Health Technology Briefing
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Pralsetinib for treating thyroid cancer

Company/Developer	Roche Products Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30586	NICE ID: 10709	UKPS ID: 661828

Licensing and Market Availability Plans

Currently in phase I/II clinical trials

Summary

Pralsetinib is in clinical development for the treatment of thyroid cancer. Thyroid cancer is a rare type of cancer that affects the thyroid gland, a small gland at the base of the neck that produces hormones. Thyroid cancer can happen when there are genetic changes in the thyroid cells, which cause them to grow uncontrollably and produce a lump. One of such genetic changes happens in the RET-activating fusions and mutations, which are key disease drivers in many cancer types, including thyroid cancer. The currently available drugs for treating thyroid cancer are associated with significant side effects, which can lead to a reduction in the effective dose of the medicine taken compared to the recommended dose. There is, therefore, a need for well-tolerated, effective treatments, particularly those that target the genetic mutations that drives the cancer.

Pralsetinib is a once-daily oral therapy designed to selectively and potently inhibit alterations in the RET gene. Early studies have shown that Pralsetinib can have improved selectivity for common RET-activating fusions and mutations when compared to similar therapies in the same class, resulting in manageable safety profile and meaningful clinical activity in patients irrespective of previous treatment history. If licensed, pralsetinib may offer a potent and well-tolerated treatment option for people with thyroid cancer, who currently have few safe and effective treatment options.

Proposed Indication

Thyroid cancer[1]

Technology

Description

Pralsetinib (Gavreto, BLU-667) is an investigational, highly potent, selective inhibitor of oncogenic rearranged during transfection (RET) alterations,[2] including fusions and mutations, regardless of the tissue of origin.[3] Preclinical data have shown that pralsetinib inhibits primary RET fusions and mutations that cause cancer in subsets of patients, as well as secondary RET mutations predicted to drive resistance to treatment.[4]

In the phase I/II trial (NCT03037385) participants received pralsetinib orally at doses of 30–600 mg once daily in the dose escalation phase (phase I). In the dose expansion phase (phase II), patients initiated pralsetinib at the recommended phase 2 dose of 400 mg once daily. All patients received pralsetinib until disease progression, intolerance, withdrawal of consent, or investigator decision.[5]

Key Innovation

RET-activating fusions and mutations are key disease drivers in many cancer types, including thyroid cancer.[3] Standard of care drug treatments for thyroid cancer include multikinase inhibitors, which despite demonstrating clinical activity, do not target RET specifically and are associated with significant side-effects.[5]

Pralsetinib has demonstrated markedly improved selectivity for RET compared to pharmacologically relevant kinases. In preclinical studies, pralsetinib consistently demonstrated sub-nanomolar potency against the most common RET fusions, activating mutations and predicted resistance mutations.[6] In the phase I/II trial (NCT03037385), pralsetinib had a manageable safety profile in patients with RET-altered thyroid cancer and provided meaningful clinical activity in patients irrespective of previous treatment history.[5]

Regulatory & Development Status

Pralsetinib does not currently have Marketing Authorisation in the EU/UK for any indication but has received a Committee for Medicinal Products for Human Use (CHMP) positive opinion for the treatment of patients with RET-fusion positive non-small cell lung cancer (NSCLC), by the EMA in September 2021.[7]

Pralsetinib is currently in phase II development for NSCLC and other advanced solid tumours.[8]

Pralsetinib has the following regulatory designations/awards:

- Breakthrough Therapy Designation for the treatment of adults with metastatic RET fusion-positive NSCLC as detected by an FDA approved test, by the US FDA in September 2020.[9]
- An Orphan Drug Designation for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC, or TRKC-positive NSCLC by the US FDA in April 2018.[10]

Patient Group

Disease Area and Clinical Need

Thyroid cancer is a rare type of cancer that affects the thyroid gland, a small gland at the base of the neck that produces hormones.[11] It is most common in people in their 30s and those over the age of 60. Women are 2 to 3 times more likely to develop it than men.[11] Symptoms of thyroid cancer include: a painless lump or swelling in the front of the neck, swollen glands in the neck, unexplained hoarseness that does not get better after a few weeks, a sore throat that does not get better and difficulty swallowing.[11] There are several different types of thyroid cancer, which are classified based on how similar they look to normal thyroid cells under a microscope and by the type of cell from which they develop.[12] Thyroid cancer can be 'differentiated' or 'undifferentiated'. 'Differentiated' thyroid cancer cells still retain the appearance of normal thyroid cells and they do not spread as rapidly as the undifferentiated type of cancer cells.[13] RET gene alterations, such as fusions and mutations, are key disease drivers in many types of cancer, including several types of thyroid cancers.[14] Approximately 10-20% of people with papillary thyroid cancer (the most common type of thyroid cancer) have RET fusion-positive tumours,[15] and roughly 90% of people with advanced MTC (a rare form of thyroid cancer) carry RET mutations.[16]

