NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING DECEMBER 2019

Selpercatinib for advanced thyroid cancer with RET alterations

NIHRIO ID	26736	**NICE ID**	10277
Developer/Company	Eli Lilly and Company Ltd	**UKPS ID**	653794

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Selpercatinib is in clinical development for the treatment of advanced thyroid cancer with RET alterations that includes RET-mutant medullary thyroid cancer (MTC) and RET-fusion-positive thyroid cancer. Thyroid cancer is a malignant neoplasm that originates from cells in the thyroid gland located in the front of the neck. Some types of thyroid cancer can have alterations (mutation or fusions) to the RET gene which leads to an overactive process that causes the cancer cells to grow uncontrolled. In the advanced stage, the primary treatment is extensive surgical resection which needs to be combined with systemic treatments such as chemotherapy and targeted therapies.

Selpercatinib is a first-in-class oral precision cancer medicine designed to selectively bind to cancers that harbour genetic abnormalities in the RET proteins. This binding inhibits the RET receptor signalling which in turn inhibits the tumour cell growth and may also prevent resistance to the treatment from developing. Selpercatinib is being developed for various RET-altered advanced thyroid cancers with early results indicating significantly improved outcomes. If licensed, selpercatinib will offer a treatment option for patients with advanced RET-mutant MTC and advanced RET fusion-positive thyroid cancer who have progressed following prior treatment and have no acceptable alternative treatment options.

PROPOSED INDICATION

Monotherapy for the treatment of: [a]

- Adolescents (12 years and older) and adult patients with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy and who have progressed following prior treatment and;
- Adult patients with advanced RET-fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior treatment.

TECHNOLOGY

DESCRIPTION

Selpercatinib (LOXO-292) is a highly selective, ATP-competitive small-molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.[1] In RET altered cancers (which include fusions and activating point mutations), gene alterations cause overactive RET signalling, allowing tumour proliferation and survival. Such cancers are often dependent on a single activated kinase which renders them highly susceptible to small molecule inhibitors targeting RET, such as selpercatinib.[1,2]

Selpercatinib is currently in phase I/II clinical trials (NCT03157128) for the treatment of patients with advanced RET-altered solid tumours including medullary thyroid cancer (MTC) with RET mutations and advanced RET-fusion positive thyroid cancer who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.[3] The drug is administered orally and the proposed dosing schedule of selpercatinib is 160mg twice daily. Treatment should be continued until disease progression or unacceptable toxicity.[4,b]

INNOVATION AND/OR ADVANTAGES

Selpercatinib is a first-in-class oral RET inhibitor.[5] Until recently, only multikinase inhibitors (MKIs) with nonselective RET inhibitory activity have been available for patients with RET-altered cancers – clinical experience has been disappointing, with only modest activity in RET-mutant MTC and substantial side effects.[6]

In contrast to MKIs, selpercatinib possesses nanomolar potency against diverse RET alterations (including anticipated acquired resistance mutations), high selectivity for RET, and favourable pharmacokinetic properties, including high bioavailability, predictable exposure, significant central nervous system (CNS) penetration, and a low potential for drug interactions.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Selpercatinib does not currently have Marketing Authorisation in the EU/UK.

In September and October 2018, selpercatinib received breakthrough therapy designation from the FDA for advanced RET-mutant MTC and advanced RET-fusion-positive thyroid cancer.[3,7]

[a] Information provided by Eli Lilly and Company Ltd
[b] Information provided by Eli Lilly and Company Ltd

Selpercatinib is in phase II development for non-small cell lung cancer, colon cancer and other advanced solid tumours harbouring RET fusions or activating RET mutations as well as infantile myofibromatosis and fibrosarcoma.[8]

PATIENT GROUP

DISEASE BACKGROUND

The thyroid is a gland located at the base of the throat near the trachea and consists of a right and left lobe connected by a thin piece of tissue called the isthmus. Thyroid cancer arises from cells in the tissues of the thyroid cancer. There are different types of thyroid cancer which include differentiated (papillary thyroid cancer [PTC] and follicular thyroid cancer [FTC]), or undifferentiated thyroid cancer and medullary thyroid cancer (MTC).[9]

