

**NIHR Innovation Observatory  
Evidence Briefing: August 2017**

**Brigatinib (Alunbrig) for anaplastic lymphoma  
kinase (ALK)-positive advanced non-small cell lung  
cancer**

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**LAY SUMMARY**

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 87% of lung cancers in the UK. A small proportion of NSCLCs (about 5%) 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. There are estimated to around 1,600 cases of this type of cancer diagnosed every year in England. The first-line treatment for ALK-positive NSCLC is a drug called crizotinib, but some patients are intolerant to this drug, or their cancer may progress while they are taking this drug.

Brigatinib is an anti-plastic agent that works in part by blocking the activity of the ALK protein, inhibiting the growth of tumour cells. It is taken orally as a tablet. Brigatinib would be offered as a second-line treatment to patients who have progressed on or are intolerant to crizotinib. If licensed, brigatinib will offer an additional treatment option for patients with ALK-positive NSCLC, and may extend patient survival time.

*This briefing is based on information available at the time of research 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.*

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## TARGET GROUP

Adult patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have been previously treated with crizotinib - second line

## TECHNOLOGY

### DESCRIPTION

Brigatinib (Alunbrig; AP-26113) is an anti-neoplastic agent. It is formulated as tablets for oral administration. Brigatinib acts as anaplastic lymphoma kinase (ALK) antagonist, epidermal growth factor receptor antagonist and ROS1 inhibitor. ALK is rearranged, mutated, or amplified in a series of tumours and non-small cell lung cancer. Epidermal growth factor receptor (EGFR) is a growth-factor-receptor tyrosine kinase that is involved in the growth of a tumour. ROS is an enzyme that in humans is encoded by the ROS1 gene, it is a proto-oncogene, highly-expressed in a variety of tumour cell lines. The protein may function as a growth or differentiation factor receptor. Brigatinib is indicated for the treatment of patients with ALK-positive NSCLC who have progressed or are intolerant to crizotinib.<sup>1</sup>

The Phase II trial (NCT02094573) (completed February 2016) included subjects who had been previously treated with crizotinib. Participants received either 90 mg of brigatinib once per day (QD) (Arm A), or 180 mg QD with a seven day lead-in at 90 mg QD (Arm B).<sup>2</sup>

Brigatinib does not currently have Marketing Authorisation in the EU for any indication.

Brigatinib is at EU pre-registration as second-line treatment for adult patients with ALK-positive NSCLC who have been previously treated with crizotinib.<sup>3</sup>

Brigatinib is in trials for the treatment of:

- ALK-positive locally advanced or metastatic NSCLC first-line (Phase III ongoing)<sup>1</sup>
- ALK-positive advanced NSCLC (Phase II completed)<sup>1</sup>
- NSCLC with ROS1 mutation (Phase II planned)<sup>1</sup>
- ALK/ROS1-mutant metastatic solid tumours (Phase II planned)<sup>1</sup>

## INNOVATION and/or ADVANTAGES

If licensed, brigatinib will offer an additional treatment option for patients with ALK-positive NSCLC who have been previously treated with crizotinib.

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.<sup>4</sup> 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.<sup>5,6</sup>

## DEVELOPER

Takeda Pharmaceuticals

## AVAILABILITY, LAUNCH or MARKETING

FDA has granted brigatinib:

- Accelerated Approval as a second-line treatment for the treatment of patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib in April 2017<sup>7</sup>
- Orphan Drug designation for the treatment of ALK-positive NSCLC in April 2016<sup>7,1</sup>
- Breakthrough Therapy designation for the treatment of patients with ALK-positive NSCLC whose tumours are resistant to crizotinib in October 2014<sup>7,1</sup>

The company submitted a Marketing Authorisation Application to the EU in February 2017.<sup>8</sup>

## PATIENT GROUP

### 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.<sup>9</sup> A small proportion of NSCLCs (about 5%) have a rearrangement in a gene called anaplastic lymphoma kinase (ALK).<sup>10</sup> This gene rearrangement identifies a population of NSCLCs in whom the dysregulation of ALK-tyrosine kinase (-TK) leads to the uncontrolled proliferation of cancer cells, thus providing the basis for the therapeutic use of ALK-TK inhibitors (-TKIs).<sup>11</sup>

This gene rearrangement is most often seen in subjects who have the adenocarcinoma subtype of NSCLC. 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.<sup>12</sup>

Key symptoms of lung cancer include a cough, breathlessness, chest pain, weight loss and loss of appetite, fatigue and chest infections.<sup>13</sup>

## 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.<sup>14</sup> In 2015 there were 37,608 new registrations of malignant neoplasms of bronchus and lung in England (ICD-10 code C34).<sup>15</sup> As NSCLC accounts for around 87% of lung cancers, and around 5% of NSCLC are ALK-positive, this equates to around 1,636 cases each year.

