NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2024

Savolitinib with osimertinib for treating EGFR- mutated, MET-overexpressed advanced non-small-cell lung cancer

Company/Developer	AstraZeneca UK Ltd
☒ New Active Substance	☐ Significant Licence Extension (SLE)

NIHRIO ID: 34848	NICE ID: Not available	UKPS ID: 670190

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Savolitinib in combination with osimertinib is in clinical development for treatment of acquired mesenchymal epithelial transition factor (MET)-mediated osimertinib resistance in epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). NSCLC is the most common form of lung cancers in the UK and at the metastatic stage, the disease has already spread from the lungs to other sites. EGFR is a protein found on cells, which helps them grow. Changes (mutations) in the EGFR gene results in the uncontrolled cell growth in cancerous cells. MET overexpression can also lead to tumour growth and metastatic progression.

Savolitinib is an orally administered and highly selective MET tyrosine kinase inhibitor, primarily developed for the treatment of NSCLC with MET mutations. Unfortunately, despite the benefit observed for patients treated with osimertinib, many cancers are expected to develop resistance to the drug over time, and a sub-population of these patients develop MET amplification or other MET-based acquired resistance mechanisms. If licensed, savolitinib in combination with osimertinib would offer an additional treatment option for patients with EGFR-mutated locally advanced or metastatic NSCLC with high levels of MET overexpression and/or amplification, who have progressed on treatment with osimertinib.

Proposed Indication

Treatment of adult patients with epidermal growth factor receptor (EGFR) mutated, mesenchymal epithelial transition (MET) factor-overexpressed and/or amplified, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on treatment with osimertinib.[1]

Technology

Description

Savolitinib (Volitinib, AZD6094, HMPL-504) is an oral potent and highly selective small molecule inhibitor of the MET- tyrosine kinase (TK), primarily developed for the treatment of NSCLC with MET mutations.[2,3] Savolitinib specifically interacts with the amino acid Y1230 residue and effectively inhibits the activity of the MET receptor. By targeting this specific region, savolitinib successfully hinders the signaling pathway associated with MET activation.[2] Savolitinib in combination with osimertinib is currently in clinical developments for treating patients with EGFR mutated, MET-overexpressed and/or amplified, locally advanced or metastatic NSCLC who have progressed on treatment with osimertinib. The findings of phase Ib clinical trial (NCT02143466, TATTON) shows that the combination of savolitinib plus osimertinib demonstrates antitumor activity across several sub cohorts of patients with EGFRm, MET-amplified/overexpressed NSCLC with a manageable safety profile that is broadly in line with other oral MET-TK inhibitors.[3]

In the phase III trial (NCT05261399, SAFFRON), participants will receive 300mg savolitinib orally twice a day and 80 mg osimertinib orally once a day.[1]

Key Innovation

Molecular targeted therapy regimens are routinely recommended to treat NSCLC patients harbouring corresponding genetic mutations.[4] EGFR-TK inhibitors are given priority for those with EGFR-sensitising mutations, including EGFR exon 19 deletion (Ex19del) and L858R mutations. Since EGFR-TK inhibitors were developed and subsequently applied in the clinic, the survival and clinical outcomes of EGFR-mutated NSCLC patients have remarkably improved, and as a consequence, EGFR-TK inhibitors are recommended as the standard first-line treatment in NSCLC patients with EGFR mutations.[4] Despite osimertinib's proven efficacy in the first-line metastatic setting, many patients with EGFRm NSCLC develop disease progression on osimertinib, with current data suggesting that approximately 25% of these patients develop MET amplification or other MET-based acquired resistance mechanisms.[3]
If licensed, savolitinib with osimertinib would offer an additional treatment option for patients with EGFR mutated locally advanced or metastatic NSCLC who have progressed on treatment with osimertinib.

Regulatory & Development Status

Savolitinib does not currently have marketing authorisation in the EU/UK for any indication.

