Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy

Confidential information redacted

Highly Specialised Technology appraisal committee, 12 June 2024

Chair: Paul Arundel

External assessment group: Liverpool Reviews and Implementation Group

Technical team: Kirsty Pitt, Claire Hawksworth, Jasdeep Hayre

Company: Eli Lilly

Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy

- ✓ **Recap**
- ❑ Response to consultation

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Recap – Committee's key conclusions from ACM 1 (1)

Selpercatinib is not recommended

Area	Key conclusion
Comparators	Most relevant for RET-mutant MTC are cabozantinib and best supportive care (BSC), and for RET fusion-positive TC are lenvatinib, sorafenib and BSC
Clinical evidence	Selpercatinib likely improves PFS and OS compared with cabozantinib, lenvatinib, sorafenib and BSC, but it is uncertain by how much, due to uncertainties in the 2 indirect treatment comparisons
Economic model	Committee would like to see analyses from the economic model that include sorafenib
Overall survival – selpercatinib	Company's extrapolations for selpercatinib can be used for decision-making • RET-mutant MTC: stratified Weibull with adjustment factor of 2 at 5 years • RET fusion-positive TC: piecewise exponential with adjustment factor of 2 at 5 years) EAG optimistic and pessimistic scenarios that aligned the predicted 10- and 20- year survival from the model with the upper and lower limits of clinicians' plausible range • These scenarios represent committee's plausible range of uncertainty
Overall survival - cabozantinib	EAG's method of generating OS curve should be used • Apply HR from EXAM trial to stratified spline knot extrapolation for BSC

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; BSC, best supportive care; PFS, progression-free survival; OS, overall survival; HR, hazard ratio

Recap – Committee's key conclusions from ACM 1 (2)

Selpercatinib is not recommended

Area	Key conclusion
Utility values	Utility values mapped from LIBRETTO-001 should be used in the model
Relative dose intensity	Should be included for selpercatinib but not the comparators
Severity	Severity modifier of 1.2 applies to comparisons with BSC in both populations. Doesn't apply to comparisons with cabozantinib or lenvatinib. Unknown whether it applies to comparison with sorafenib.
Acceptable ICER	Around £20,000 per QALY gained

