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Brigatinib for locally advanced or metastatic, ALK-positive, non-small cell lung cancer – first line

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LAY SUMMARY

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. A small proportion of NSCLC patients have a rearrangement in a gene called anaplastic lymphoma kinase (ALK). Younger patients, people who have never smoked (or smoked very little), women, and those with East Asian ethnicity are more likely to have ALK gene rearrangement. Locally advanced or metastatic cancer means the cancer has spread outside the lungs where it started, to other parts of the body and cannot be cured. However, treatment can shrink the cancer, slow its growth, help relief symptoms, and help patients to live longer.

Brigatinib is a new treatment option being developed specifically for ALK-positive NSCLC. It acts by blocking the activity of some specific proteins encoded by the ALK gene, thereby reducing the growth of cancer cells. Brigatinib is taken orally once daily as a tablet and potentially has a broader range of resistance when compared other treatment options in its class. Brigatinib would be offered to patients with locally advanced or metastatic ALK-positive NSCLC, who have not received prior treatment. If licensed, brigatinib will offer an additional treatment option for this patient group.

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TARGET GROUP

Non-small cell lung cancer (NSCLC) (anaplastic lymphoma kinase positive (ALK+), locally advanced or metastatic) – first line

TECHNOLOGY

DESCRIPTION

Brigatinib (AP-26113, Alunbrig) is an anti-neoplastic agent formulated as tablets for oral route of administration. Brigatinib acts as a tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK), insulin-like growth factor 1 receptor (IGF-1R) and ROS1 (proto-oncogene tyrosine-protein kinase ROS, an enzyme that in humans is encoded by the ROS1 gene).[1,2] This leads to the inhibition of ALK kinase and 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. ALK belongs to the insulin receptor superfamily and plays an important role in nervous system development; ALK dysregulation and gene rearrangements are associated with a series of tumours.[3]

The phase III trial (NCT02737501) included participants who have not previously been treated with an ALK inhibitor. Participants in the experimental arm received brigatinib at a dose of 90mg once daily for 7 days, then 180mg once daily, continuously until disease progression, unacceptable toxicity, and withdrawal of consent or death.[4]

Brigatinib does not currently have Marketing Authorisation in the EU for any indication. In April 2017, it received a new drug application approval by the FDA for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.[5]

INNOVATION and/or ADVANTAGES

Laboratory studies suggest that brigatinib can overcome a broader range of the resistance mechanisms that result from secondary mutations in the ALK gene compared with crizotinib, ceritinib or alectinib.[6] This broad range of resistance means that brigatinib, given at a higher dose of 180mg/day, may have the potential to increase progression-free survival compared to other next-generation ALK inhibitors.[7,8] Also, there is a high propensity for ALK-positive NSCLC to metastasise to the brain, and crizotinib penetration into the cerebrospinal fluid is negligible.[9]

If licensed, brigatinib will offer an additional treatment option for patients with locally advanced or metastatic ALK-positive NSCLC who have not been treated previously.

DEVELOPER

Takeda UK Ltd

REGULATORY INFORMATION/ MARKETING PLANS

The US FDA granted brigatinib an Orphan Drug designation for the treatment of ALK-positive NSCLC in April 2016.[1,10]

PATIENT GROUP

BACKGROUND

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 88.5% of lung cancers in the UK.[11] A small proportion of NSCLCs (about 3.8%) have a rearrangement in a gene called anaplastic lymphoma kinase (ALK).[12] 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).[13]

The ALK gene rearrangement is most often seen in subjects who have the adenocarcinoma subtype of NSCLC (36% of NSCLC in the UK).[11] Younger patients, people who have never smoked (or smoked very little), women, and those with East Asian ethnicity are more likely to have ALK gene rearrangement.[14]

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 NSCLC cannot be cured.[15]

Key symptoms of lung cancer include a cough, breathlessness, chest pain, weight loss and loss of appetite, fatigue and chest infections.[16]

CLINICAL NEED and BURDEN OF DISEASE

Lung cancer was the third most common cancer in the UK in 2014, with an incidence rate in England of 76.6 per 100,000.[17] In 2015 there were 37,608 new registrations of malignant neoplasms of bronchus and lung in England (ICD-10 code C34).[18]

In 2016/17 there were 91,902 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 112,905 finished consultant episodes (FCEs), resulting in 267,931 FCE bed days.[19]

Latest figures report 1-year survival rate of 32.1% and a predicted 5-year survival rate of 9.5% for all lung cancer patients.[17]

Lung cancer was the most common cause of cancer death in 2014, accounting for 22% of all cancer deaths.[17] In 2015 there were 28,565 registrations of death from cancer in England for malignant neoplasms of bronchus and lung in England (ICD-10 code C34).[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (ID925). Expected date of issue August 2018.
- NICE technology appraisal in development. Ceritinib for untreated anaplastic lymphoma kinase positive non-small-cell lung cancer (TA500). January 2018.