MTC is a rare malignant tumour.[10] It is also different from other types of thyroid cancers because it originates from parafollicular cells (C cells) of the thyroid gland. These cells do not make thyroid hormone and instead make a different hormone called calcitonin.[11] MTC can and often spread to lymph nodes and also spread to other organs. While PTC is derived from thyroid hormone producing thyroid follicular cells, it grows slowly and is clinically indolent, although rare, aggressive forms with local invasion or distant metastases can occur.[12,13]

The receptor tyrosine kinase RET can be activated by point mutation or by gene fusions. RET mutations affect most MTCs and rarely other malignancies while RET-fusions occur in a variety of malignancies including 10%-20% PTCs.[6] RET fusions are more common in paediatric, adolescent and young adult.[14] MTCs and PTCs are characterised by the activation of the same RET gene with different types of alternations: RET point mutations in MTC and RET/PTC rearrangement in PTC.[15]

The most common risk factors of developing thyroid cancer include age, genetics, radiation exposure, diet low in iodine and ethnicity.[16] The common symptoms include rash, flushing and diarrhoea, fatigue, bone pain, bone fractures, muscle weakness, breathing difficulties from lung metastases, swallowing difficulties causing weight loss through poor nutrition, anxiety and depression.[17]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK in 2016, thyroid cancer was the 20th most common cancer in the UK, accounting for 1% of all new cancer cases.[18] In England in 2017, there were 3,254 registrations of new diagnosed cases of malignant neoplasm of the thyroid gland (ICD-10 code C73) and the direct age-standardised rate per 100,000 population was 8.5 among females and 3.6 among males.[19] Thyroid cancer rates are projected to rise by 74% and 77% in females and males respectively between 2014 and 2035 in the UK.[20]

In England, in 2018-19 there were 7,044 finished consultant episodes (FCEs) for malignant neoplasm of thyroid gland (ICD-10 code C73), 6,719 admissions resulting in 13,772 bed days and 1,570 day cases.[21] The age-standardised 1-year and 5-year survival for persons diagnosed with thyroid cancer in England in 2017 was 91.4 and 87.4% respectively.[22]

The company estimate a UK patient population range of less than 1 per 50,000. RET diagnostic testing is required, and this is not currently routine practice.[c]

[c] Information provided by Eli Lilly and Company Ltd on UK PharmaScan

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of thyroid depends upon the stage of the cancer, the patient's overall health and the patient's desires.[23] Treatment of MTC is based on complete surgical resection, including total thyroidectomy along with central and later cervical nodal dissection. For locally advanced or metastatic thyroid cancer, complete cervical surgery may be required and needs to be combined with other systemic treatments. As chemotherapy is not very effective, radioimmunotherapy and RET target gene therapy (mainly tyrosine kinase inhibitors) are currently used.[24]

Treatment options for differentiated thyroid cancer include surgery, chemotherapy and radiotherapy. Surgery is most common with the aim of removing some or all of the thyroid gland (and sometimes the lymph nodes). Radioactive iodine ablation can be provided after surgery to destroy any remaining cancer cells whilst external beam radiotherapy and chemotherapy are used for palliative care in the small proportion of patients where further surgery or radioiodine is ineffective or impractical.[25]

CURRENT TREATMENT OPTIONS

Currently NICE recommends the following treatment options for patients with differentiated thyroid and medullary thyroid cancer:[26]

- Lenvatinib and sorafenib for treating progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine, only if
    - they have not had a tyrosine kinase inhibitor before or
    - they have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity (specifically, toxicity that cannot be managed by dose delay or dose modification)
- Cabozantinib for treating progressive medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease

Treatment options for patients with advanced or metastatic MTC that have progressed following first-line systemic therapy are limited and consists of supportive or palliative care.

PLACE OF TECHNOLOGY

If licensed, selpercatinib will offer a treatment option for patients with advanced RET-altered thyroid cancers who require systemic therapy and who have progressed following prior treatment.

