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Newcastle University

Health Technology Briefing
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Cabozantinib for treating differentiated thyroid cancer

Company/Developer	Ipsen Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26980	NICE ID: 10715	UKPS ID: 662273

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Cabozantinib is being developed for the treatment of progressive differentiated thyroid cancer (DTC). Thyroid cancer is rare, and DTC is the most common type of this. It is usually found by a hard lump on the neck that does not move and may grow. It can cause a sore throat, neck pain, hoarseness, and difficulty swallowing and/or breathing. People with DTC have limited options if their previous treatment has been unsuccessful.

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases, which are signalling proteins implicated in tumour growth; angiogenesis (blood vessel growth); pathologic bone remodelling; drug resistance; metastatic progression of cancer. Cabozantinib is in development for people who have had previous treatment, but where the cancer has persisted or returned. It will be given orally as tablets. If licensed, cabozantinib will offer an additional treatment option for patients with DTC.

Proposed Indication

For the treatment of people aged 16 or older with radioiodine-refractory DTC who have progressed after prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy.[1]

Technology

Description

Cabozantinib (XL184; Cabometyx) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer.[2] It is an inhibitor of various kinases including, but not limited to, vascular endothelial growth factor receptors (VEGFR), MET, AXL and RET.[2,3]

Cabozantinib is in phase III clinical development for people with RAI-refractory DTC after VEGFR-tyrosine kinase inhibitor (TKI) therapy. In the phase III trial, NCT03690388, 60mg of cabozantinib is administered as an oral tablet once daily.[1]

Key Innovation

Patients with differentiated thyroid cancer who have progressed following prior therapy and are radioactive iodine-refractory often face a poor prognosis and have limited treatment options.[4] In a pivotal phase III clinical trial (COSMIC-311, NCT03690388) cabozantinib has demonstrated positive efficacy and safety data, with significant progression-free survival benefit observed.[3]

Regulatory & Development Status

Cabozantinib is licenced in the UK for the treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma, and advanced renal cell carcinoma.[5]

Cabozantinib is also in phase II/III development in ~150 trials including:[6]

- Cervical cancer
- Hepatocellular carcinoma
- Urothelial carcinoma
- Salivary gland cancer
- Cholangiocarcinoma
- Prostate cancer

Cabozantinib has Priority Review, Breakthrough Designation and Orphan Drug Designation by the United States Food and Drug Administration (US FDA).[7]

Patient Group

Disease Area and Clinical Need

Thyroid cancer is a rare type of cancer that affects the thyroid gland, a gland at the base of the neck that produces hormones.[8] The most common type of thyroid cancers are DTC, which are usually slow growing and divided into three groups: papillary (~90%), follicular (~4%) and Hürthle cell (~2%).[9] The most common symptom of thyroid is a painless lump or swelling on the front of the neck. Other associated symptoms include swollen neck glands, unexplained hoarseness, a persistent sore throat, neck pain, and difficulty swallowing and/or breathing.[10] Risks and causes of thyroid cancer include age, gender, being overweight, benign thyroid disease, family history of thyroid cancer, inheritance, radiation, acromegaly (overproduction

of growth hormone), systemic lupus erythematosus and having previous cancers.[11] DTC may progress or relapse (return) after treatment, resulting in locally advanced cancer (where the cancer has grown outside of the thyroid gland) and metastatic cancer (where it has spread to other areas of the body).[12]

Thyroid cancer is rare, and the UK incidence is approximately 5 per 100,000 in women and 2 per 100,000 in men.[13] Based on people treated in the UK and Ireland between 2000-07 the survival rate of 5 years or more after diagnosis was more than 85% of men for papillary and follicular thyroid cancers, 95% of women for papillary thyroid cancers and 90% of women for follicular thyroid cancers.[14]In England, 2020-21, there were 6,040 finished consultant episodes (FCE) of malignant neoplasm of thyroid gland (ICD-10 code C73, DTC) with 11,144 FCE bed days and 1,280 day cases.[15]

