Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final protocol [ID56] 2016

1. Title of the project:

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer

2. Name of TAR team and 'lead'

TAR team

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3. Plain English Summary

Thyroid cancer is the most common malignant endocrine tumour, but represents only about 1% of all malignancies.[1] According to Cancer Research UK, 2,791 new cases of thyroid cancer were reported in England in 2013.[2] The disease is more common in females than males: the age-standardised incidence rate is reported to be 7.7 per 100,000 persons in women and 3.1 per 100,000 persons in men.[2] There are four main types of thyroid cancer: papillary, follicular, medullary and anaplastic. Medullary thyroid carcinoma (MTC), the disease type which will be considered within this appraisal, is a rare type of cancer that presents as a mass of tumours in the thyroid gland of the neck. MTC occurs in the parafollicular cells (also known as C-cells). Symptoms relating to pressure effects may include dysphagia (difficulty or discomfort in swallowing) and dysphonia (difficulty in speaking). There are four types of MTC: sporadic, multiple endocrine neoplasia (MEN) 2A and 2B and familial medullary thyroid carcinoma; approximately 75% of cases of MTC are sporadic in nature. MTC is rare and accounts for approximately 5% of all thyroid cancers 3% (adult) to 10% (paediatric) of all thyroid cancers.[1]

Treatment options for MTC include surgery, chemotherapy and radiotherapy. Recent guidelines from the British Thyroid Association (BTA)[1] note that the use of surgery is common; surgery aims to remove some or all of the thyroid gland, and sometimes the lymph nodes. The BTA guidelines highlight that re-operative surgery in the neck and mediastinum provides long-term disease eradication in at least one third of patients and should be considered even when there are known distant metastases in order to minimise the risk of large volume disease compromising the airway, oesophagus or laryngeal nerves.[1] In addition, palliative radiotherapy may serve a valuable role in the management of unresectable masses and painful bone metastases. Chemotherapy is rarely used and doxorubicin produces symptomatic response in fewer than 30 per cent of cases; most of these responses are partial and of short duration. Targeted therapies (vandetanib and cabozantinib) are the modality of choice for inoperable progressive and symptomatic MTC. Decisions concerning the use of these therapies in the first-line setting are guided by licensed indications and toxicity.[1]

4. Decision problem

4.1 Purpose of the decision to be made

This review will assess the clinical effectiveness and cost-effectiveness of cabozantinib and vandetanib within their marketing authorisations for treating unresectable or metastatic MTC.

4.2 Clear definition of interventions

Cabozantinib (Cometriq®) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, and metastatic progression of cancer.[3] Cabozantinib has a European marketing authorisation from the European Medicines Agency (EMA) for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. Cabozantinib is administered orally and is available as 80mg and 20mg capsules. The recommended dose of cabozantinib is 140mg once daily, taken as one 80mg capsule and three 20mg capsules. According to the SmPC, treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.[3]

Vandetanib (Caprelsa®) is a potent inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2 also known as kinase insert domain containing receptor [KDR]), epidermal growth factor receptor (EGFR) and Rearranged during Transfection (RET) tyrosine kinases. Vandetanib is also a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase. The precise mechanism of action of vandetanib in locally advanced or metastatic MTC is not known.[4] Vandetanib has a European marketing authorisation from the EMA for the treatment of aggressive and symptomatic MTC in patients with unresectable locally

advanced or metastatic disease. Vandetanib is administered orally and is available as 100mg tablets. The recommended dose is 300mg once daily. Vandetanib may be administered until patients are no longer benefiting from treatment.[4]

4.3 Place of the intervention in the treatment pathway

Cabozantinib and vandetanib are currently available on the Cancer Drugs Fund (CDF) as first-line treatments for unresectable, locally advanced or metastatic MTC only if the disease is progressive and symptomatic, and if no previous tyrosine kinase therapy has been given, unless intolerant to vandetanib and cabozantinib (respectively) and in the absence of disease progression. Decisions concerning the use of these therapies in the first-line setting are guided by licensed indications and toxicity.[1] Best supportive care, with or without locally ablative treatments, may be given as an alternative treatment.

4.4 Relevant comparators

Cabozantinib and vandetanib will be compared with:

- Each other
- Best supportive care including locally ablative treatments such as radiotherapy.

4.5 Population and relevant sub-groups

Population: People with unresectable locally advanced or metastatic MTC.

Subgroups: If the evidence allows, subgroup analyses will be undertaken for people in whom RET mutation status is not known or is negative.