CLINICAL TRIAL INFORMATION

Trial	**LIBRETTO-001, NCT03157128, LOXO-RET-17001, EudraCT2017-000800-59; 12 years and older; LOXO-292; Phase I/II.**
Sponsor	Loxo Oncology, Inc.
Status	Ongoing
Source of Information	Trial registry[27,28] Press release[29]
Location	EU (including UK), USA, Canada and other countries
Design	Single group assignment, open label

Participants	N=970; aged 12 and older
	For phase 1
	• Patients with a locally advanced or metastatic solid tumour who:
	  ○ have progressed on or are intolerant to standard therapy, or
	  ○ no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or
	  ○ decline standard therapy
	• Prior MKIs with anti-RET activity are allowed
	• A RET gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of RET gene alteration in tumour and/or blood is required as identified through molecular assays, as performed for clinical evaluation
	• Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumour type
	• Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 or Lansky Performance Score (LPS) ≥ 40% (age < 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment
	• Adequate hematologic, hepatic and renal function
	• Life expectancy of at least 3 months
	
	For phase 2
	As for phase 1 with the following modifications:
	• For Cohorts 1 and 3 Subjects must have received prior standard therapy appropriate for their tumour type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy
	• Cohorts 1-4: enrolment will be restricted to patients with evidence of a RET gene alteration in tumour. However, a positive germline DNA test for a RET gene mutation is acceptable in the absence of tumour tissue testing for patients with MTC
	• Cohorts 1-4: at least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumour type and not previously irradiated
	• Cohort 4: radiographic PD within the previous 14 months
	• Cohort 5: (up to 150 patients):
	  ○ Cohorts 1-4 without measurable disease;
	  ○ MTC not meeting the requirements for Cohorts 3 or 4; (a known RET mutation is not required)
	  ○ MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior Sponsor approval;
	  ○ cfDNA positive for a RET gene alteration not known to be present in a tumour sample
	• Cohort 6: Patients who otherwise are eligible for Cohorts 1-5 who discontinued another RET inhibitor due to intolerance may be eligible with prior Sponsor approval

Schedule	The trial will be conducted in 2 parts: phase 1 (dose escalation) and phase 2 (dose expansion). In phase 1, subjects receive multiple doses of LOXO-292 In phase 2, subjects receive LOXO-292 to assess the maximum tolerated dose (MTD)/recommended dose. A dose of 160 mg twice a day (BID) has been selected as the recommended phase 2 dose (RP2D)
Follow-up	Treatment every 28 dys for approximately 12 mths and observation for up to 2 yrs
Primary Outcomes	Phase 1: • Maximum tolerated dose (Time frame: the first 28 days of treatment (cycle 1)) • Recommended Phase 2 dose (Time frame: the first 28 days of treatment (cycle 1) and every cycle (28 days) for approximately 12 months (or earlier if the patient discontinues from the study)) Phase 2: • Objective Response Rate (ORR), (Time frame: approximately every 8 weeks for one year, then every 12 weeks, and 7 days after the last dose (for up to 2 years) in patients who have not progressed).
Secondary Outcomes	Phase 1: • Frequency, severity, and relatedness of Treatment emergent adverse events (TEAEs) and serious adverse events (SAEs), changes in haematology and blood chemistry values, assessments of physical examinations, vital signs, and electrocardiograms (ECGs). (Time frame: from the time of informed consent, for approximately 24 months (or earlier if the patient discontinues from the study), and through safety follow-up (28 days after the last dose)) • Plasma concentration of LOXO-292 and pharmacokinetic (PK) parameters, including but not limited to area under the curve from time 0 to 24 hours (AUC0-24), maximum drug concentration (Cmax), time to maximum plasma concentration (Tmax), and degree of accumulation. (Time frame: day 8 of cycle 1 and day 8 after Intra-patient dose escalation (Phase 1 only)) • ORR based on RECIST 1.1 or RANO, as appropriate to tumour type. (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) Phase 2: • ORR (by Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Best change in tumour size from baseline (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Duration of response (DOR) (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • CNS ORR (by IRC) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.)

	• CNS DOR (by IRC) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Time to any and best response (by IRC and Investigator) (Time frame: every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • CBR (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Progression-free survival (PFS) (by IRC and Investigator) (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • OS (Time frame: approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in patients who have not progressed.) • Frequency, severity and relatedness of TEAEs and SAEs, changes in haematology and blood chemistry values, assessments of physical examinations, vital signs and ECGs. (Time frame: from the time of informed consent, for approximately 24 months (or earlier if the patient discontinues from the study), and through safety follow-up (28 days after the last dose)) • Plasma concentrations of LOXO-292 and PK parameters, including but not limited to AUC0-24, Cmax, and Tmax. (Time frame: day 8 of cycle 1 and day 8 after Intra-patient dose escalation).
Key Results	• In this primary analysis set, patients with previously treated *RET*-mutant MTC demonstrated an ORR per investigator assessment of 56% (95% confidence interval [CI], 42-70%). Confirmation is pending for two of the partial responses (PR). The cohort of 31 patients with a response included 3 patients with a RET V804M/L gatekeeper mutation who achieved one complete response (CR) and 2 PR • At median follow-up of 10.6 months, 6 DOR events occurred; the median DOR has not been reached (95% CI, 11.1 months-NE) • Among these patients, the ORR was 62% (95% CI, 41-80%); 16 patients showed a response (including two PRs awaiting confirmation)
Adverse effects (AEs)	Interim results: • Most commonly observed adverse events, regardless of attribution, were dry mouth, diarrhoea, hypertension, increased liver enzymes, fatigue, constipation, and headache.
Expected reporting date	Primary completion date is March 2022.

