

HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2020

Pralsetinib for RET-fusion positive metastatic non-small-cell lung cancer

NIHRIO ID	26830	NICE ID	10479
Developer/Company	Roche Products Ltd	UKPS ID	657825

Licensing and market availability plans	Currently in phase III clinical development.
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SUMMARY

Pralsetinib is in clinical development for the treatment of metastatic RET-fusion positive non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer and at the metastatic stage the disease has already spread from the lungs to other sites. Around 2% of these patients will have tumours that contain fusion mutations in the RET gene. Cells in these tumours allow uncontrolled cancer growth. There are currently no therapies recommended for the treatment of NSCLC with a RET mutation.

Pralsetinib is an investigational, once-daily oral precision therapy designed to selectively target, and potentially inhibit, RET mutations, regardless of the tissue of origin. If licensed, pralsetinib will offer a treatment option for adult patients with RET-fusion positive advanced NSCLC, who currently have no highly selective therapies available.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Treatment of adult patients with rearranged during transfection (RET)-fusion positive metastatic non-small cell lung cancer (NSCLC).¹

TECHNOLOGY

DESCRIPTION

Pralsetinib (Gavreto, BLU-667) is an investigational, once-daily oral, small-molecule RET inhibitor specifically designed for highly potent and selective targeting of oncogenic RET alterations, including the most prevalent RET fusions (e.g., KIF5B-RET and CCDC6-RET) and RET-activating mutations (e.g. C634W, M918T, and V804L/M), regardless of the tissue of origin.² Preclinical data have shown that pralsetinib potently 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.³

In the phase III trial (NCT04222972) the starting dose of pralsetinib is 400 mg administered orally once daily.⁴

INNOVATION AND/OR ADVANTAGES

There are currently no therapies recommended by NICE specifically for the treatment of RET-fusion positive NSCLC.⁵

Patients with RET-altered NSCLC, which accounts for 1% to 2% of all NSCLCs, have seen poor outcomes from treatment with immunotherapy, making this an unmet medical need that can be addressed with targeted therapy.⁶

Pralsetinib is a potent and selective RET inhibitor that induces tumour regression in cancer models with RET mutations and fusions.² In the phase I/II ARROW clinical trial, pralsetinib demonstrated potent, durable and broad antitumor activity and was well tolerated in patients with advanced RET-fusion positive NSCLC.⁷

Pralsetinib has demonstrated markedly improved selectivity for RET compared to pharmacologically relevant kinases, including approximately 90-fold improved potency for RET versus Vascular Endothelial Growth Factor Receptor 2 (VEGFR2). By suppressing primary and secondary mutants, pralsetinib has the potential to overcome and prevent the emergence of clinical resistance.⁸

Pralsetinib is a potential TAT (tumour-agnostic therapy) as it targets a specific genomic anomaly or molecular feature regardless of tumour site of origin.²⁶

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

This product is not licensed for any other cancer indications in the EU/UK.

In May 2019 the FDA has granted Breakthrough Therapy Designation to pralsetinib for the treatment of RET-fusion positive NSCLC that has progressed following platinum-based chemotherapy.⁹

On the 4th September 2020, the FDA approved pralsetinib for the treatment of adults with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.¹⁰

Pralsetinib is currently in phase II development for medullary thyroid cancer RET-altered papillary thyroid cancer and other advanced solid tumours.¹¹

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 87% of lung cancers.¹² There are three common types of NSCLC; adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways), squamous cell cancer (develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).¹³

Metastatic cancers refer to cancers that have spread from where they started to other parts of the body, metastatic cancers cannot be cured.¹⁴ In Stage III NSCLC the cancer is locally advanced, it is in more than one lobe of the lung, or it has spread to lymph nodes or nearby structures in the chest. In Stage IV the cancer has spread to the other lung or to a distant part of your body such as the liver or bones.

RET activating fusions and mutations are key disease drivers in many cancer types, including NSCLC and multiple types of thyroid cancer. RET fusions are implicated in approximately 1 to 2 percent of patients with NSCLC.³

Common risk factors for the development of lung cancer include tobacco smoking, exposure to air pollution, radon gas, silica and asbestos, previous lung disease such as COPD and family history of lung cancer.¹⁵ RET-fusion mutations are most common in patients with the adenocarcinoma subtype of NSCLC, in patients younger than 60 years, females, and former light smokers, or never smokers.¹⁶

Key symptoms of lung cancer include a cough, breathlessness, coughing up blood, chest pain, weight loss and loss of appetite, fatigue and chest infections.¹⁷

CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.¹⁸ Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. There are around 47,800 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 years (2015-2016). Incidence

rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.¹⁹

In 2017, 39,108 people were diagnosed with NSCLC in England & Wales, and around 57% had stage IIIB or stage IV disease.²⁰ Rearranged during transfection (RET) fusion-positive tumours occur in 1-2% of NSCLC.²¹ If these figures are applied to 2017 registrations, there were potentially 223 to 446 new cases of stage IIIB or stage IV RET-fusion positive NSCLC.