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year

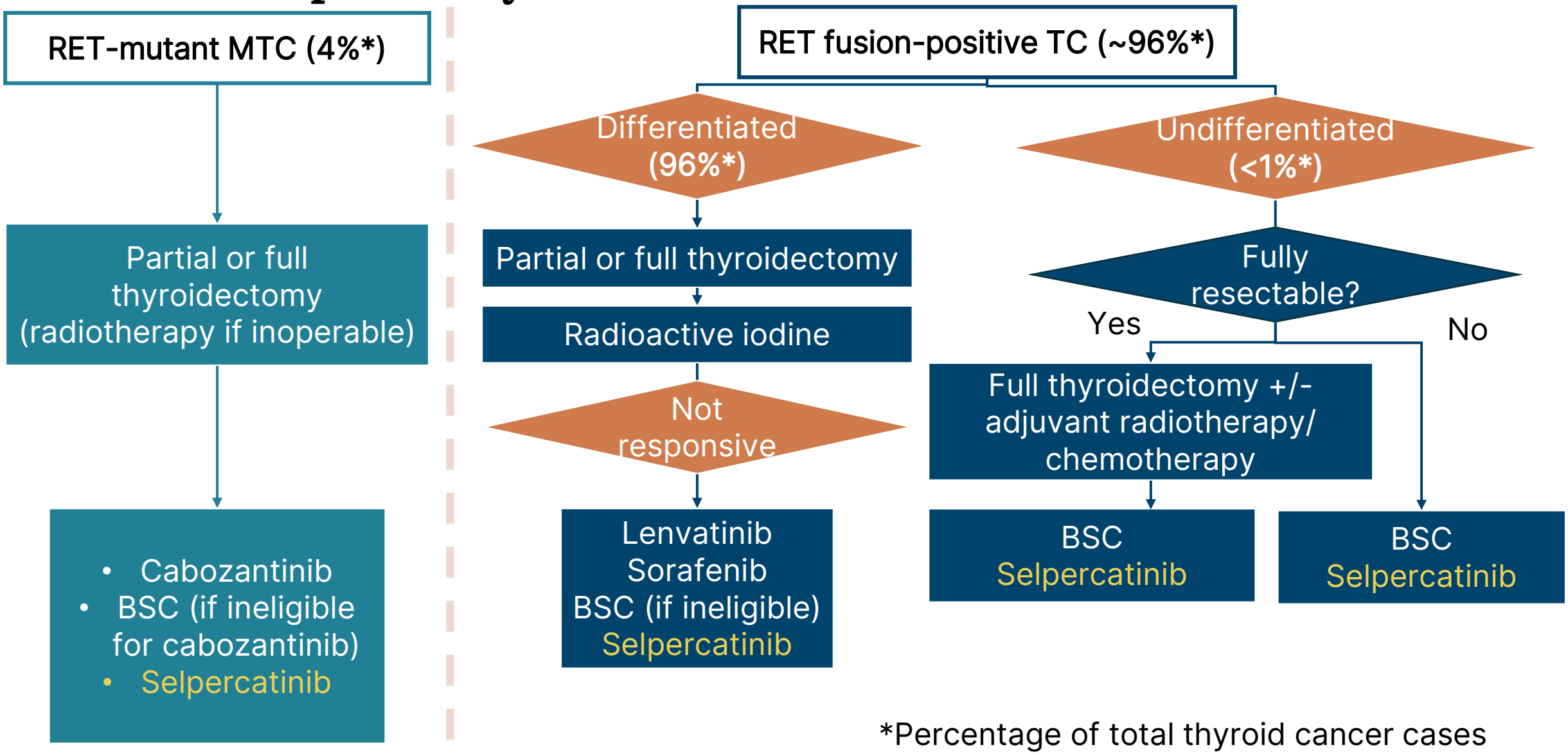
Selpercatinib (Retsevmo, Eli Lilly)

Marketing authorisation	RET-mutant MTC
	• MHRA conditional marketing authorisation (MA) granted February 2023:
	  • Patients aged ≥12 years with advanced RET-mutant MTC
	RET fusion-positive TC
	• EU marketing authorisation (GB MA not yet granted):
	  • Adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)

Mechanism of action	Selective kinase inhibitor, targeting the RET tyrosine kinase receptor
Administration	Oral capsules
Price	List price: • 56 capsules of 40 mg selpercatinib: £2,184.00 • 168 capsules of 40 mg selpercatinib: £6,552.00 • 56 capsules of 80 mg selpercatinib: £4,368.00 • 112 capsules of 80 mg selpercatinib: £8,736.00 At list price, the cost of a 28-day cycle of selpercatinib is £8,736.00 A PAS is in place

Abbreviations: MTC, medullary thyroid cancer; TC, follicular thyroid cancer; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme

Treatment pathway



*Percentage of total thyroid cancer cases

Abbreviations: BSC, best supportive care

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- ❑ Recap
- ✓ **Response to consultation**

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Summary of consultation responses

Responses received from company and patient expert

Consultation responses received from

- Company (see following slides)
    - Revised patient access scheme
    - Further analyses and commentary
    - Minor clarifications and typographical errors
- Patient expert
    - Ease of administration, monitoring and lack of side effects with selpercatinib are not reflected adequately in the draft guidance
    - Small numbers of patients with this condition, which makes evidence difficult to obtain
    - Best supportive care is a relevant comparator but is not an acceptable treatment option for patients

Overview of company's response

Company has incorporated committee's preferences from first meeting

Issue	Has company incorporated committee preference?
Comparators	Scenario analysis that includes sorafenib is presented
Overall survival – selpercatinib	Yes, although not incorporated pessimistic and optimistic scenarios as range of plausible uncertainty • EAG has provided these – see part 2 slides
Overall survival - cabozantinib	Yes
Utility values	Yes
Relative dose intensity	Yes
Severity	Yes