Thyroid cancer is the 20th most common cancer in the UK, accounting for 1% of all new cancer cases (2016-2018 data). There are around 3,900 new thyroid cancer cases in the UK every year.[17] In England, in 2020-21 there were 6,040 finished consultant episodes (FCE) for malignant neoplasm of thyroid gland (ICD-10 code C73), which resulted in 11,144 FCE bed days and 1,280 day cases.[18] There are around 400 thyroid cancer deaths in the UK every year.[17] For people diagnosed with thyroid cancer between 2013 and 2017 the 1-year and 5-year age standardised survival rates were 91.4% (95% CI 90.9 to 92.0%) and 87.4% (95% CI 86.3 to 88.5%) respectively.[19]

Recommended Treatment Options

Treatment options for differentiated thyroid cancer include surgery, chemotherapy and radiotherapy.[20] 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.[13]
NICE currently recommends the following pharmacological treatment options for patients with differentiated thyroid and medullary thyroid cancer:[21]

- 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.

Clinical Trial Information

Trial	**ARROW; NCT03037385, Eudra-CT - 2016-004390-41; A phase 1/2 study of the highly-selective RET inhibitor, BLU-667, in patients with thyroid cancer, non-small cell lung cancer (NSCLC) and other advanced solid tumours**

	Phase I/II – Recruiting **Location(s):** Six EU countries, UK, USA, Canada and other countries **Primary completion date:** December 2021
Trial Design	Non-randomised, parallel assignment, open-label
Population	N=647; pathologically documented, definitively diagnosed non-resectable advanced solid tumour (phase I); oncogenic RET-rearrangement/fusion or mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumour, as determined by local or central testing of tumour or circulating tumour nucleic acid in blood (phase II)
Intervention(s)	Pralsetinib (oral)
Comparator(s)	None
Outcome(s)	Phase 1: • Determination of maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of pralsetinib [Time Frame: Cycle 1 (28 days) of treatment for MTD and at the end of every cycle (28 days) for RP2D for approximately 12 months or earlier if patient terminates from the study] • Number of patients with adverse events and serious adverse events [Time Frame: Every cycle (28 days) for approximately 24 months or earlier if patient terminates from the study, and 30 days after the last dose] Phase 2: • Overall response rate, assessed by RECIST v1.1 or RANO, as appropriate per tumour type [Time Frame: Approximately every 8 weeks or 16 weeks based on the treatment cycle] • Number of patients with adverse events and serious adverse events [Time Frame: Every cycle (28 days) for approximately 24 months or earlier if patient terminates from the study, and 30 days after the last dose] See trial record for full list of other outcomes.
Results (efficacy)	Among patients with baseline measurable disease who received pralsetinib by July 11, 2019 (enrolment cut-off for efficacy analysis), overall response rates were 15 (71%) of 21 (95% CI 48–89) in patients with treatment-naive RET-mutant medullary thyroid cancer and 33 (60%) of 55 (95% CI 46–73) in patients who had previously received cabozantinib or vandetanib, or both, and eight (89%) of nine (95% CI 52–100) in patients with RET fusion-positive thyroid cancer (all responses confirmed for each group).[5]
Results (safety)	Common (≥10%) grade 3 and above treatment-related adverse events among patients with RET-altered thyroid cancer enrolled by May 22, 2020, were hypertension (24 patients [17%] of 142), neutropenia (19 [13%]), lymphopenia (17 [12%]), and anaemia (14 [10%]). Serious treatment-related adverse events were reported in 21 patients (15%), the most frequent (≥2%) of which was pneumonitis (five patients [4%]). Five patients [4%] discontinued owing to treatment-related events. One (1%) patient died owing to a treatment-related adverse event.[5]

Estimated Cost

The cost of pralsetinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Selpercatinib for treating advanced thyroid cancer with RET alterations (GID-TA10614). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Selumetinib for treating differentiated thyroid cancer (GID-TA10207). Expected date of issue to be confirmed.
- NICE technology appraisal. Vandetanib for treating medullary thyroid cancer (TA550). December 2018.
- NICE technology appraisal. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (TA535). August 2018.
- NICE technology appraisal. Cabozantinib for treating medullary thyroid cancer (TA516). March 2018.
- NICE Guideline in development. Thyroid disease: assessment and management (GID-NG10150). Expected November 2022.
- NICE Guideline. Thyroid disease: assessment and management (NG145). November 2019.
- NICE interventional procedure guidance. Minimally invasive video-assisted thyroidectomy (IPG499). August 2014.
- NICE interventional procedure guidance. Vandetanib for treating medullary thyroid cancer (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.
- NHS England. NHS Standard Contract for Specialised Endocrinology Services (Adult). A03/S/a.

Other Guidance

- European Society for Medical Oncology (ESMO). Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.[22]
- The American Thyroid Association. Management guidelines for adults with thyroid nodules and differentiated thyroid cancer. 2015.[23]
- British Thyroid Association. Guidelines for the management of thyroid cancer. 2014.[24]
- London Cancer Alliance. LCA head and neck/thyroid cancer clinical guidelines. 2014.[25]

Additional Information

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