Recommended Treatment Options

The National Institute of Health and Care Excellence (NICE) recommends Lenvatinib and sorafenib as treatment options for progressive, locally advanced, or metastatic DTC in adults whose disease does not respond to radioactive iodine only if they have not had tyrosine kinase inhibitor before or have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity.[13,16] Selpercatinib is recommended for advanced RET fusion-positive thyroid cancer in adults who need systemic therapy after sorafenib or lenvatinib, and for advanced RET-mutant medullary thyroid cancer in people ≥12 years who need systemic therapy after cabozantinib or vandetanib.[17]

Clinical Trial Information

Trial	**COSMIC-311; NCT03690388;** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Cabozantinib (XL184) in Subjects With Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed After Prior Vascular Endothelial Growth Factor Receptor (VEGFR) -Targeted Therapy **Phase III –** Active, not recruiting **Location(s):** 12 EU countries, UK, US, Canada, and other countries **Primary completion date:** August 2020
Trial Design	Randomised, triple-masked, parallel assignment.
Population	N=258 (actual); aged 16 years and older; confirmed diagnosis of DTC; previously treated or deemed ineligible for RAI; previously treated with at least one VEGFR-targeting TKI
Intervention(s)	Cabozantinib 60mg or 20mg oral tablet once daily.
Comparator(s)	Matched placebo.
Outcome(s)	• Progression Free Survival (PFS) [Time Frame: Up to approximately twenty months after the first subject is randomized. Time from randomization to the earlier of the following events: radiographic PD as determined by the blinded independent central review (BIRC) or death due to any cause.] Time to the earlier of either radiographic progressive disease (PD) or death from any cause. • Objective Response Rate (ORR) [Time Frame: Six months after 100 subjects are randomized. Time from randomization to best overall

	response of confirmed complete response (CR) or confirmed partial response (PR) per BIRC per RECIST 1.1.] Proportion of subjects with the best overall response of complete response (CR) or partial response (PR). For full list of other outcomes, see trial registry.
Results (efficacy)	At final analysis 258 pts (170 C, 88 P) were randomized (data cut-off 8 Feb 2021); 96 had received prior S/no L, 102 prior L/no S, and 60 prior S and L. Median follow-up was 10.1 mo. Forty pts crossed over from P to receive C. Median PFS (ITT population) was 11 mo for C vs 1.9 mo for P (HR 0.22, 96% CI 0.15–0.32; p<0.0001). For subgroups, median PFS was 16.6 vs 3.2 mo for prior S/no L (HR 0.13, 95% CI 0.06–0.26); 5.8 vs 1.9 mo for prior L/no S (HR 0.28, 95% CI 0.16-0.48), and 7.6 vs 1.9 mo for prior S and L (HR 0.27, 95% CI 0.13–0.54). ORR (ITT population) was 11% for C vs 0% for P; overall survival HR 0.76 (95% CI 0.45–1.31).[18]
Results (safety)	Grade 3/4 treatment-emergent adverse events (TEAEs) were 62% in the C arm vs 28% in the P arm with no treatment-related grade 5 events; 67% vs 5% required dose reductions due to TEAEs; 8.8% vs 0% discontinued treatment due to TEAEs not related to disease.[18]

Estimated Cost

Cost of cabozantinib was confidential at the time of producing this briefing

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Selpercatinib for treating advanced thyroid cancer with RET alterations (TA742). November 2021.
- NICE technology appraisal guidance. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (TA535). August 2018.
- NICE clinical guideline in development. Thyroid cancer: assessment and management. Expected publication: November 2022.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology Services (Adults). A03/S/a

Other Guidance

- NHS Scotland. Consensus Guidance on Routine Practice for Differentiated Thyroid Cancer in Scotland. May 2020.[19]
- British Thyroid Association (BTA). Current BTA guidelines and statements. March 2020.[20]

- European Society for Medical Oncology (ESMO). Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. December 2019.[21]
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Additional Information

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