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# Osimertinib (Tagrisso) for locally advanced or metastatic non-small cell lung cancer, EGFR mutation positive (Ex19del or L858R) - first line

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## LAY SUMMARY

Lung cancer is the third most common cancer in the UK. Most lung cancer cases are diagnosed at a late stage in the UK. Treatment of lung cancer depends on its exact location, how far it has grown or spread (the stage), how abnormal the cells look under a microscope (the grade), and on the patient's general health and level of fitness.

There are two types of lung cancer: non-small cell lung cancer (NSCLC), which forms the vast majority of lung cancers; and small cell lung cancer. In some types of NSCLC, genetic alterations can occur in a protein receptor called the epidermal growth factor receptor (EGFR). These specific alterations are a deletion in Exon 19 (Ex19del) and a mutation which results in substitution of leucine for arginine at position 858 (L858R).

Osimertinib is a drug that prevents, inhibits or halts the development of a tumour. It is administered as a tablet. If licensed, osimertinib could offer an additional treatment option for patients with advanced NSCLC that is EGFR mutation positive (Ex19del or L858R) in the first line setting.

## TARGET GROUP

Locally advanced or metastatic non-small cell lung cancer, EGFR mutation positive (Ex19del or L858R) - first line

## TECHNOLOGY

### DESCRIPTION

Osimertinib mesylate (AZD-9291 /Tagrisso) acts as an antineoplastic agent. It is formulated as film coated tablets and tablets for oral route of administration. Osimertinib is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) that is resistant to EGFR tyrosine kinase inhibitor (TKI) therapy who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. Osimertinib is a highly selective and irreversible inhibitor of activating sensitising EGFR mutation (EGFRm+) and activating resistance mutation T790M without affecting the activity of wild type EGFR. Inhibition of phosphorylation of EGFR and downstream signalling leads to tumour growth inhibition and it also induces cell cycle arrest.[1,2]

In the phase III FLAURA clinical trial (NCT02296125);[3] osimertinib (80 mg orally, once daily) is being assessed versus a standard of care (SoC) EGFR-TKI (either gefitinib or erlotinib). A cycle of treatment is defined as 21 days of once daily treatment. Cycles continue as long as patients are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Osemertinibe 80mg daily was evaluated in a pre-planned pooled analysis of two clinical trials (Phase I/II AURA and Phase II AURA2) that included a total of 411 patients. The overall response rates (the proportion of patients whose tumours shrank) with osimertinib was 66% and the average length of time the response lasted was 12.5 months.[4,5]

In NICE technology appraisal guidance (TA416);[6] osimertinib is already recommended as an option for use within the Cancer Drugs Fund for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC in adults whose disease has progressed only:

- after first-line treatment with an EGFR tyrosine kinase inhibitor, and
- if the conditions in the managed access agreement for osimertinib are followed.

Common or very common adverse effects of osimertinib are diarrhoea; dry skin disorders; interstitial lung disease (including pneumonitis); nail disorders; pruritus; rash; stomatitis. QTc interval prolongation is an uncommon adverse effects.[7]

Osimertinib is under development for the treatment of solid tumour like NSCLC and leptomeningeal disease.[1] It is in phase III trial (NCT02972333) for EGFR T790M positive NSCLC patients with brain metastases.[8]

### INNOVATION and/or ADVANTAGES

There is a significant unmet need for the treatment of EGFRm+ NSCLC despite several treatment options. Studies outcomes so far suggest that if licensed, osmertinib could offer an additional treatment option in the first line setting for patients with locally advanced or metastatic NSCLC that is EGFR mutation positive (Ex19del or L858R).

### DEVELOPER

AstraZeneca Pharmaceuticals Ltd.

# PATIENT GROUP

## BACKGROUND

Lung cancer starts when cells of the lung become abnormal and begin to grow out of control. As more cancer cells develop, they can form into a tumour and spread to other areas of the body.[9] There are two main types of lung cancer:[10]

- Non-small cell lung cancer (NSCLC): forms about 87 out of 100 lung cancers in the UK
- Small cell lung cancer (SCLC): forms about 12 out of every 100 diagnosed lung cancers.

There are three common types of NSCLC. They are grouped together because they behave in a similar way and respond to treatment in a similar way. The three types are: [10]

- Adenocarcinoma:

This is the most common type and starts in the mucus making gland cells in the lining of the airways.

- Squamous cell cancer:

This type develops in the flat cells that cover the surface of the airways. It tends to grow near the centre of the lung.

- Large cell carcinoma

The cancer cells appear large and round under the microscope.