In 2018/19 there were 107,010 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 128,985 finished consultant episodes (FCEs), resulting in 249,196 FCE bed days.²²

In England between 2013 to 2017 the age-standardised net cancer survival rate at 1-year for stage III and IV were 48.7% and 19.3% respectively. The age-standardised net cancer survival rate at 5-years for stage III and IV were 12.6% and 2.9% respectively.²³

Lung cancer was one of the most common causes of cancer death in 2017, accounting for approximately 21% of all cancer deaths.¹⁹ In 2019 there were 29,443 registrations of death from malignant neoplasms of bronchus and lung in adults in England and Wales (ICD-10 code C34).²⁴

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. The main treatment options for early stage (I, II and III) NSCLC are surgery, chemotherapy, radiotherapy, chemoradiotherapy and immunotherapy.²⁵

At advanced stage (III and IV) NSCLC treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally include chemotherapy, targeted drugs, radiotherapy and symptom control treatment.²⁵ There are specific treatment pathways for cancers positive for EGFR-TK, ALK or ROS-1 gene mutations but not for RET fusions/mutations.²⁶

CURRENT TREATMENT OPTIONS

Patients with NSCLC (with no gene mutation or fusion protein that has a specific treatment pathway) who progress after platinum-based therapy receive:²⁶

- Immunotherapy treatment with pembrolizumab, nivolumab or without PD-L1 expression; atezolizumab.
- docetaxel with or without the multikinase inhibitor nintedanib.

PLACE OF TECHNOLOGY

If licensed, pralsetinib will offer another treatment option for metastatic RET-fusion positive NSCLC, who currently have no highly selective therapies available.

CLINICAL TRIAL INFORMATION

Trial	<p>AcceleRET; NCT04222972, EudraCT2019-002463-10; A Randomized, Open-Label, Phase 3 Study of Pralsetinib Versus Standard of Care for First Line Treatment of RET Fusion-positive, Metastatic Non-Small Cell Lung Cancer</p> <p>Phase III - Recruiting</p> <p>Location(s): Belgium, France, Italy, Republic of Korea, Norway, Poland, Spain, Taiwan, and United States</p> <p>Primary completion date: September 2023</p>
Trial design	Randomized, Parallel Assignment, Open Label
Population	N = 250 (planned), metastatic NSCLC that has not been treated with systemic anticancer therapy for metastatic disease, documented RET-fusion, aged 18 years and older.
Intervention(s)	Pralsetinib administered orally
Comparator(s)	Platinum doublet chemotherapy with or without pembrolizumab administered intravenously
Outcome(s)	<p>Primary outcome(s):</p> <ul style="list-style-type: none"> • Progression Free Survival (PFS) [Time Frame: Estimated at up to 32 months] <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	
Results (safety)	

Trial	<p>ARROW; NCT03037385; 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 Tumors</p> <p>Phase II - Recruiting</p> <p>Location(s): Belgium, China, France, Germany, Hong Kong, Italy, Republic of Korea, Netherlands, Singapore, Spain, Taiwan, United Kingdom and United States</p> <p>Primary completion date: December 2021</p>
Trial design	Non-Randomized, Parallel Assignment, Open Label
Population	N = 647 (planned), oncogenic RET-rearrangement/fusion or mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumour, aged 18 years and older
Intervention(s)	<ul style="list-style-type: none"> • Phase I Multiple doses of pralsetinib (BLU-667) for oral administration. • Phase II Oral dose of pralsetinib (BLU-667) as determined during Dose Escalation.
Comparator(s)	No comparator
Outcome(s)	Primary outcome(s):

	<ul style="list-style-type: none"> • (Phase 1) Determination of maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of BLU-667 [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] • (Phase 1) 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 [Time Frame: Approximately every 8 weeks during treatment, 14 days after the last dose, and every 3 months after the last dose (up to 2 years) in patients without progressive disease] • (Phase 2) 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] <p>See trial record for full list of other outcomes.</p>
Results (efficacy)⁷	<ul style="list-style-type: none"> • The overall response rate (ORR) among 57 response-evaluable patients with measurable disease and at least one follow-up disease assessment was 56% (95% CI: 42, 69; 32 partial responses (PR), 9 PR pending confirmation, 20 stable disease, 5 progressive disease). • 91% (29/32) of responding patients remain on treatment; 6 have achieved response duration \geq 6 months. Disease control rate (DCR) was 91% (52/57). Among 30 patients at the recommended phase 2 dose previously treated with platinum chemotherapy, ORR was 60% (18 PRs; 7 pending confirmation). • Responses occur regardless of prior treatment or RET fusion genotypes. Intracranial activity has been observed with shrinkage of brain metastases. • 80% of NSCLC patients treated at RP2D remain on treatment and only 3% discontinued due to related adverse event.
Results (safety)⁷	<p>In NSCLC patients, treatment-related toxicity (TRT), generally low-grade and reversible (28% had \geq grade 3 events), included increased AST (22%), hypertension (18%), increased ALT (17%), constipation (17%), fatigue (15%) and decreased neutrophils (15%).</p>

ESTIMATED COST

The cost of pralsetinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Avelumab for treating non-small-cell lung cancer after platinum-based chemotherapy (TA10341). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer (TA10618). June 2021.
- NICE technology appraisal. Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation (TA578). May 2019.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- NICE technology appraisal. Nivolumab for previously treated non-squamous non-small-cell lung cancer (TA484). November 2017.
- NICE technology appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). August 2016.
- NICE Technology appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). August 2016.
- NICE technology appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA374). December 2015.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE clinical guideline. Lung cancer: diagnosis and management (update) (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

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. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

OTHER GUIDANCE

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- European Society for Medical Oncology. Early and locally advanced non-small-cell-lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2017.²⁷
- National Comprehensive Cancer Network (NCCN). Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.²⁸
- Scottish Intercollegiate Guidelines Network (SIGN) Management of lung cancer: A national clinical guideline. 2014.²⁹

ADDITIONAL INFORMATION

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