Osimertinib currently has marketing authorisation in the EU/UK for:[5]

- 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
- first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations
- treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC

Savolitinib as a monotherapy and in combination with other therapies is also in phase II/III clinical development for:[6]

- Gastric cancer and esophagogastric junction adenocarcinoma

- Locally advanced or metastatic papillary renal cell carcinoma
- Kidney cancer

Patient Group

Disease Area and Clinical Need

NSCLC is the most common type of lung cancer which accounts for around 80-85 out of 100 lung cancers.[7] There are three main types of NSCLC, including adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Adenocarcinoma is the most common type and starts in the mucus-making gland cells in the lining of the airways. Squamous cell cancer develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung. Large cell carcinoma cancer cells appear larger than a typical cell under the microscope.[7] Metastatic (also known as advanced) means that the cancer has spread from where it started in the lung.[8] The most common symptoms of lung cancer are a new or prolonged cough, breathlessness, coughing up phlegm with blood, shoulder and chest aches, recurrent chest infections and appetite loss.[9] The main risk factor for lung cancer is smoking tobacco. Other risk factors include exposure to chemicals such as asbestos, silica and diesel exhaust, as well as air pollution, previous lung disease and family history.[10] Most NSCLC are diagnosed at an advanced stage with traditional chemotherapy and radiotherapy showing limited efficacy.[11] Epidermal growth factor receptor (EGFR) is a transmembrane receptor tyrosine kinase protein that is expressed in some normal epithelial, mesenchymal, and neurogenic tissue. Overexpression of EGFR has been reported and implicated in the pathogenesis of many human malignancies, including NSCLC.[12] Amplification, mutation, or overexpression of the mesenchymal epithelial transition (MET) gene can result in aberrant activation of the MET axis, leading to migration, invasion, proliferation, metastasis, and neoangiogenesis of cancer cells.[13] Approximately one-third of NSCLC patients harbour an EGFR mutation. NSCLC patients who are Asian, female, non-smokers, and have adenocarcinoma are more likely to harbour an EGFR mutation.[14,15]

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2016-18). The age standardised incidence rate of lung cancer in England is 18,662 in females and 20,678 in males per 100,000 population.[16] In England (2022-23) there were 122,866 finished consultant episodes (FCEs) and 104,232 hospital admissions for NSCLC (ICD-10 code C34), which resulted in 80,131 day cases and 217,569 FCE bed days.[17] In England between 2013 and 2018, the predicted 10-year net survival for lung cancer for both men and women was 7.6% and 11.3% respectively.[18]

Recommended Treatment Options

Treatment for lung cancer includes surgery, chemotherapy, radiotherapy, immunotherapy, and other targeted therapy drugs. People may be offered one or more different treatments depending on the stage, histology, and type of lung cancer as well as their general health. Systemic anti-cancer treatments are increasingly used to treat advanced NSCLC.[19]

The National Institute for Health and Care Excellence (NICE) currently recommends the following monotherapy treatment options for EGFR mutated advanced NSCLC:[20-25]

- Osimertinib is recommended 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.

- 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.
- 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.
- Dacomitinib is recommended as an option for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults.
- Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer.

NICE currently recommends erlotinib with gefitinib as a combination for treating advanced NSCLC that has progressed after chemotherapy:[26]

Clinical Trial Information	
Trial	**SAFFRON,** NCT05261399; 2021-006374-24 A Phase III, Randomised, Open-Label Study of Savolitinib in Combination With Osimertinib Versus Platinum-Based Doublet Chemotherapy in Participants With EGFR Mutated, MET-Overexpressed and/or Amplified, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed on Treatment With Osimertinib **Phase III**- recruiting **Location(s):** Ten European countries, UK, US, and other countries **Primary completion date:** May 2025
Trial Design	Randomised, parallel assignment, open label
Population	N=324 (estimated); patients with EGFR mutated, MET-overexpressed and/or amplified, locally advanced or metastatic NSCLC who have progressed on treatment with Osimertinib; aged 18 years and over
Intervention(s)	Osimertinib 80 mg tablet, oral, once a day with savolitinib 300mg tablets, oral, twice a day
Comparator(s)	Participants will receive chemotherapy including pemetrexed (500 mg/m2) with either cisplatin (75 mg/m2) or carboplatin (AUC5) on Day 1 of 21-day cycles (Q3W) for 4 cycles, followed by pemetrexed maintenance (500 mg/m2) Q3W
Outcome(s)	Primary outcome measures: • Progression-free survival (PFS) / savolitinib + osimertinib versus platinum doublet chemotherapy in participants with EGFR mutated, MET-overexpressed and/or amplified, locally advanced or metastatic NSCLC who have progressed on osimertinib [Time frame: Approximately 55 months post first subject randomized] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**SAVANNAH, NCT03778229: 2018-003012-51;** A Phase II Study Assessing the Efficacy of Osimertinib in Combination With Savolitinib in Patients With EGFRm+ and MET+, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed Following Treatment With Osimertinib **Phase II**-recruiting **Location(s):** Four EU, US, Canada and other countries **Primary completion date**: August 2024
Trial Design	Randomised, parallel assignment, open label
Population	N=360 (estimated); patients with locally advanced or metastatic non-small cell lung cancer who have progressed following treatment with osimertinib
Intervention(s)	Osimertinib 80 mg oral once a day with savolitinib 300 mg oral once a day or 300 mg oral twice a day or 600 mg oral once a day
Comparator(s)	Savolitinib 300 mg oral once a day or 300 mg oral twice a day or 600 mg oral once a day, in combination with placebo oral once a day
Outcome(s)	Primary outcome measures: • Objective response rate by investigator assessment in accordance with RECIST 1.1 [time frame: The primary (ORR) analysis for the study will be performed at 6 months after the last patient under CSP version 7.0 has been randomised to treatment] • Objective response rate by investigator assessment in accordance with RECIST 1.1 [time frame: The primary (ORR) analysis for the study will be performed at 6 months after the last patient under CSP version 7.0 has been randomised to treatment] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of savolitinib is not yet known. The NHS indicative price for osimertinib 80mg (a pack of 30 tablets) is £5,770.[27]