- NICE technology appraisal. Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA422). December 2016.
- NICE technology appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). September 2016.
- NICE clinical guideline in development. Lung cancer: diagnosis and management (update) (NG10061). Publication anticipated January 2019.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

NHS ENGLAND and POLICY 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. Early and locally advanced non-small-cell-lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017.[20]
- European Society for Medical Oncology. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines. 2016.[21]

CURRENT TREATMENT OPTIONS

Both NICE and European guidelines state that first-line treatment with crizotinib is the preferred treatment of patients with ALK-positive NSCLC.[9,22] Crizotinib is an inhibitor of tyrosine kinase, and binds to the tyrosine kinase receptor on the surface of lung cancer cells and inhibits the abnormal ALK protein.[14] Studies have found that treatment with crizotinib results in a median progression-free survival of 7 to 10 months[14], but all patients will eventually experience disease progression through primary or acquired resistance.[22]

Both NICE and European guidelines recommend ceritinib for patients with ALK-positive NSCLC who progress on treatment with or are intolerant to crizotinib.[9,23]

EFFICACY and SAFETY

Trial	ALTA-1L, NCT02737501, EudraCT-2015-003447-19; brigatinib versus crizotinib, phase III
Sponsor	Takeda UK Ltd
Status	Active, not recruiting
Source of Information	Trial registries[4, 24]
Location	13 EU countries (incl. UK), USA, Australia, Canada, Asia
Design	Randomised, active controlled parallel assignment, open label

Participants	N=275[a]; aged 18 years and older; stage IIIB or stage IV NSCLC; ALK rearrangement; not previously treated with an ALK inhibitor;
Schedule	Participants are randomised to one of two study arms at a ratio of 1:1: 1. Experimental arm: Brigatinib administered orally at a dose of 90 mg once daily for 7 days, then 180 mg once daily, continuously, with or without food until disease progression, unacceptable toxicity, or withdrawal of consent or death. 2. Active comparator: Crizotinib administered orally at a dose if 250mg twice daily with or without food until disease progression, unacceptable toxicity, withdrawal of consent or death
Follow-up	The total estimated duration of the study is at least 5 years, including 2 years to accrue patients, with at least 3 years for treatment and follow-up.
Primary Outcomes	Progression-free survival (PFS) as assessed by a blinded Independent Review Committee (bIRC) per RECIST 1.1 [Time Frame: At least 36 months]
Secondary Outcomes	• Objective response rate (ORR) [Time Frame: At least 36 months] • Intracranial ORR [Time Frame: At least 36 months] • Intracranial PFS [Time Frame: At least 36 months] • Overall survival (OS) [Time Frame: At least 36 months] • Health-related quality of life (HRQoL) [Time Frame: Until 30 days after the last dose of study treatment] • Percentage of patients with adverse events [Time Frame: Until at least 30 days after the last dose of study treatment] • Steady state pharmacokinetic (PK) parameter: Maximum Plasma Concentration [Cmax] [Time Frame: Up to 28 months] • Steady state pharmacokinetic (PK) parameter: Minimum plasma concentration [Cmin] [Time Frame: Up to 28 months] • Steady state pharmacokinetic (PK) parameter: Area Under the Curve [AUC] [Time Frame: Up to 28 months] • Steady state pharmacokinetic (PK) parameter: Time to maximum plasma concentration (Tmax) [Time Frame: Up to 28 months] • Steady state pharmacokinetic (PK) parameter: Apparent oral clearance [CL/F] [Time Frame: Up to 28 months] • Duration of response (DOR)[a] • Time to response[a] • Disease control rate[a]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date April 2019. Estimated study completion date April 2021.

ESTIMATED COST and IMPACT

COST

The cost of brigatinib is not yet known.

[a] Information provided by company

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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