ESTIMATED COST

The cost of selpercatinib is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Cabozantinib for treating medullary thyroid cancer (TA516). March 2018.
- NICE technology appraisal. Vandetanib for treating medullary thyroid cancer (TA550). December 2018.
- NICE interventional procedure guidance. Vandetanib for treating medullary thyroid cancer (IPG499). August 2014.
- NICE interventional procedures guidance. Minimally invasive video-assisted thyroidectomy (IPG499). August 2014.
- NICE interventional procedure guidance. Intraoperative nerve monitoring during thyroid surgery (IPG255). March 2008.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. NHS Standard Contract for Cancer: Head and Neck (Adult). B16/S/a.

OTHER GUIDANCE

- The American Thyroid Association. Management guidelines for adults with thyroid nodules and differentiated thyroid cancer. 2015.[30]
- British Thyroid Association. Guidelines for the management of thyroid cancer. 2014.[31]
- London Cancer Alliance. LCA head and neck/thyroid cancer clinical guidelines. 2014.[32]
- European Society for Medical Oncology. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012.[33]

ADDITIONAL INFORMATION

REFERENCES

1 LOXO oncology. *LOXO-292*. 2019. Available from: https://www.loxooncology.com/pipeline/ret-program [Accessed 21 November 2019].

2 National Cancer Institute. *NCI Drug Dictionary: RET inhibitor LOXO-292*. 2019. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/ret-inhibitor-loxo-292 [Accessed 21 November 2019].

3 Eli Lilly and Company. *Lilly Announces Positive Registrational Data for Selpercatinib (LOXO-292) in Heavily Pretreated RET-Altered Thyroid Cancers*. Available from: https://investor.lilly.com/news-releases/news-release-details/lilly-announces-positive-registrational-data-selpercatinib-loxo [Accessed 02 January 2020].

4 Clincaltrial.gov. *Phase 1/2 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001). Trial ID: NCT03157128*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/study/NCT03157128 [Accessed 11 November 2019].

5 Eli Lilly and Company. *Lilly Completes Acquisition of Loxo Oncology*. 2019. Available from: https://investor.lilly.com/news-releases/news-release-details/lilly-completes-acquisition-loxo-oncology [Accessed 21 November 2019].

6 Subbiah V, Velcheti V, Tuch BB, Ebata K, Busaidy NL, Cabanillas ME, et al. Selective RET kinase inhibition for patients with RET-altered cancers. *Annals of Oncology*. 2018. Available from: https://doi.org/10.1093/annonc/mdy137 10.1093/annonc/mdy137.

7 Targeted Oncology. *Selpercatinib Demonstrates Robust ORR in Thyroid Cancer.* 2019. Available from: https://www.targetedonc.com/conference/esmo-2019/selpercatinib-demonstrates-robust-orr-in-thyroid-cancer [Accessed 21 November 2019].

8 Clincaltrial.gov. *Search: Loxo-292*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=LOXO-292&cntry=&state=&city=&dist [Accessed 25 November 2019].

9 National Cancer Institute. *Thyroid Cancer Treatment (Adult) (PDQ®)–Patient Version.* Available from: https://www.cancer.gov/types/thyroid/patient/thyroid-treatment-pdq [Accessed 02 January 2020].

10 Figlioli G, Landi S, Romei C, Elisei R, Gemignani F. Medullary thyroid carcinoma (MTC) and RET proto-oncogene: mutation spectrum in the familial cases and a meta-analysis of studies on the sporadic form. *Mutat Res*. 2013 Jan-Mar;752(1):36-44. Available from: https://www.sciencedirect.com/science/article/pii/S1383574212000622?via%3Dihub 10.1016/j.mrrev.2012.09.002.

