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HEALTH TECHNOLOGY BRIEFING
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Brigatinib for ALK-positive, locally advanced or metastatic, non-small cell lung cancer previously treated with alectinib or ceritinib

NIHRIO ID	24300	**NICE ID**	10235
Developer/Company	Takeda UK Ltd	**UKPS ID**	Not available

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

SUMMARY

Brigatinib is a medicinal product that is being developed for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) whose disease have progressed following treatment with alectinib or ceritinib. NSCLC is the most common type of lung cancer although a small proportion of NSCLC patients have a rearrangement in the ALK gene. Locally advanced or metastatic cancer means cancer has spread outside the lungs where it started, to other parts of the body and cannot be cured. Current treatment with drugs such as alectinib or ceritinib are effective in slowing the disease and helping patients to live longer, although some patients eventually develop treatment resistance and will require other therapies.

Brigatinib acts by blocking specific pathways in the activity of the ALK gene that leads to inhibition of cancer cell growth. Early studies have shown that brigatinib may be effective against cancer cells that have developed resistance to other treatments. Brigatinib is taken orally once daily as a tablet and is currently licensed in the EU/UK as a monotherapy for the treatment of patients with ALK-positive advanced NSCLC previously treated with crizotinib. If licensed, brigatinib will offer a treatment option for patients with locally advanced or metastatic ALK-positive NSCLC, whose disease has progressed on therapy with alectinib or ceritinib.

PROPOSED INDICATION

As monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (stage IIIB) or metastatic (stage IV) non-small cell lung cancer (NSCLC), previously treated with alectinib or ceritinib.[1]

TECHNOLOGY

DESCRIPTION

Brigatinib (AP-26113, Alunbrig®) is an anti-neoplastic agent formulated as tablets for oral route of administration. Brigatinib is a tyrosine kinase inhibitor (TKI) that targets ALK, insulin-like growth factor 1 receptor (IGF-1R) and c-Ros proto-oncogene 1 receptor tyrosine kinase (ROS1).[2,3] This leads to the inhibition of ALK kinase and epidermal growth factor receptor (EGFR) kinase, disrupts their signalling pathways and eventually inhibits tumour cell growth in susceptible tumour cells. In addition, brigatinib appears to overcome mutation-based resistance.[4] Brigatinib inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice. Brigatinib inhibited the *in vitro* and *in vivo* viability of cells expressing mutant forms of EML4-ALK associated with resistance to ALK inhibitors, including G1202R and L1196M.[3]

Brigatinib is in clinical development for the treatment of patients with ALK-positive locally advanced or metastatic NSCLC whose disease has progressed on therapy with alectinib or ceritinib. In the phase II clinical trial (ALTA-2; NCT03535740), participants received brigatinib 90 mg orally, once daily for 7 days, followed by brigatinib 180 mg, once daily until objective disease progression per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, or intolerable toxicity.[1] Treatment beyond progression or escalation to brigatinib 240 mg is permitted.[5]

INNOVATION AND/OR ADVANTAGES

Alectinib and ceritinib have demonstrated efficacy and acceptable safety in ALK TKI-pre-treated and TKI-naive NSCLC. However, as with crizotinib, resistance to alectinib and ceritinib eventually develops, with secondary resistance mutations detected in approximately 50% of patients. Brigatinib is a next-generation ALK TKI designed to have potent and broad activity against ALK mutants.[5]

In preclinical studies, brigatinib potently inhibited all ALK resistance mutations tested, including G1202R, and overcame mechanisms of resistance to other ALK inhibitors at clinically achievable brigatinib levels.[6]

Post-crizotinib, brigatinib demonstrated high systemic and central nervous system (CNS) objective response rates (ORR) and the longest reported median progression-free survival (PFS) as compared to other ALK inhibitors. Based on nonclinical and clinical data, brigatinib may offer a potential treatment option for patients with ALK+ advanced NSCLC that have developed resistance or failed to respond to alectinib or ceritinib.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Brigatinib is currently licensed in the EU/UK as a monotherapy for the treatment of patients with ALK-positive advanced NSCLC previously treated with crizotinb.[3] The most common adverse reactions (≥ 25%) reported in patients treated with brigatinib at the recommended

dosing regimen were hyperglycaemia, hyperinsulinaemia, anaemia, increased lipase, decreased lymphocyte count, increased ALT, diarrhoea, increase amylase, fatigue, cough, headache, increased alkaline phosphatase, hypophosphataemia, increased APTT, rash, vomiting, dyspnoea, hypertension, decreased white blood cell count myalgia and peripheral neuropathy.[3]

Brigatinib is in phase III clinical development for the first-line treatment for adults with ALK-positive advanced NSCLC untreated (i.e. ALK-naïve) patients.[7]

PATIENT GROUP

DISEASE BACKGROUND

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 87% of lung cancers in the UK.[8,9] A small proportion of NSCLCs (about 3.9%) have an ALK-positive test result.[10] This gene rearrangement identifies a population of NSCLCs in whom the dysregulation of ALK-tyrosine kinase leads to the uncontrolled proliferation of cancer cells, thus providing the basis for the therapeutic use of ALK-TK inhibitors (TKIs).[11]

The ALK gene rearrangement is most often seen in subjects who have the adenocarcinoma subtype of NSCLC.[12] Younger patients, people who have never smoked (or smoked very little), and those with East Asian ethnicity are more likely to have ALK gene rearrangement.[12]

Metastatic cancers refer to cancers that have spread from where they started to other parts of the body and locally advanced cancer is used to describe cancer that has grown outside the organ it started in but has not yet spread to distant parts of the body. Locally advanced or metastatic cancers cannot be cured.[13] Key symptoms of lung cancer include a cough, breathlessness, coughing up blood, chest pain, weight loss and loss of appetite, fatigue and chest infections.[14]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer was the third most common cancer in the UK in 2016, with an incidence rate in England of 72.2 per 100,000.[15] In 2017, there were 38,888 new registrations of malignant neoplasms of bronchus and lung in England (ICD-10 code C34).[16]

