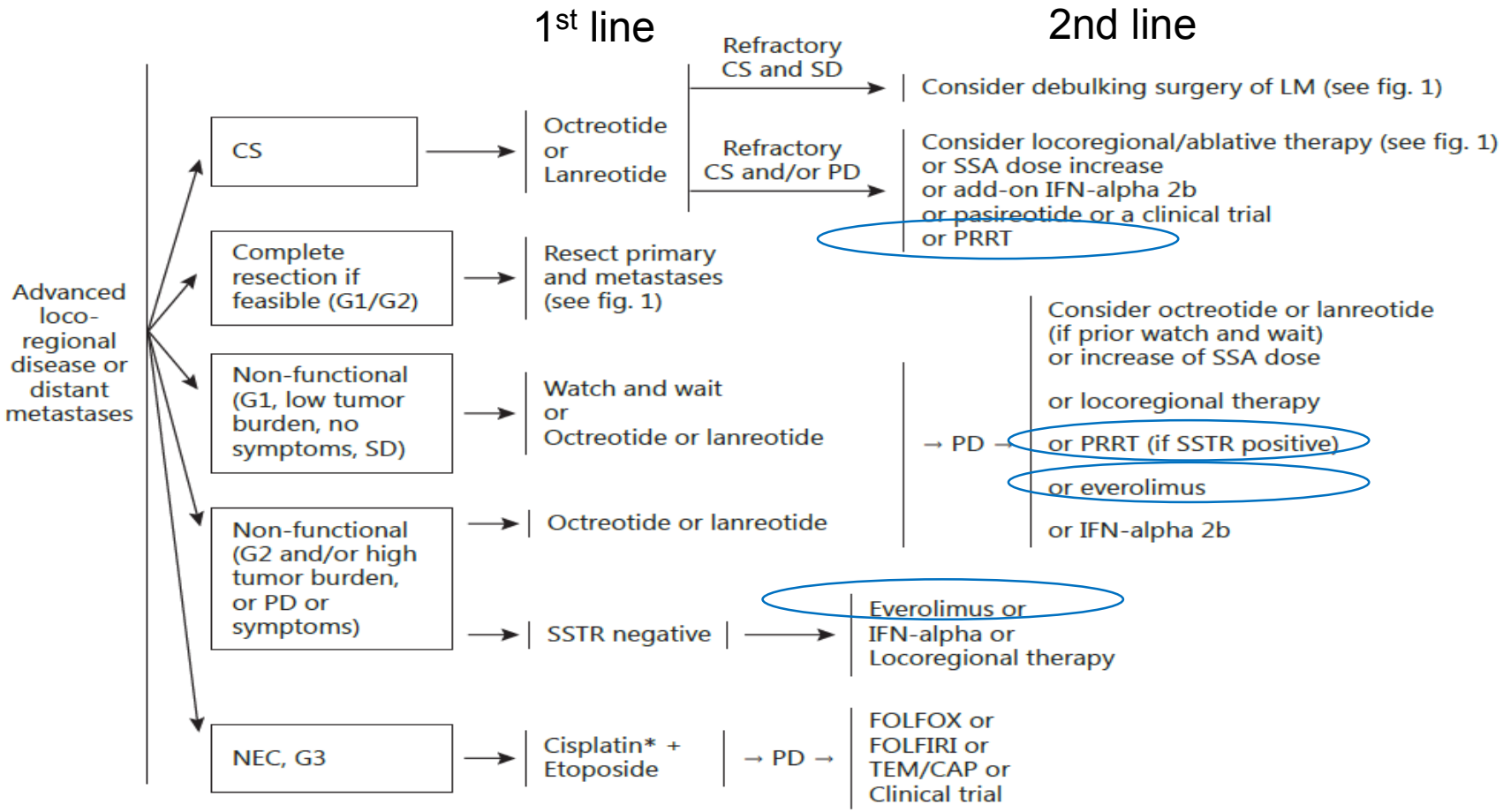
- Response from clinical experts
- Company's revised PAS discount

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 infusions is 8 weeks
Mechanism of action	A Peptide Receptor Radionuclide Therapy (PRRT), which targets neuroendocrine tumours with radiolabelled somatostatin (SSA) peptides
Acquisition cost	• £71,500.00 for a course of treatment • Confidential patient access scheme available

***AAA – Advanced Accelerated Applications**

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

SSA definitions in the models

- Company's base case - based on NETTER-1 (BSC arm only)
- AG's base case – based on RADIANT-4 (GI-NETs)

Disease and stage	Strategy	Proportion using SSRAs – AG model	Proportion using SSRAs – AAA model
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)

Key: HD – high dose (60mg octreotide), LD – low dose (30mg octreotide)

Source: AG addendum report, table 20, page 46

AG's scenario analysis on SSA use
(GI-NETs; List price)

Scenarios	ICER Lutetium versus:	
	BSC	**Everolimus**
AG's Base case ICER (£)	***37,737***	***38,557***
Alternative definition of BSC 1: high dose 60mg octreotide in 40% patients (pre-progression only, BSC arm only)	34,185	38,557
Alternative definition of BSC 2: high dose 60mg octreotide in 100% patients (pre-progression only, BSC arm only)	28,591	38,557
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 • Applied to all treatment groups in the model (BSC, 177Lu-DOTATATE and Everolimus)	38,848	29,041

Note: The committee previously considered that BSC is the most relevant comparator because everolimus is licensed for non-functional GI NETs only (a subgroup)

Question to clinical experts

⊙ *Which of these scenarios best reflects the use of SSAs for GI NETs in the NHS – in terms of proportion of patients and SSA dose?*

Response from clinical expert

Post-progression (when lutetium is indicated):

- For hormonal syndrome (approx. 40%): all patients would continue SSA with the escalation of therapy
- Non hormonal syndrome (approx. 60%): practice varies
- There is variability of opinion on whether patients should continue SSA with lutetium.
  - Evidence from NETTER-1 suggests this is continued (at MA dose)

Most appropriate analysis

- AG base case too low, but would not be 100% of patients
- About 95% of patients would be on SSA at study entry
  - about 20% of patients with higher dose.
  - Lutetium plus SSA in line with NETTER-1
  - Upon progression – some continue SSA, but approx. 10% will stop or reduce dose (particularly for non hormonal syndrome)

Issue for consideration

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  - Proportion of patients having SSAs
  - Octreotide dose