11 American Thyroid Association. *Cancer of the Thyroid.* Available from: https://www.thyroid.org/medullary-thyroid-cancer/ [Accessed 21 November 2019].

12 Dikbas O, Duman AA, Guvendi GF. Medullary Thyroid Carcinoma and Papillary Thyroid Carcinoma in the Same Patient as a Collision Tumour. *Case Rep Endocrinol*. 2019;2019:4038628. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30993022 10.1155/2019/4038628.

13 Turkish Journal of Endocrinology and Metabolism. *Papillary Thyroid Carcinoma and RET/PTC Oncogenes - Review*. Available from: http://www.turkjem.org/fulltext/papillary-thyroid-carcinoma-and-retptc-oncogenes-review-3207 [Accessed 02 January 2020].

14 De Falco V, Carlomagno F, Li HY, Santoro M. The molecular basis for RET tyrosine-kinase inhibitors in thyroid cancer. *Best Pract Res Clin Endocrinol Metab*. 2017 Jun;31(3):307-18. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28911727 10.1016/j.beem.2017.04.013.

15 Prescott JD, Zeiger MA. The RET oncogene in papillary thyroid carcinoma. *Cancer*. 2015 Jul 1;121(13):2137-46. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25731779 10.1002/cncr.29044.

16 Cancer.Net. *Thyroid Cancer: Risk Factors.* Available from: https://www.cancer.net/cancer-types/thyroid-cancer/risk-factors [Accessed 20 November 2019].

17 National Insitute for Health and Care Excellence. *Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]: Committee papers.* Available from: https://www.nice.org.uk/guidance/ta516/documents/committee-papers [Accessed 20 November 2019].

18 Cancer Research UK. *Thyroid cancer statistics.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer#heading-Zero [Accessed 20 November 2019].

19 Office for National Statistics. *Cancer registration statistics* 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 20 November 2019].

20 Cancer Research UK. *Cancer incidence for common cancers.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Accessed 20 November 2019].

21 NHS Digital. *Hospital Admitted Patient Care Activity 2018-19*. 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 09 December 2019].

22 Office for National Statistics. *Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 21 November 2019].

23 Thyroid Cancer Center. *Medullary Thyroid Cancer Treatment.* Available from: https://www.thyroidcancer.com/thyroid-cancer/medullary/treatment [Accessed 25 November 2019].

24 Orphanet. *Medullary thyroid carcinoma.* Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=1332 [Accessed 25 November 2019].
25 National Insitute for Health and Care Excellence. *Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine.* Available from: https://www.nice.org.uk/guidance/ta535/documents/final-scope [Accessed 02 January 2020].
26 National Insitute for Health and Care Excellence. *Endocrine cancers overview*. Available from: https://pathways.nice.org.uk/pathways/endocrine-cancers#content=view-node%3Anodes-thyroid-cancer [Accessed 25 November 2019].
27 Clinicaltrials.gov. *Phase 1/2 Study of LOXO-292 in Patients With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001). Trial ID: NCT03157128*. 2017. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03157128 [Accessed 21 November 2019].
28 EU Clinical Trials Register. *A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation (LIBRETTO-001). Trial ID: 2017-000800-59*. 2018. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000800-59/GB [Accessed 15 November 2019].
29 European Society for Medical Oncology (ESMO). *LOXO-292 Demonstrates Promising Anti-Tumour Activity in RET-Altered Thyroid Cancer.* Available from: https://www.esmo.org/Oncology-News/LOXO-292-Demonstrates-Promising-Anti-Tumour-Activity-in-RET-Altered-Thyroid-Cancer [Accessed 25 November 2019].
30 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016 Jan;26(1):1-133. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26462967 10.1089/thy.2015.0020.
31 Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. *Clin Endocrinol (Oxf)*. 2014 Jul;81 Suppl 1:1-122. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/cen.12515 10.1111/cen.12515.
32 London Cancer Alliance. *LCA Head and Neck / Thyroid Cancer : Clinical Guideline* Last Update Date: Available from: http://www.londoncanceralliance.nhs.uk/media/75780/LCA_Head_Neck_Guidelines2014_Final.pdf [Accessed 25 November 2019].
33 Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2019. Available from: https://doi.org/10.1093/annonc/mdz400.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.