Comparators – inclusion of sorafenib in the economic model (1)

RET fusion-positive TC

Background

- At ACM1 the committee concluded that it would like to see analyses comparing selpercatinib with sorafenib because it is a treatment currently used in the NHS for RET fusion-positive TC
- DECISION trial compared sorafenib (n=207) with placebo (n=210) for locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer. No prior targeted cancer therapy was permitted

Company

- Maintain that sorafenib is not a relevant comparator but has presented a scenario analysis to include sorafenib in the model
- Trial and ITC results indicate that lenvatinib results in higher PFS when compared with sorafenib, but OS is higher with sorafenib – company considers this implausible
- Clinical advice to the company also indicates efficacy of lenvatinib is superior to sorafenib
- Kim et al 2023 (retrospective cohort study, n=136) reported an increase in PFS with lenvatinib compared with sorafenib (HR 0.34, 95% CI: 0.19, 0.60)
- So, company has applied an adjustment to the OS KM data for sorafenib from the DECISION trial to make results clinically plausible

Other considerations

- TA535 (MTA: lenvatinib and sorafenib for TC) concluded it is not appropriate to use an indirect treatment comparison of lenvatinib and sorafenib using evidence from SELECT and DECISION because of differences in patient characteristics, previous and subsequent treatments, and treatment crossover

Abbreviations: ACM, appraisal committee meeting; BSC, best supportive care; ITC, indirect treatment comparison; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; KM, Kaplan-Meier

Comparators – inclusion of sorafenib in the economic model (2)

Company

- Selected stratified Weibull extrapolation for sorafenib PFS and piecewise exponential curve for OS
- Asked clinicians to provide survival estimates for patients with RET fusion-positive TC receiving sorafenib at 5, 10, 15 and 20 years
- Company applied adjustment factor (as had done previously for selpercatinib OS) to sorafenib OS to align survival estimates predicted by the model with estimates provided by clinical experts
  - Adjustment factor of 2.7 applied at 26 months

Year	Sorafenib OS estimates		
	Clinician landmark estimate	Before adjustment factor application	After adjustment factor application
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]

EAG comments

- Agree with company that OS ITC results do not align with clinical opinion or published evidence
- Company OS ITC results should be considered exploratory – results are unreliable, and resulting cost-effectiveness results are unreliable

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Abbreviations: OS, overall survival; ITC, indirect treatment comparison

Comparators – inclusion of sorafenib in the economic model (3)

Company

- Presents adjusted survival curves for selpercatinib, lenvatinib (SELECT), BSC (SELECT) and sorafenib (DECISION)
- Notes OS estimates still higher for sorafenib than lenvatinib until the adjustment factor is applied

Abbreviations: OS, overall survival; KM, Kaplan-Meier; BSC, best supportive care

Severity

Background

- At ACM1, committee concluded that in a pairwise analysis, a severity modifier of 1.2 could be applied to the comparisons with BSC for both populations, but not to the comparisons with cabozantinib or lenvatinib. It was unknown whether a severity modifier would apply to a comparison with sorafenib

Company

- Updated severity calculations to correct mean age in RET-mutant MTC population (now matches mean starting age in model, [redacted]) and use committee's preferred utility values, and to include calculations for sorafenib

Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
RET-mutant MTC			
Cabozantinib	11.44	81.59%	1
BSC	12.11	86.37%	1.2
RET-fusion positive TC			
Lenvatinib	10.41	77.74%	1
Sorafenib	11.05	82.52%	1
BSC	11.74	87.67%	1.2