4.6 Key factors to be addressed

The review will aim to:

1) Evaluate the clinical effectiveness and safety of cabozantinib and vandetanib within their marketing authorisations for treating unresectable locally advanced or metastatic MTC.
2) Estimate the incremental cost effectiveness of cabozantinib and vandetanib compared with each other and best supportive care.
3) Identify key areas for primary research.
4) Estimate the overall cost in England.

4.7 Factors that are outside the scope of the appraisal

The interventions will be assessed according to their respective marketing authorisations. The use of cabozantinib and vandetanib in paediatric patients will not be considered within this appraisal. The use of other TKI inhibitors will not be considered within the appraisal.

5. Methods for the synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care' and the principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[5;6]

5.1. Search strategy

5.1.1 Search scope

The scope of the search for clinical effectiveness evidence will take into account the following requirements:

- The potential need to make indirect comparisons, including, if possible, a network meta-analysis.
- Evidence relating to the subgroup of people in whom RET mutation status is not known or is negative.

Potentially relevant studies will be identified by:

- Searching of electronic databases
- Contact with experts in the field
- Examination of bibliographies of any relevant primary studies and systematic reviews
- Company submissions related to interventions within the scope of this review.

A comprehensive literature search will be undertaken to systematically identify randomised controlled trials (RCTs) and systematic reviews (for the identification of additional trials) of the clinical effectiveness of cabozantinib and vandetanib. The search strategy will be broad in order to identify additional evidence on the best supportive care comparator.

5.1.2 Electronic searches

The following electronic databases will be searched from inception: MEDLINE (Ovid); MEDLINE in Process; MEDLINE Epub Ahead of Print, CINAHL; EMBASE; the Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials

Register (CENTRAL), DARE, and HTA databases; Web of Science (Science Citation Index (SCI) and Conference Proceedings Citation Index (CPCI).

In order to identify ongoing or recently completed studies, trial registers will be searched using the World Health Organisation's International Clinical Trials Registry Portal (WHO ICTRP) which regularly compiles and updates data from more than 15 clinical trial registers. Citation searches of key included studies will be undertaken using the Web of Science database.

5.1.2 Search strategy

Searches will not be limited by language or publication date. Search terms will include Medical Subject Heading (MeSH) terms and free text synonyms for medullary thyroid cancer combined with an RCT or systematic reviews study design filter. The proposed draft of the MEDLINE search strategy is presented in Appendix 1. Search filters designed to retrieve clinical trials, systematic reviews and economic evaluations will be used on MEDLINE and other databases, where appropriate. The search will be adapted for other databases. Subsequent searches for observational studies will be undertaken if required, in the event that identified RCTs do not provide sufficient evidence for long-term outcomes such as adverse events.

5.1.3 Supplementary searches

To identify additional studies, examination of reference lists of relevant studies, systematic reviews, clinical guidelines and submissions to regulatory authorities will be undertaken. In addition to reviewing company submissions related to the interventions within the scope of this review, experts in the field will also be contacted.

5.1.4 Data management

A comprehensive database of relevant published and unpublished articles will be constructed using EndNote® software.

5.2 Inclusion and exclusion criteria

5.2.1 Inclusion criteria

Inclusion criteria based on the scope provided by NICE are outlined below.

5.2.1.1 Populations

Studies reporting on participants with unresectable locally advanced or metastatic MTC, aged 18 years or older. Studies with populations broader than unresectable locally advanced or

metastatic MTC will be considered only if data for the relevant study population are available and are reported separately.

5.2.1.2 Interventions

- Cabozantinib (oral)
- Vandetanib (oral)

5.2.1.3 Comparators

Interventions will be compared with each other and against best supportive care (including locally ablative treatments such as radiotherapy).

5.2.1.4 Outcomes

The following outcomes will be included in the assessment:

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rates
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

5.2.1.5 Study design

RCTs will be included in the clinical effectiveness systematic review. If no relevant RCTs are identified for an intervention, non-randomised comparative studies may be considered for inclusion. Non-randomised comparative studies may also be included, where necessary, as a source of additional evidence (e.g., regarding adverse events related to the interventions).

5.2.2 Exclusion criteria

Studies conducted in paediatric populations will be excluded. Pre-clinical or biologic studies as well as studies of animal models will be excluded. The following publication types will not be considered for inclusion, although the reference lists of reviews and guidelines will be checked for additional relevant trials (see Sections 5.1.1 and 5.1.3 above): narrative reviews, systematic reviews, clinical guidelines, editorials, letters, opinion pieces, abstracts with insufficient details to assess study quality or results, as well as non-English articles. Study selection will be presented in a PRISMA flow diagram. A list of all excluded full-text articles, with reasons for exclusion, will be provided in an appendix to the submitted assessment report.

