

Health Technology Briefing November 2022

Lazertinib with amivantamab and platinum-based chemotherapy for EGFR-mutated locally advanced or metastatic non-small-cell lung cancer after osimertinib failure

Company/Developer

Janssen-Cilag Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 33871

NICE TSID: 11822

UKPS ID: 665922

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Lazertinib with amivantamab and platinum-based chemotherapy are currently in clinical development for patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) Exon 19del or Exon 21 L858R substitution non-small cell lung cancer (NSCLC) after osimertinib failure. NSCLC is the most common type of lung cancer. Metastatic and advanced cancer means that the cancer has spread and where curative treatment with surgery is unsuitable. EGFR is a protein found on certain types of cells that is involved in cell signalling pathways that control cell division and survival. Mutations in this protein can cause increased cell division resulting in tumour growth. However, there is a lack of effective treatments for this population group.

Lazertinib, administered orally, is a type of targeted therapy. It, along with amivantamab and platinum-based chemotherapy, has shown to be safe and effective in a number of clinical trials. If licensed, lazertinib with amivantamab and platinum-based chemotherapy will offer an additional treatment option for participants with locally advanced or metastatic EGFR Exon 19del or Exon 21 L858R substitution NSCLC after osimertinib failure.

Proposed Indication

This briefing reflects the evidence available at the time of writing 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. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Locally advanced or metastatic epidermal growth factor receptor (EGFR) Exon 19del or Exon 21 L858R substitution non-small cell lung cancer (NSCLC) after osimertinib failure.¹

Technology

Description

Lazertinib (Leclaza) is a brain-penetrant, irreversible EGFR tyrosine kinase inhibitor (TKI) that targets the EGFR T790M mutation and the activating EGFR mutations Ex19del and L858R, while sparing wild type-EGFR. Lazertinib inhibited EGFR downstream signalling pathways, including phosphorylation of EGFR, AKT and ERK, in lung cancer cell lines bearing EGFR activating and T790M mutations. It induced apoptosis in EGFR-mutant lung cancer cell lines, as indicated by an increase in cleaved Bim-EL protein and activated caspase 3/7 activation.²

Lazertinib with amivantamab and platinum-based chemotherapy is currently in clinical development for advanced or metastatic EGFR Exon 19del or Exon 21 L858R substitution NSCLC after osimertinib failure. In the phase III trial (NCT04988295), Lazertinib will be administered orally along with amivantamab, pemetrexed, and carboplatin as intravenous (IV) infusion for up to 4 cycles (each cycle consists of 21 days). After 4 cycles, participants will receive lazertinib, pemetrexed, and amivantamab as maintenance until disease progression.¹ The recommended dose of lazertinib is 240mg.²

Key Innovation

Platinum-based chemotherapy is the current standard of care for patients with NSCLC whose disease progresses on osimertinib. However, osimertinib-relapsed disease may still be sensitive to EGFR and/or MET inhibition, as demonstrated by the antitumor activity observed with amivantamab and lazertinib in this setting. Combining platinum-based chemotherapy with targeted inhibition of EGFR/MET signaling through the action of amivantamab and lazertinib may lead to improved outcomes in EGFR TKI-relapsed/refractory disease.³

Recently, treatment for patients with advanced or metastatic NSCLC has been modified. EGFR-TKIs have revealed significant efficacy in NSCLC patients with EGFR mutations, are associated with fewer side effects and have improved quality of life, particularly in patients harboring the exon 19 deletion (19-del) or exon 21 point mutation (21-L858R).⁴

If licensed, lazertinib with amivantamab and platinum-based chemotherapy will offer an additional treatment option for participants with locally advanced or metastatic epidermal growth factor receptor (EGFR) Exon 19del or Exon 21 L858R substitution NSCLC after osimertinib failure.

Regulatory & Development Status

Lazertinib does not currently have Marketing Authorisation in the EU/UK for any indication.