In 2017/18 there were 97,544 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 118,643 finished consultant episodes (FCEs), resulting in 249, 287 FCE bed days.[17]

2010-2011 figures report a 1-year survival rate of 32.1% and a predicted 5-year survival rate of 9.5% for all lung cancer patients in England and Wales.[18]

Lung cancer was one of the most common causes of cancer death in 2017, accounting for approximately 21% of all cancer deaths.[16] In 2017 there were 28,170 registrations of death from cancer in England for malignant neoplasms of bronchus and lung in England (ICD-10 code C34).[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of cancer and the general health of the patient.[19] The main treatment option for the locally advanced or metastatic disease includes surgery, systemic anti-cancer therapy (SACT) and radiotherapy.[20]

At this stage, NSCLC treatment aims to control the cancer for as long as possible and help with symptoms.[21] Treatment for NSCLC with ALK gene rearrangement generally includes targeted therapy drugs in the first line and relapsed setting.[20]

CURRENT TREATMENT OPTIONS

Currently, no ALK-TKI is recommended by NICE for use after progression on either alectinib or ceritinib. Lorlatinib has recently received a conditional authorisation by EMA for treating ALK-positive NSCLC that has worsened despite treatment with other ALK-TKI.[22] At present, lorlatinib is undergoing NICE technology appraisal for advanced ALK-positive NSCLC that has:[23]

- progressed after treatment with alectinib or ceritinib as the first ALK-TKI, or
- progressed after treatment with crizotinib and at least one other ALK-TKI

PLACE OF TECHNOLOGY

If licenced, brigatinib will offer an additional treatment option for patients with anaplastic ALK-positive, locally advanced or metastatic NSCLC whose disease has progressed on therapy with alectinib or ceritinib.

CLINICAL TRIAL INFORMATION

Trial	**ALTA-2, NCT03535740, EudraCT-2018-000635-27, aged 18 years and older; brigatinib; phase II**
Sponsor	Takeda UK Ltd
Status	Ongoing
Source of Information	Trial registry[1]; Publication[5]
Location	EU (not UK), USA and Canada, and other countries
Design	Non-randomised, single group assignment open-label
Participants	n=103 (planned); aged 18 years and older; histologically or cytologically confirmed stage IIIB or stage IV NSCLC, have documentation of ALK rearrangement by a positive result, had been on any one of the ALK tyrosine kinase inhibitor (TKIs) (alectinib, ceritinib, crizotinib) for at least 12 weeks before progression, progressive disease while on alectinib or ceritinib; had alectinib or ceritinib as the most recent ALK inhibitor therapy; at least 1 measurable lesion per response evaluation criteria in solid tumours (RECIST) version 1.1; recovered from toxicities related to prior anticancer therapy; life expectancy of ≥3months.
Schedule	Brigatinib 90 mg, tablets, once daily for 7 days, followed by brigatinib 180 mg, tablets, orally, once daily for until objective disease progression per RECIST version 1.1, as assessed by the investigator, or intolerable toxicity.

	Treatment beyond progression or escalation to brigatinib 240 mg is permitted.
Follow-up	The overall study duration is approximately 5 years and 30 days after last dose of study drug for a follow-up assessment.
Primary Outcomes	Confirmed Objective Response Rate (ORR) using RECIST v1.1 as assessed by the Independent Review Committee (IRC)- [Time frame: every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)]
Secondary Outcomes	• Confirmed ORR using RECIST v1.1 as assessed by the investigator (Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years) • Duration of Response (DOR) as assessed by the investigator and IRC [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Progression-Free Survival (PFS) as assessed by the investigator and IRC [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Disease Control Rate (DCR) as assessed by the investigator and IRC [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Time to Response as assessed by the investigator and IRC [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Confirmed Intracranial Objective Response Rate (iORR) in participants with brain metastases at baseline as assessed by the IRC [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Duration of Intracranial Response in participants with brain metastases at baseline as assessed by the IRC [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Intracranial Progression-Free Survival (iPFS) in participants with brain metastases at baseline, as assessed by the IRC [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Overall Survival (OS) [Time Frame: Every 8 weeks for 52 weeks and every 12 weeks after, until the radiological disease progression (approximately 5 years)] • Number of Participants With One or More Treatment-emergent Adverse Event (TEAE) [Time Frame: First dose of study drug up to 30 days after last dose (approximately 5 years)] • Health-Related Quality of Life (HRQOL) from European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Score [Time Frame: First dose of study drug up to 30 days after last dose (approximately 5 years)] • HRQOL from EORTC QLQ- Lung Cancer [Time Frame: First dose of study drug up to 30 days after last dose (approximately 5 years)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as Dec 2019. Estimated study completion date reported as Apr 2022.

ESTIMATED COST

Brigatinib is already marketed in the UK; £4,900 for 28×180 mg tablets (the recommended dose), £4,900 for a starter pack (7×90 mg plus 21×180 mg tablets), £3,675 for 28×90 mg tablets, £1,225 for 28×30 mg tablets. [24] There is a simple discount patient access scheme for brigatinib.[25]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Lorlatinib for treating ALK-positive advanced non-small-cell lung cancer (ID1338). Expected publication date: TBC
- NICE clinical guideline. Lung cancer: diagnosis and management (update) (NG122). March 2019.

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: Robotic-assisted lung resection for primary lung cancer. 16024/P. July 2016.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment follow-up 2018.[19]
- 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.[26]

ADDITIONAL INFORMATION

Takeda UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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