5.2.3 Study selection

Study selection will be conducted in two stages according to the specified inclusion and exclusion criteria in Sections 5.2.1 and 5.2.2. Retrieved records will be assessed for relevance by examination of title/abstract first, followed by a detailed examination of the full text version, excluding at each step studies which do not satisfy the eligibility criteria. All records will be independently screened by two reviewers. Disagreements will be resolved by discussion, and involvement of a third researcher if needed.

5.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised, piloted data extraction form, and checked by a second reviewer. Disagreements will be resolved by discussion. Data will be extracted with no blinding to authors or journal. A draft data extraction form is presented in Appendix 2. Data extracted will include information relating to the author and publication year of study, study population, interventions, comparators and outcomes. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

5.4 Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using the Cochrane Risk of Bias tool or (adapted) criteria for RCTs based on those proposed by the NHS Centre for Reviews and Dissemination.

5.5. Methods of analysis/synthesis

Characteristics of included RCTs including population characteristics, intervention details, comparator details and outcomes will be tabulated and discussed in a narrative review.

Where appropriate (i.e. depending on the number of studies that report data on specific outcome measures), RCTs that meet the inclusion criteria for the target patient population for the decision may be subjected to evidence synthesis. Primary outcome measures of interest, including those used to inform the economic model, will be analysed using random effects models to account for heterogeneity between RCTs in estimates of treatment effect arising from differences in study protocol. Other outcome measures will be analysed using either random effects models or fixed effect models when there is interest in estimating the treatment effect conditional on the studies satisfying the inclusion criteria for the target patient population. For outcome measures about which there is interest in simultaneously comparing all treatments, and where data allow, a network meta-analysis (NMA) will be

undertaken. Where possible, explanations for heterogeneity between RCTs in treatment effects will be explored using meta-regression.

Random effects models will be implemented using a Bayesian framework using the freely available software packages WinBUGS and R. Results will be summarised using point estimates and 95% credible intervals (CrIs) of the effect of each treatment relative to the reference treatment. Other summary measures may also be presented such as 95% CrIs for all pairwise comparisons and probabilities of treatment rankings. Evidence required to inform parameters in the economic model will be generated by taking draws from the posterior predictive distribution of a new study. Absolute goodness-of-fit will be assessed using residual deviance. Where possible, consistency between direct and indirect estimates of treatment effect in NMAs will be assessed using the node splitting approach.

5.6 Methods for estimating health-related quality of life

HRQoL data reported by studies included in the clinical effectiveness systematic review will be extracted. In the absence of such evidence, the health economic model may use evidence on HRQoL drawn from alternative sources.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Studies relating to the cost-effectiveness of interventions for treating unresectable locally advanced or metastatic MTC will be identified from the search strategy detailed in Section 5.1.combined with an economics study design filter (Appendix 1). Any economic evaluation which meets the inclusion criteria outlined in Section 5.2 with regards to the population, intervention and comparator will be included. Included studies will be synthesised within a qualitative analysis. The quality of economic literature will be assessed using a combination of key components of the checklists published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Taskforce[7] and Drummond *et al.*[8]

6.2 Development of a *de novo* economic model

It is expected that the development of a *de novo* health economic model will be necessary in order to estimate the incremental cost-effectiveness of cabozantinib, vandetanib and best supportive care. The model structure will be determined through consideration of existing models, analyses submitted by the companies within this appraisal, and using expert input from the Assessment Group's clinical advisors. The health economic analysis will be undertaken from a National Health Services (NHS) and Personal Social Services (PSS) perspective over a lifetime horizon. The final outcome measure estimated from the analysis

will be the incremental cost per quality-adjusted life year (QALY) gained. All costs and QALYs will be discounted at 3.5%.

It is anticipated that the model will use efficacy data from the key RCTs identified through the systematic searches. Cost data for the economic model will be extracted from published sources and using standard reference cost tariffs. Costs will include the direct costs of the interventions and their administration, as well as the costs of best supportive care and the management of adverse events. If available, HRQoL data will be identified from the studies identified in the clinical review; in the absence of such data, the model may use indirect evidence on HRQoL from alternative sources. Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be informed by guidance from NICE Decision Support Unit Technical Support Document 13.[9]

Uncertainty surrounding the model outputs will be assessed using deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA). The results of the PSA will be represented using cost-effectiveness acceptability curves (CEACs). Expected value of perfect information (EVPI) will be used to quantify the value of conducting further research.