Amivantamab as monotherapy is indicated for treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.⁵

Lazertinib is in phase III/II clinical development for:⁶

- Lung neoplasms
- NSCLC

Patient Group

Disease Area and Clinical Need

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. Metastatic cancer occurs when the disease has spread, either to both lungs, the chest or beyond.⁷ Advanced cancer normally means a cancer that cannot be cured.⁸ EGFR is a member of the ErbB receptor TK family and serves a key role in the development and progression of NSCLC. Overexpression of EGFR may lead to cell proliferation, promote angiogenesis, tumour invasion and metastasis, and inhibit cell apoptosis, serving an important role in the evolution of malignant tumours. Numerous studies have confirmed that EGFRs are uniquely expressed in tumour tissues, particularly NSCLC.⁴ Certain factors can increase the risk of developing lung cancer, including; smoking tobacco, exposure to radiation (by exposure to radon gas and previous radiotherapy treatment), exposure to certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes), previous lung disease (e.g. tuberculosis and COPD), family history of lung cancer and certain genetic mutations and lowered immunity (e.g. due to certain conditions e.g. HIV/AIDS, rheumatoid arthritis and systemic lupus erythematosus, or immunosuppressive medications).⁹ Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.¹⁰

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017.¹¹ According to the National Cancer Registration and Analysis Service (NCRAS), there were 25,777 diagnosed cases of stage III-IV lung cancer in 2017 in England.¹² In the UK, it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage III-IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 21,910 cases diagnosed with stage III-IV in 2017 were NSCLC.¹³ Exon 19-del and 21-L858R mutations are common, accounting for 85% of all EGFR mutations in NSCLC.⁴ Thus, according to the numbers above, there were 18,624 cases of advanced/metastatic NSCLC EGFR Exon 19del or Exon 21 L858R mutations in 2017. In 2021/22 there were 99,551 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 119,396 finished consultant episodes (FCEs), resulting in 206,640 FCE bed days and 75,969 day cases.¹⁴ In England between 2013 and 2017, the age-standardised net lung cancer survival for stage III was 48.7% at one year and 12.6% at five years and for stage IV, 19.3 % at one year and 2.9% at five years.¹⁵ There are around 34,800 lung cancer deaths in the UK every year (based on data from 2017-2019). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035, to 58 deaths per 100,000 people by 2035.¹¹

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following treatment options for non-squamous EGFR positive NSCLC patients after failure of first-line or second line Osimertinib:¹⁶

- Platinum doublet chemotherapy
- Pemetrexed and cisplatin
- Pemetrexed and carboplatin
- Atezolizumab with bevacizumab, carboplatin and paclitaxel

Clinical Trial Information

Trial	<p>MARIPOSA-2; NCT04988295; EudraCT 2021-001825-33; A Phase 3, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure</p> <p>Phase III – Recruiting</p> <p>Location(s): 12 EU countries, UK, USA, Canada and other countries</p> <p>Primary completion date: May 2023</p>
Trial Design	Randomised, parallel assignment, open-label
Population	N=600 (planned); adults who have histologically or cytologically confirmed, locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC), characterised at or after the time of locally advanced or metastatic disease diagnosis by either epidermal growth factor receptor (EGFR) Exon 19del or Exon 21 L858R mutation
Intervention(s)	<ul style="list-style-type: none"> • Oral Lazertinib • IV Amivantamab • IV Pemetrexed • IV Carboplatin
Comparator(s)	<ul style="list-style-type: none"> • IV Carboplatin • IV Pemetrexed
Outcome(s)	<p>Primary outcome measure: Progression-Free Survival (PFS) According to RECIST v1.1 Guidelines as Assessed by Blinded Independent Central Review (BICR) [Time Frame: Up to 17 months]</p> <p>See trial record for full list of other outcomes</p>
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price for amivantamab is £1079.00 per 350mg/7 ml vial.¹⁷

The cost of lazertinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology guidance. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (TA584). June 2019.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). Updated March 2019.
- NICE Diagnostics guidance. EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer (DG8). 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