In 2015/16 there were 89,945 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 110,013 finished consultant episodes (FCEs), resulting in 266,522 FCE bed days.<sup>16</sup>

Latest figures report 1-year survival rate of 32.1% and a predicted 5-year survival rate of 9.5%.<sup>14</sup>

Lung cancer was the most common cause of cancer death in 2014, accounting for 22% of all cancer deaths.<sup>14</sup> 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).<sup>15</sup>

## PATIENT PATHWAY

## RELEVANT GUIDANCE

## NICE GUIDANCE

- NICE technology appraisal in development. Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA10206). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (TA10182). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy (TAG506). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for previously treated locally advanced or metastatic non-squamous non-small-cell lung cancer (TAG524). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab for treating unresectable non-small-cell lung cancer after platinum-based chemoradiation (TA10187). Expected January 2019.
- NICE technology appraisal in development. Ceritinib for untreated anaplastic lymphoma kinase positive non-small-cell lung cancer (TA10145). Expected April 2018.
- NICE technology appraisal in development. Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy (TA10108). Expected October 2017.
- NICE technology appraisal. Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA422). December 2016.
- NICE technology appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). September 2016.
- NICE technology appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). September 2016.
- 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. Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer (TA395). June 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 technology appraisal. Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer (TA227). June 2011.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE technology appraisal. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (TA190). June 2010.

- NICE technology appraisal. Pemetrexed for the first-line treatment of non-small-cell lung cancer (TA181). September 2009.
- NICE technology appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). August 2007.
- 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. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines. 2016.
- 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. Annals of Oncology 28 (Supplement 4): iv1-iv21, 2017

## 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.<sup>17,18</sup> 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.<sup>12</sup> Studies have found that treatment with crizotinib results in a median progression-free survival of 7 to 10 months,<sup>12</sup> but all patients will eventually experience disease progression through primary or acquired resistance.<sup>18</sup> Also, there is a high propensity for ALK-positive NSCLC to metastasise to the brain, and crizotinib penetration into the cerebrospinal fluid is negligible.<sup>18</sup>

Both NICE and European guidelines recommend ceritinib for patients with ALK-positive NSCLC who progress on treatment with or are intolerant to crizotinib.<sup>18,19</sup>

## EFFICACY and SAFETY

<b>Trial</b>	ALTA, NCT02094573, EudraCT-2013-002134-21
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<b>Sponsor</b>	Ariad Pharmaceuticals (Ariad Pharmaceuticals was acquired by Takeda Pharmaceutical Company Limited in February 2017)
<b>Status</b>	Published <sup>20</sup>
<b>Source of Information</b>	Trial registry <sup>2</sup> , GlobalData <sup>1</sup>
<b>Location</b>	EU (incl UK), USA, Canada and other countries (71 centres across 18 countries)
<b>Design</b>	Open-label, randomised, parallel assignment
<b>Participants</b>	n=222; aged 18+ years; ALK-positive NSCLC; previously treated with crizotinib
<b>Schedule</b>	Subjects received either 90 mg of brigatinib once daily (Arm A), or 180 mg once daily with a seven day lead-in at 90 mg once daily (Arm B). Treatment continued until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal.
<b>Follow-up</b>	Visits were scheduled to occur on days 1, 8, and 15 of the first 28-day cycle and then every 4 weeks, at treatment discontinuation and at 30 days post-treatment. Follow-up for survival and subsequent therapy continued every 3 months after treatment discontinuation.
<b>Primary Outcomes</b>	Confirmed Objective Response Rate per RECIST v1.1 (per investigator)
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>- ORR per central IRC</li> <li>- Intracranial ORR</li> <li>- Intracranial CNS progression free survival (PFS)</li> <li>- Time to response (CR/PR)</li> <li>- Duration of response (CR/PR)</li> <li>- Disease control rate</li> <li>- PFS</li> <li>- Overall survival</li> <li>- Number of participants with at least one treatment-emergent adverse event</li> <li>- Pre-dose brigatinib plasma concentration</li> <li>- Patient-reported Quality of Life score</li> </ul>
<b>Key Results</b>	Brigatinib yielded substantial whole-body and intracranial responses as well as robust progression-free survival in ALK fusion–positive pts with a range of crizotinib-resistance mutations. 180mg (with lead-in) showed consistently better efficacy than 90mg, with acceptable safety. Neither primary nor secondary resistance to brigatinib was associated with any single plasma ALK mutation. The therapeutic implications of complex secondary resistance patterns associated with brigatinib require further exploration. <sup>20, 21</sup>
<b>Adverse effects (AEs)</b>	The most common treatment-emergent adverse events included nausea, diarrhoea, cough and headache. <sup>21</sup>
<b>Expected reporting date</b>	-

## ESTIMATED COST and IMPACT

### COST

The cost of brigatinib is not yet known.

## IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

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|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other   | <input type="checkbox"/> No impact identified                      |

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- |   |   |
|---|---|
| <input type="checkbox"/> Increased use of existing services   | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services              |
| <input type="checkbox"/> Other                                | <input checked="" type="checkbox"/> None identified         |

### IMPACT ON COSTS and OTHER RESOURCE USE

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs                   | <input type="checkbox"/> Other reduction in costs     |
| <input type="checkbox"/> Other                                     | <input type="checkbox"/> None identified              |

### OTHER ISSUES

- |   |   |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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