Relevant Guidance

NICE Guidance

- 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

- The European Society for Medical Oncology. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 2020.[28]
- NHS Northern Cancer Alliance. Lung Cancer Clinical Guidelines. May 2019.[29]
- London Cancer Alliance. LCA Lung Cancer Clinical Guidelines. March 2016.[30]
- Scottish Intercollegiate Guidelines Network. SIGN 137 – Management of lung cancer. February 2014.[31]

Additional Information

References

1 Clinical Trials.gov. *Savolitinib Plus Osimertinib Versus Platinum-based Doublet Chemotherapy in Participants With Non-Small Cell Lung Cancer Who Have Progressed on Osimertinib Treatment (SAFFRON)*. *Trial ID: NCT05261399*. 2022. Status: Recruiting Available from: https://clinicaltrials.gov/study/NCT05261399 [Accessed 22/05/2024].

2 Lee TS, Kim JY, Lee MH, Cho IR, Paik WH, Ryu JK, et al. Savolitinib: A Promising Targeting Agent for Cancer. *Cancers*. 2023;15(19):4708. Available from: https://doi.org/10.3390/cancers15194708.

3 Hartmaier RJ, Markovets AA, Ahn MJ, Sequist LV, Han J-Y, Cho BC, et al. Osimertinib + Savolitinib to Overcome Acquired MET-Mediated Resistance in Epidermal Growth Factor Receptor–Mutated, MET-Amplified Non–Small Cell Lung Cancer: TATTON. *Cancer Discovery*. 2023;13(1):98-113. Available from: https://doi.org/10.1158/2159-8290.cd-22-0586.

4 Fu K, Xie F, Wang F, Fu L. Therapeutic strategies for EGFR-mutated non-small cell lung cancer patients with osimertinib resistance. *Journal of Hematology & Oncology*. 2022;15(1). Available from: https://doi.org/10.1186/s13045-022-01391-4.

5 Electronic medicines compendium (emc). *TAGRISSO 80 mg film-coated tablets*. 2023. Available from: https://www.medicines.org.uk/emc/product/7615 (login required) [Accessed 22/05/2024].

6 ClinicalTrials.gov. *Volitinib | Recruiting, Active, not recruiting studies | Phase: 2, 3*. Available from: https://clinicaltrials.gov/search?intr=Volitinib&aggFilters=phase:2%203,status:rec%20act&viewType=Table [Accessed 22/05/2024].

7 Cancer Research UK. *Types of lung cancer* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types?_ga=2.127892366.2050282321.1597656190-643938485.1593693933 [Accessed 20/05/2024].

8 Cancer Research UK. *What is metastatic lung cancer?* 2023. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/metastatic/what-is#:~:text=Metastatic%20lung%20cancer%20means%20that,of%20life%20for%20some%20time. [Accessed 20/05/2024].

9 Cancer Research UK. *Symptoms of lung cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/symptoms [Accessed 20/05/2024].

10 Cancer Research UK. *Risks and causes of lung cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/risks-causes [Accessed 20/05/2024].

11 Zhu X, Lu Y, Lu S. Landscape of Savolitinib Development for the Treatment of Non-Small Cell Lung Cancer with MET Alteration—A Narrative Review. *Cancers*. 2022;14(24):6122. Available from: https://doi.org/10.3390/cancers14246122.