- European Society of Medical Oncology (ESMO). ESMO Guideline. Early and locally advanced non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow up. 2020.¹⁸
- National Comprehensive Cancer Network (NCCN). Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.¹⁹
- Scottish Intercollegiate Guidelines Network (SIGN). Management of lung cancer (SIGN 137). 2014.²⁰

Additional Information

References

- 1 ClinicalTrials.gov. *A Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure (MARIPOSA-2)*. 2021. Available from: <https://clinicaltrials.gov/ct2/show/NCT04988295> [Accessed 26 September 2022].
- 2 Dhillon S. Lazertinib: First Approval. *Drugs*. 2021;81(9):1107-13. Available from: <https://doi.org/10.1007/s40265-021-01533-x>.
- 3 Marmarelis ME, Lee SH, Spira AI, Ou SHI, Waqar S, Li S, et al. *MA07.04 Amivantamab and Lazertinib in Combination with Platinum-Based Chemotherapy in Relapsed/Refractory EGFR-mutant NSCLC*. 2022. Available from: <https://doi.org/10.1016/j.jtho.2022.07.114> [Accessed 27 September 2022].
- 4 Hong W, Wu Q, Zhang J, Zhou Y. Prognostic value of EGFR 19-del and 21-L858R mutations in patients with non-small cell lung cancer. *Oncol Lett*. 2019 2019/10/01;18(4):3887-95. Available from: <https://doi.org/10.3892/ol.2019.10715>.
- 5 Electronic Medicines Compendium (EMC). *Rybrevant (amivantamab) 50mg/mL concentrate for solution for infusion*. 2022. Available from: <https://www.medicines.org.uk/emc/product/13084/smpc> [Accessed 27 September 2022].
- 6 ClinicalTrials.gov. *Lazertinib | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=Lazertinib&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 27 September 2022].
- 7 Cancer Research UK. *Stage 4*. 2020. Available from: <https://about-cancer.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/stage-4> [Accessed 27 September 2022].
- 8 American Cancer Society. *Understanding Advanced and Metastatic Cancer*. 2020. Available from: <https://www.cancer.org/treatment/understanding-your-diagnosis/advanced-cancer/what-is.html> [Accessed 27 September 2022].

- 9 Cancer Research UK. *Lung cancer: risks and causes*. 2019. Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes> [Accessed 23 August 2022].
- 10 Cancer Research UK. *Lung cancer symptoms*. 2019. Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms> [Accessed 23 August 2022].
- 11 Cancer Research UK. *Lung cancer statistics*. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer> [Accessed 27 September 2022].
- 12 National Cancer Registration and Analysis Service (NCRAS). *Survival by stage*. Available from: http://www.ncin.org.uk/publications/survival_by_stage [Accessed 23 August 2022].
- 13 Cancer Research UK. *Types of lung cancer*. 2020. Available from: <https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types> [Accessed 23 August 2022].
- 14 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22> [Accessed 11 October 2022].
- 15 Office for National Statistics. *Cancer survival in England - adults diagnosed*. 2019. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed> [Accessed 23 August 2022].
- 16 National Institute for Health and Care Excellence (NICE). *Systemic anti-cancer therapy for advanced non-small-cell lung cancer: treatment options*. 2022. Available from: <https://www.nice.org.uk/guidance/ng122/resources/nonsquamous-pathway-egfrtk-positive-pdf-402835974231> [Accessed 28 October 2022].
- 17 British National Formulary (BNF). *Amivantamab: Medicinal forms*. Available from: <https://bnf.nice.org.uk/drugs/amivantamab/medicinal-forms/#solution-for-infusion> [Accessed 24 November 2022].
- 18 Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2017;28:iv1-iv21. Available from: <https://doi.org/10.1093/annonc/mdx222>.
- 19 Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network J Natl Compr Canc Netw*. 2017;15(4):504-35. Available from: <https://doi.org/10.6004/jnccn.2017.0050>.
- 20 Scottish Intercollegiate Guidelines Network (SIGN). *Management of lung cancer*. 2014. Available from: <https://www.sign.ac.uk/our-guidelines/management-of-lung-cancer/> [Accessed 23 August 2022].

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