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Health Technology Briefing
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Osimertinib + pemetrexed + carboplatin +/ cisplatin as a first line treatment for non-small cell lung cancer with EGFR mutation

Company/Developer	AstraZeneca UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30434	NICE ID: N/a	UKPS ID: 668899

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Osimertinib in combination with pemetrexed, carboplatin and cisplatin are in clinical development as a first line treatment for metastatic, epidermal growth factor receptor (EGFR)-positive, non-small cell lung cancer (NSCLC). NSCLC is the most common form of lung cancers in the UK and at the metastatic stage (stage IV), the disease has already spread from the lungs to other sites. Symptoms of lung cancer include cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness. However, lung cancer may not always have symptoms early on. EGFR is a protein found on cells, which helps them grow therefore, mutation in the EGFR gene results in the uncontrolled cell growth leading to cancer. Osimertinib combined with platinum-based chemotherapy may offer a well-tolerated treatment option for EGFR NSCLC.

Osimertinib is an orally administered EGFR tyrosine kinase inhibitor (TKI) that targets EGFR mutations by blocking EGFR activity and reducing the growth and division of cells. Unfortunately, despite the benefit observed for patients treated with osimertinib, many cancers are expected to develop resistance to the drug over time. There is currently no 'standard-of-care' approach to the treatment of the acquired EGFR TKI resistance. If licensed, it is hoped that combining osimertinib with another type of anti-cancer therapy known as chemotherapy and administered as a first line treatment will delay the onset of resistance and the worsening of a patient's cancer.

Proposed Indication

Osimertinib in combination with pemetrexed and platinum chemotherapy is indicated as first line treatment of patients with locally advanced or metastatic EGFR mutated NSCLC .[1]

Technology

Description

Osimertinib (Tagrisso, AZD9291) is an oral, third-generation, irreversible EGFR-tyrosine kinase inhibitor (TKI) that selectively inhibits both EGFR-TKI–sensitising and EGFR T790M resistance mutations.[1,2] It blocks the activity of EGFR, which normally controls growth and division of cells. In lung cancer cells, EGFR is often overactive, causing uncontrolled growth of cancer cells. By blocking EGFR, osimertinib helps to reduce the growth and spread of the cancer.[3]

In a phase III clinical trial FLAURA2 (NCT04035486), osimertinib 80 mg is administered in combination with pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC5) on day 1 of 21 day cycles (every 3 weeks) for 4 cycles, followed by osimertinib daily with pemetrexed maintenance (500 mg/m^2) every 3 weeks. Dose may be reduced to allow for the management of investigational product (IP) related toxicity.[1]

Key Innovation

Acquired resistance to EGFR TKIs is the most important limiting factor for treatment efficiency in EGFR-mutant NSCLC.[4] Preclinical data suggest that EGFR-TKIs combined with chemotherapy may act synergistically to restrict the development of acquired resistance.[5] Currently osimertinib is recommended for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults and also as an option for treating EGFR T790M mutation-positive locally advanced or metastatic NSCLC in adults, only if their disease has progressed after first-line treatment with an EGFR-TKI.[6 7] However, the phase III FLAURA2 (NCT04035486) study evaluates efficacy and safety of first-line osimertinib with platinum–pemetrexed chemotherapy versus osimertinib monotherapy in EGFR mutation-positive (EGFRm) advanced/metastatic NSCLC.[5] Osimertinib combined with chemotherapy was generally well tolerated and most adverse events (AEs) were mild to moderate in severity and there was no evidence of additive or emerging toxicities with the combination therapy.[5]

If licensed, osimertinib plus chemotherapy as a new combination will be beneficial in addressing the long unmet need of acquired resistance to EGFR-TKIs experienced while treating patients with locally advanced and metastatic EGFR mutated NSCLC.

Regulatory & Development Status

Osimertinib monotherapy has Marketing Authorisation in the EU/UK for:[8]

- the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.
- the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations
- the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Osimertinib as a monotherapy and in combination with other therapies is also in phase II/III clinical development for the treatment of various other lines of NSCLC and for NSCLC with brain metastases.[9]

Osimertinib has the following designation/awards:[10-12]

- an orphan drug in the USA in April 2014 for the treatment of EGFR mutation-positive NSCLC
- a breakthrough therapy by the USA in July 2020 as an adjuvant treatment for EGFR NSCLC
- received marketing authorisation from the MHRA UNDER Project Orbis for the adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection.

Patient Group

Disease Area and Clinical Need

NSCLC is the most common form of lung cancer. Around 80 to 85% of lung cancer cases in the UK are NSCLC. The three main types are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[13] Smoking tobacco is the cause of most lung cancers and the biggest risk factor. Other risk factors include second-hand smoke, exposure to workplace chemicals, radiation exposure, air pollution and family history of lung cancer.[14] Symptoms of lung cancer include cough, repeated chest infections, breathlessness, unexplained pain, weight loss or tiredness. However, lung cancer may not always have symptoms early on. Sometimes it is found by chance when a person is having tests for another condition.[15]