7. Handling the company submission(s)

The TAR team will be happy to consider any evidence submitted by the companies if received by 9th February 2017. It may not be possible to consider data arriving after this date. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the company submissions, provided they comply with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. If the TAR team judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or by developing a *de novo* health economic model.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in turquoise in the assessment report (followed by an indication of the relevant company name, e.g. in brackets). Any academic in confidence data will be underlined and highlighted in yellow.

8. Competing interests of authors

None

9. Appendices

Appendix 1: Search strategy

Medline search strategy of medullary thyroid cancer population terms:

1 exp Thyroid Neoplasms/
2 exp Goiter, Nodular/
3 (thyr?oid* adj5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)).mp.
4 Thyroid Gland/
5 exp Neoplasms/
6 4 and 5
7 or/1-3,6
8 exp Carcinoma, medullary/
9 (medullary or MTC).mp.
10 8 or 9
11 7 and 10

Medical Subject Heading (MesH) terms and free text synonyms for medullary thyroid cancer (statements 1-11) will be combined with and RCT (statements 12-39) or systematic reviews filter (statements 12-22).

RCT study design filter:

12. Randomized controlled trials as Topic/
13. Randomized controlled trial/
14. Random allocation/
15. randomized controlled trial.pt.
16. Double blind method/
17. Single blind method/
18. Clinical trial/
19. exp Clinical Trials as Topic/
20. controlled clinical trial.pt.
21. clinical trial$.pt.
22. multicenter study.pt.
23. or/12-22
24. (clinic$ adj25 trial$).ti,ab.
25. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
26. Placebos/
27. Placebo$.tw.
28. (allocated adj2 random).tw.
29. or/24-28
30. 23 or 29
31. Case report.tw.
32. Letter/
33. Historical article/
34. 31 or 32 or 33
35. exp Animals/
36. Humans/
37. 35 not (35 and 36)

38. 34 or 37
39. 30 not 38

Systematic reviews study design filter:

12. meta-analysis/
13. meta-analysis as topic/
14. (meta analy* or metanaly* or metaanaly*).ti,ab.
15. ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
16. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
17. (search strategy or search criteria or systematic search or study selection or data extraction).ab.
18. (search* adj4 literature).ab.
19. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or scie nce citation index or bids or cancerlit).ab.
20. cochrane.jw.
21. ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
22. or/12-21

Medical Subject Heading (MesH) terms and free text synonyms for medullary thyroid cancer (statements 1-11) will be combined with an economics study design filter (statement 12-33) to identify published cost-effectiveness studies.

Cost-effectiveness study design search strategy

12. exp "Costs and Cost Analysis"/
13. Economics/
14. exp Economics, Hospital/
15. exp Economics, Medical/
16. Economics, Nursing/
17. exp models, economic/
18. Economics, Pharmaceutical/
19. exp "Fees and Charges"/
20. exp Budgets/
21. budget$.tw.
22. ec.fs.
23. cost$.ti.
24. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
25. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
26. (price$ or pricing$).tw.
27. (financial or finance or finances or financed).tw.
28. (fee or fees).tw.
29. (value adj2 (money or monetary)).tw.
30. quality-adjusted life years/
31. (qaly or qalys).af.
32. (quality adjusted life year or quality adjusted life years).af.
33. or/12-32

Appendix 2: Draft data extraction form

Date	
Name of reviewer:	
Study ID	Author/ year
Study ID of multiple reports (if any):	
Study characteristics:	Study design
	Trial name (if any)
	Location(s)
	Length of follow-up
	Funding
Study population:	Sample size
	Selection/Eligibility criteria
	Participants' characteristics (including: mean age/ gender/ underlying condition(s), previous treatment, concomitant treatment, MTC disease type, RET mutation status etc.)
Interventions and comparators:	Pharmacologic agent (dose, route of administration, treatment schedule) according to number of participants in each treatment group
Outcomes (for intervention and comparator groups):	Reported outcomes and method and time of assessment, according to number of participants in each treatment group

Appendix 3: Timetable/milestones

Milestone	**Date**
Draft protocol	29th September 2016
Final protocol	20th October 2016
Progress report	23rd February 2017
Draft assessment report	24th April 2017
Final assessment report	22nd May 2017

10. References

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