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year

Further comments

Additional benefits not captured in the QALY

Company

- Substantial benefits of selpercatinib that cannot be captured in the QALY calculations
  - Rarity of the condition
  - Devastating effect of disease on children and young people
    - Adolescents would experience a larger QALY detriment compared with the age-matched general population than overall appraisal population – severity modifier would be met if calculated just in adolescent population
  - Lack of effective treatment options due to high toxicity profile of currently available treatments – particularly for adolescent patients who cannot have cabozantinib, lenvatinib and sorafenib
  - Benefits of selpercatinib to carers not captured in economic model
- Selpercatinib is the first targeted treatment for advanced RET-altered thyroid cancer

Abbreviations: QALY, quality-adjusted life year

Cost-effectiveness results

All ICERs are reported in PART 2 slides because there are confidential comparator PAS discounts

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Managed access

Could data collection resolve key uncertainties?

Background

- At ACM1, committee noted that the ongoing LIBRETTO-531 trial could provide relevant evidence for the RET-mutant medullary thyroid cancer population, although the company considered that LIBRETTO-531 had limited follow-up and that median PFS would be unlikely to be reached within the period of managed access
- Committee considered that further survival data collected through a managed access arrangement would be valuable in reducing the uncertainty in the evaluation, even if median PFS or OS was not reached. Also agreed that more data on quality of life in this population would help to inform the choice of utility values

Company

- Selpercatinib should be considered for routine commissioning in the first instance
- Available data from LIBRETTO-001 has greater follow-up and patient numbers in this appraisal than when used to inform submission for second line use of selpercatinib (TA742)

Ongoing trial evidence collection

- For LIBRETTO-001, [redacted]
- LIBRETTO-531 is ongoing in MTC only. Median follow-up at last data cut in May 2023 was 12 months Expected completion February 2026

Key questions for committee

- What are the most appropriate comparators?
    - Are best supportive care and sorafenib (RET fusion-positive TC only) relevant comparators?
- Is the company's approach to modelling sorafenib appropriate?
- What would be an acceptable ICER, given the considerations raised around additional benefits not captured in the QALY?
- Can a recommendation for routine commissioning be made?
    - If not, is managed access an option?

Back up slides

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Key clinical trials

LIBRETTO-531 has shorter follow-up than LIBRETTO-001

Clinical trial designs and outcomes

	LIBRETTO-001 (n=837)	LIBRETTO-531 (n=291)
Design	Phase 1/2	Phase 3
Date	Started May 17, latest data cut off Jan 23	Started Feb 20, latest data cut off May 23
Population	Patients with locally advanced or metastatic solid tumours (including with *RET* alterations), aged ≥18 years (aged ≥12 years where permitted by local regulatory authorities) who previously had, could not have standard therapy, or no standard therapy exists	Patients aged ≥18 years (aged ≥12 years where permitted by local regulatory authorities) with locally advanced or metastatic MTC with a *RET* alteration (somatic or germline) and no previous treatment with kinase inhibitors
Comparator(s)	None	Cabozantinib or vandetanib (physician's choice, but only cabozantinib since Nov 2021)
Locations	16 countries incl. UK	21 countries incl. UK
Used in model?	Yes	No

Abbreviations: MTC, medullary thyroid cancer

LIBRETTO-531

Multicentre, randomised, open-label, phase 3 trial comparing selpercatinib to cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naive, RET-mutant MTC – expected completion February 2026

Outcomes being collected in LIBRETTO-531 trial

- Primary outcome measure
  - Progression-free survival
- Secondary outcome measure
  - Treatment failure-free survival
  - Overall response rate
  - Duration of response
  - Overall survival
  - Progression-free survival by investigator
  - Comparative tolerability
  - Concordance of local lab and central lab RET results

NB. Further evidence collection within CDF is limited to 5 years

- At ACM1, committee noted that collecting more data would be useful but also that the survival extrapolations presented could be used for decision-making. Which of these 2 scenarios is committee most happy with?
- If considering managed access, given the above, are the committee satisfied that the burden of additional data collection, a managed access process and a reappraisal at managed access exit will produce benefits that outweigh that burden?

Abbreviations: ACM, appraisal committee meeting; RET, rearranged during transfection; MTC, medullary thyroid cancer