12 Bethune G, Bethune D, Ridgway N, Xu Z. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. *J Thorac Dis*. 2010;2(1):48-51. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256436/.

13 Landi L, Minuti G, D'Incecco A, Salvini J, Cappuzzo F. MET overexpression and gene amplification in NSCLC: a clinical perspective. *Lung Cancer (Auckl)*. 2013;4:15-25. Available from: https://doi.org/10.2147/lctt.S35168.

14 Zhang Y-L, Yuan J-Q, Wang K-F, Fu X-H, Han X-R, Threapleton D, et al. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*. 2016;7(48):78985-93. Available from: https://doi.org/10.18632/oncotarget.12587.

15 Shi Y, Au JS-K, Thongprasert S, Srinivasan S, Tsai C-M, Khoa MT, et al. A Prospective, Molecular Epidemiology Study of EGFR Mutations in Asian Patients with Advanced Non–Small-Cell Lung Cancer of Adenocarcinoma Histology (PIONEER). *Journal of Thoracic Oncology*. 2014;9(2):154-62. Available from: https://doi.org/10.1097/jto.0000000000000033.

16 Cancer Research UK. *Lung cancer statistics* 2023. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer#heading-Zero [Accessed 20/05/2024].

17 NHS Digital. *Hospital Admitted Patient Care Activity 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 19/04/2024].

18 Office of National Statistics (ONS). *Cancer survival in England: adult, stage at diagnosis and childhood - patients followed up to 2018*. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsfollowedupto2018 [Accessed 20/04/2024].

19 National Institute for Health and Care Excellence (NICE). *Treatment for lung cancer*. Available from: https://www.nice.org.uk/about/what-we-do/into-practice/measuring-the-use-of-nice-guidance/impact-of-our-guidance/niceimpact-lung-cancer/ch4-treatment-for-lung-cancer [Accessed 21/05/2024].

20 National Institute for Health and Care Excellence (NICE). *Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer*. 2014. Available from: https://www.nice.org.uk/guidance/ta310 [Accessed 21/05/2024].

21 National Institute for Health and Care Excellence (NICE). *Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy*. 2022. Available from: https://www.nice.org.uk/guidance/ta850 [Accessed 21/05/2024].

22 National Institute for Health and Care Excellence (NICE). *Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer*. 2019. Available from: https://www.nice.org.uk/guidance/ta595 [Accessed 21/09/2024].

23 National Institute for Health and Care Excellence (NICE). *Everolimus with exemestane for treating advanced breast cancer after endocrine therapy*. 2016. Available from: https://www.nice.org.uk/guidance/ta421/chapter/1-Recommendations [Accessed 04/08/2023].

24 National Institute for Health and Care Excellence (NICE). *Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer*. 2020. Available from: https://www.nice.org.uk/guidance/ta654 [Accessed 21/05/2024].

25 National Institute for Health and Care Excellence (NICE). *Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer*. 2010. Available from: https://www.nice.org.uk/guidance/ta192 [Accessed 22/05/2024].

26 National Institute for Health and Care Excellence (NICE). *Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy*. 2015. Available from: https://www.nice.org.uk/guidance/ta374 [Accessed 21/05/2024].

27 British National Formulary (BNF). *Osimertinib [Specialist drug]Medicinal forms*. 2024. Available from: https://bnf.nice.org.uk/drugs/osimertinib-specialist-drug/medicinal-forms/ [Accessed 09/07//2024].

28 Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv192-iv237. Available from: https://doi.org/10.1093/annonc/mdy275.

29 NHS Northen Cancer Alliance. *Lung Cancer Clinical Guidelines*. 2019. Available from: https://www.northerncanceralliance.nhs.uk/wp-content/uploads/2018/11/Lung-Clinical-Guidelines-v13.2-2.pdf [Accessed 13/06/2024].

30 London Cancer Alliance West and South. *LCA Lung Cancer Clinical Guidelines*. 2016. Available from: https://rmpartners.nhs.uk/wp-content/uploads/2017/03/lca-revised-lung-cancer-clinical-guidelines-december-2013-updated-march-2016-.pdf [Accessed 13/06/2024].

31 Scottish Intercollegiate Guidelines Network. *SIGN 137 – Management of lung cancer*. 2014. Available from: https://www.sign.ac.uk/media/1378/qrg137.pdf [Accessed 13/06/2024].

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.