When the cancer cells are undeveloped under the microscope, this is considered as undifferentiated NSCLC

Genomic studies have identified genetic alterations common to both adenocarcinoma and squamous cell carcinoma. Among these mutations or fusion genes, alterations in the EGFR have been identified in about 12% to 13% of cases examined so far worldwide. EGFR is a member of the ERBB family of receptor tyrosine kinases involved in the pathogenesis of many malignant cancers. Abnormal activity of EGFR results in deregulated cell proliferation and growth, which makes EGFR an important drug target in cancer cells. TKIs, such as gefitinib and erlotinib, have been shown to significantly prolong the survival of EGFRm(+) lung cancer patients. Among the TKI-sensitive mutations in EGFR, a point mutation in exon 21, which substitutes an arginine for a leucine (L858R), and a small in-frame deletion in exon 19, which removes several amino acids, are the most common activating mutations that confer treatment benefits (together accounting for approximately 90% of TKI-sensitive mutations). Despite the therapeutic benefits of EGFR TKIs, about 50% of EGFRm(+) patients develop acquired resistance via a second-site mutation in the threonine gatekeeper residue at position 790, i.e., T790M. Hence, the three mutation biomarkers can be used as genetic determinants for decision-making about treatment and monitoring the treatment course.[11]

Risk factors for lung cancer:

- Smoking tobacco.[12,13]
- Exposure to radon gas.[12]
- Chemical and workplace risk: such as asbestos, silica, and diesel exhaust.[12, 13,14]
- Air pollution.[12]
- Previous lung disease: such as Tuberculosis (TB), Chronic Obstructive Lung Disease (COPD), and Pneumonia. These risks are usually higher in smokers.[12]
- Family history of lung cancer.[12]
- Previous radiotherapy treatment.[12,13]
- Lowered immunity: such as people with HIV, AIDS, and those people with autoimmune diseases like rheumatoid arthritis or systemic lupus erythematosus (SLE) have higher risk for lung cancer.[12]

The symptoms of lung cancer include a persistent cough which could be painful, bring up blood,

mucus or phlegm; shortness of breath; chest or shoulder pain; loss of appetite; weight loss; fatigue; and persistent chest infections.[15]

## CLINICAL NEED and BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK (2014). In England, it is more common in people living in the most deprived areas. There were around 46,400 new cases of lung cancer in the UK in 2014. Over the last decade, lung cancer incidence rates have increased by four per cent in the UK. However, incidence rates are projected to fall by seven per cent in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035. Most lung cancer patients in England, Scotland and Northern Ireland are diagnosed at an advanced stage (III or IV). 85-90% of lung cancer cases are classified as NSCLC.[16] EGFR have been identified in about 12%–13% of NSCLC cases examined so far worldwide, and are much more frequent in Asian populations (~50%).[11]

In 2015 to 2016, there were 89,945 admissions for malignant neoplasm of bronchus and lung (ICD-10: C34) in England, resulting in 266,522 bed days and 110,013 finished consultant episodes.[17] It is estimated that around 22% of cancer deaths in the UK (2014) were lung cancer related deaths. Lung cancer mortality is strongly related to age, with the highest mortality rates being in older males and females. In the UK in 2012-2014, on average each year almost half (48%) of deaths were in people aged 75 and over.[18] Survival rates are low. Only about five per cent of patients survive lung cancer for more than 10 years. In England, five-year survival for lung cancer is highest in the youngest men and women and decreases with increasing age.[19]

## PATIENT PATHWAY

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE Technology Appraisal in development. Durvalumab with tremelimumab for untreated EGFR-positive, ALK-negative non-small-cell lung cancer (ID1143). Expected date of issue Jan 2019.
- NICE Technology Appraisal. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428). Jan 2017.
- NICE Technology Appraisal. Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA422). Dec 2016.
- NICE Technology Appraisal. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (TA416). Oct 2016.
- NICE Technology Appraisal. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). Sept 2016.
- NICE Technology Appraisal. Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer (TA411). Sept 2016.
- NICE Technology Appraisal. Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (TA402). Aug 2016.
- NICE Technology Appraisal. Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (TA403). Aug 2016.
- NICE Technology Appraisal. Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer (TA395). Jun 2016.
- NICE Technology Appraisal. Nivolumab for treating advanced (unresectable or metastatic) melanoma (TA384). Feb 2016.
- NICE Technology Appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA374). Dec 2015.

- NICE Technology Appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small‑cell lung cancer (TA347). Jul 2016.
- NICE Technology Appraisal. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343) Jun 2015.
- NICE Technology Appraisal. Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small-cell lung cancer (TA310). Apr 2014.
- NICE Technology Appraisal. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (TA258). Jun 2012.
- NICE Technology Appraisal. Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer (TA227). Jun 2011.
- NICE Technology Appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). Jul 2010.
- NICE Technology Appraisal. Pemetrexed for the maintenance treatment of non-small-cell lung cancer (TA190). Jun 2010.
- NICE Technology Appraisal. Topotecan for the treatment of relapsed small-cell lung cancer (TA184). Nov 2009.
- NICE Technology Appraisal. Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal) (TA175). Jul 2009.
- NICE Technology Appraisal. Pemetrexed for the treatment of non-small-cell lung cancer (TA124). Nov 2007.
- NICE guidelines. Lung cancer: diagnosis and management (CG121). April 2011
- Quality Standard. Lung cancer in adults. March 2012.
- Diagnostics guidance. EGFR‑TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. August 2013.

## NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013 Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small Cell Lung Cancer (Adult). B01/P/a
- NHS England. 2016 Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a

## OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014.[20]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (137). 2014.[21]
- National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology. Non-small cell lung cancer. 2013.[22]
- American College of Chest Physicians. Treatment of stage IV non-small cell lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. 2013.[23]
- American Society of Clinical Oncology. 2011 focused update of 2009 American Society of Clinical Oncology clinical practice guideline update on chemotherapy for stage IV non-small cell lung cancer. 2011.[24]

## CURRENT TREATMENT OPTIONS

The aim of treatment for locally advanced or metastatic NSCLC is to prolong survival, improve quality of life, and control disease-related symptoms.[25] Treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient's age, performance status,

comorbidities, and preferences. Patients who smoke should be encouraged to stop, as smoking cessation improves treatment outcomes.[26]

Current NICE Pathways recommends afatinib, erlotinib and gefitinib in the treatment of NSCLC cases with EGFR-TK positive test as follows:[27]

Afatinib is recommended as a possible treatment for adults with locally advanced or metastatic non-small-cell lung cancer if:

- their cancer tests positive for the EGFR-TK mutation and
- they have not had a type of drug called an EGFR-TKI before.[28]

Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if:

- they test positive for the EGFR-TK mutation and
- the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).[29]

Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if:

- they test positive for EGFR-TK mutation and
- the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.[30]

## EFFICACY and SAFETY

| | |
|---|---|
| **Trial** | FLAURA; NCT02296125; osimertinb vs gefitinib or erlotinib; Phase III trial |
| **Sponsor** | AstraZeneca |
| **Status** | ongoing |
| **Source of Information** | Global data[31], trial registry.[3] |
| **Location** | EU (incl UK), USA, Canada and other countries. |
| **Design** | Randomised, parallel Assignment |
| **Participants** | n= 530; aged at least 18 years; male or female; Pathologically confirmed adenocarcinoma of the lung; one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R); Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy. |
| **Schedule** | Experimental Arm:<br>osimertinib + placebo Standard of Care<br>osimertinib (80 mg orally, once daily) plus placebo Erlotinib (150 mg or 100 mg orally, once daily) or placebo Gefitinib (250 mg orally, once daily), in accordance with the randomisation schedule.<br>Active Comparator: Standard of Care + placebo osimertinib<br>EGFR-TKI (either erlotinib [150 mg orally, once daily] or gefitinib [250 mg orally, once daily]) plus placebo osimertinib (80 mg, once daily), in accordance with the randomisation schedule. |

| | |
|---|---|
| | A cycle of treatment is defined as 21 days of once daily treatment. Number of cycles: as long as patients are continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria<br>Following objective disease progression according to RECIST 1.1, as per investigator assessment, patients who were randomised to Standard of Care arm may have the option to receive open-label osimertinib (crossover to active osimertinib). |
| **Follow-up** | Duration 2 yrs 6 mths 21 days.[31] |
| **Primary Outcomes** | Progression Free Survival (PFS) |
| **Secondary Outcomes** | - Objective Response Rate (ORR)<br>- Progression Free Survival (PFS) in patients with: positive (or negative) T790M mutation<br>- Overall survival (OS)<br>- Patient Reported Outcome by Therapy Satisfaction (CTSQ-16 Questionnaire)<br>- Plasma concentrations of osimertinib and metabolites AZ5104 and AZ7550; and ratio of metabolite to osimertinib<br>- Patients reported disease-related symptoms and HRQoL by EORTC QLQ-C30<br>- Duration of Response (DoR)<br>- Disease Control Rate (DCR)<br>- Depth of response<br>- Patients reported disease-related symptoms and HRQoL by EORTC QLQ-LC13<br><br><u>Other Outcome Measures:</u><br>- Incidence of Adverse Events (AEs)<br>- AEs graded by CTCAE version 4.0 |
| **Key Results** | - |
| **Adverse effects (AEs)** | - |

## ESTIMATED COST and IMPACT

### COST

For the treatment of locally advanced or metastatic EGFR T790M mutation-positive NSCLC, NHS indicative price of 30 tablets osimertinib (as Osimertinib mesylate) 80mg is £5770.00.[32]

### 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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