Lung cancer is the 3rd most common cancer in the UK, accounting for 13% of all new cancer cases (2016-18).[16] Age-standardised mortality rates per 100,000 for lung cancers in males and females, in England (2017) were; 65.8, and 46.1, while the incidence rates were 86.9 and 67.0 respectively.[17] In England (2021-22), there were 119,396 finished consultant episodes (FCEs) and 99,551 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), which resulted in 75,969 day cases and 206,640 FCE bed days.[18] In England (2017), there were 38,888 patients diagnosed with malignant neoplasm of bronchus and lung and 28,170 deaths registered had malignant neoplasm of bronchus and lung as the underlying cause,[19] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for stage III lung cancer were 48.7% and 12.6% respectively.[19] A study, found that approximately one-third of NSCLC patients harbour an EGFR mutation. Patients who are Asian, female, non-smokers, and have adenocarcinoma are more likely to harbour an EGFR mutation, which is consistent with previous studies.[20,21]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for EGFR mutated NSCLC:[6,7,22-28]

- Mobocertinib for locally advanced or metastatic NSCLC after platinum-based chemotherapy in adults whose tumours have EGF exon 20 insertion mutations. Only if the company provides it according to the commercial arrangement.
- Erlotinib for first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for EGFR-TK mutation and it is provided at the discounted price agreed under the patient access scheme.
- Osimertinib is recommended for use within the Cancer Drugs Fund as adjuvant treatment after complete tumour resection in adults with stage 1b to 3a NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. It is only recommended if Osimertinib is stopped at 3 years, or earlier if there is a disease recurrence or unacceptable toxicity and the company provides it according to the managed access agreement.
- Osimertinib is recommended as an option for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults

- Osimertinib is recommended as an option for treating EGFR T790M mutation-positive locally advanced or metastatic NSCLC in adults if their disease has progressed after first-line treatment with an EGFR tyrosine kinase inhibitor
- Dacomitinib is recommended as an option for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults.
- Afatinib is recommended as an option for treating adults with locally advanced or metastatic NSCLC if the tumour tests positive for the EGFR-TK mutation and the person has not previously had an EGFR-TK inhibitor
- Gefitinib 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
- Erlotinib is recommended as an option for treating locally advanced or metastatic NSCLC that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive
- Erlotinib is recommended as an option for treating locally advanced or metastatic NSCLC that has progressed after non-targeted chemotherapy in people with tumours of unknown EGFR-TK mutation status, if the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA and the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive and the person's disease responds to the first 2 cycles of treatment with erlotinib

Clinical Trial Information

Trial	**FLAURA2;** NCT04035486; 2019-000650-61; A Phase III, Open-label, Randomized Study of Osimertinib With or Without Platinum Plus Pemetrexed Chemo, as First-line Treatment in Patients With Epidermal Growth Factor Receptor (EGFR) Mutation Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer **Phase: III** – Active, not Recruiting **Location(s):** 4 EU countries, UK, USA, Canada, and other countries **Primary completion date:** April 2023
Trial Design	Randomised, open label, parallel assignment
Population	N=587 (actual); patients aged 18 years and older; newly diagnosed locally advanced (stage IIIB, IIIC) or metastatic NSCLC (stage IVA or IVB) or recurrent NSCLC not amenable to curative surgery or radiotherapy; the tumour harbours 1 of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, which may include T790M.
Intervention(s)	Osimertinib 80 mg in combination with pemetrexed (500 mg/m2) plus cisplatin (75 mg/m2) or carboplatin (AUC5) on Day 1 of 21 day cycles (every 3 weeks) for 4 cycles, followed by Osimertinib daily with pemetrexed maintenance (500 mg/m2) every 3 weeks. Dose may be reduced to allow for the management of IP related toxicity.
Comparator(s)	Osimertinib 80mg once daily
Outcome(s)	Primary outcome measure was progression-free survival (PFS) [Time Frame: The primary analysis of Progression-free survival (PFS) based on investigator

	assessment will occur when PFS maturity is observed at approximately 33 months after the first patient is randomized]. See trial record for full list of other outcomes
Results (efficacy)	Thirty patients (15 per group) received treatment [Asian, 73%; female, 63%; median age (range) 61 (45-84) years]. Adverse events (AEs) were reported by 27 patients (90%): osimertinib–carboplatin–pemetrexed, 100%; osimertinib–cisplatin–pemetrexed, 80%. Most common AEs were constipation (60%) with osimertinib–carboplatin–pemetrexed and nausea (60%) with osimertinib–cisplatin–pemetrexed. In both groups, 20% of patients reported serious AEs. No specific pattern of AEs leading to dose modifications/discontinuations was observed; one patient discontinued all study treatments including osimertinib due to pneumonitis (study-specific discontinuation criterion). Hematologic toxicities were as expected and manageable.[5]
Results (safety)	Osimertinib–chemotherapy combination had a manageable safety and tolerability profile in EGFRm advanced/metastatic NSCLC.[5]

Estimated Cost

Osimertinib is already marketed in the UK; a pack of 30 x 80mg or 30 x 40mg tablets costs £5,770.[29]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Aumolertinib for untreated EGFR mutation-positive non-small-cell lung cancer (GID-TA10899). Expected date of issue to be confirmed.
- NICE technology appraisal. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer (TA654). October 2020.
- NICE technology appraisal. Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer (TA595). August 2019.
- NICE technology appraisal. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (TA310). April 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). June 2012.
- NICE technology appraisal. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (TA192). July 2010.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019. Last updated March 2023.
- NICE quality standard. Lung cancer in adults (QS17). March 2019.
- NICE Diagnostics guidance. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (DG9). August 2013.

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.

Other Guidance

- National Comprehensive Cancer Network (NCCN) Guidelines Insights: Non–Small Cell Lung Cancer, Version 2. 2021.[30]
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up 2019.[31]
- Scottish Intercollegiate Guideline Network (SIGN). Management of lung cancer. 2014.[32]

Additional Information

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