NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of adagrasib within its marketing authorisation as monotherapy for treating KRAS G12C mutation positive advanced NSCLC which is not suitable for, or has progressed after treatment with, platinum based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

Background

Lung cancer is the third most common cancer and the most common cause of cancer death in the UK, accounting for 10% of all new cancer cases and 20% of all cancer deaths in 2020.[1] Most lung cancers are diagnosed at an advanced stage when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage 3) or to other parts of the body (metastatic disease; stage 4). In 2022, 92% (around 33,000) of people diagnosed with lung cancer in England had NSCLC.[2]

KRAS is a protein that controls a signalling pathway crucial for cell growth, differentiation and survival. KRAS is the most frequently mutated oncogene in cancer, including lung cancer, with KRAS G12C mutation occurring in about 11% of NSCLC.[3] It is more common in non-squamous NSCLC, and relatively rare in squamous NSCLC.[4]

For untreated metastatic non-squamous NSCLC people may be offered pembrolizumab with pemetrexed and platinum chemotherapy (TA683) or pemetrexed and platinum chemotherapy irrespective of PD-L1 expression. If the non-squamous NSCLC expressed PD-L1 on less than 50% of tumour cells, people may be offered atezolizumab plus bevacizumab, carboplatin and paclitaxel (TA584) or pemetrexed with platinum doublet chemotherapy. If the non-squamous NSCLC expressed PD-L1 on over 50% of tumour cells they may be offered pembrolizumab (TA531) or atezolizumab (TA705) monotherapy.

For untreated squamous NSCLC people may be offered pembrolizumab with carboplatin and paclitaxel (TA770) if the NSCLC expresses PD-L1 on less than 50% of cells or on over 50% of cells if there is a need for urgent clinical intervention. If the squamous NSCLC expresses PD-L1 on more than 50% of its tumour cells people may be offered pembrolizumab (TA531) or atezolizumab (TA705) monotherapy.

For KRAS G12C positive NSCLC that has been previously treated sotorasib is recommended within the cancer drugs fund (TA781).

Docetaxel or docetaxel with nintedanib (TA347) may be offered as a second line treatment, irrespective of first-line treatment. If chemotherapy without immunotherapy was used as a first-line treatment, then people may be offered an immunotherapy monotherapy consisting of either nivolumab (TA655 & TA713), atezolizumab (TA520)

or pembrolizumab (for PD-L1 positive disease, TA428). If an immunotherapy monotherapy was used at first line, then people may be offered platinum-based chemotherapy as a second-line treatment.

The technology

Adagrasib (Krazati, Bristol Myers-Squibb) has a marketing authorisation for the treatment of adult patients with advanced NSCLC with KRAS G12C mutation who have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

Intervention(s)	Adagrasib
Population(s)	Adults with advanced NSCLC that is positive for a KRAS G12C mutation and is not suitable for, or has progressed after treatment with, platinum chemotherapy and/or an anti-PD-1/PD-L1 immunotherapy.
Subgroups	If the evidence allows the following subgroups will be considered: • Disease stage • Histology • Previous treatment • Newly diagnosed or recurrent distant metastatic disease
Comparators	• Docetaxel • Docetaxel with nintedanib • Sotorasib (subject to NICE appraisal)
Outcomes	The outcome measures to be considered include: • progression free survival • overall survival • response rates • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be

	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. The use of adagrasib is conditional on the presence of a KRAS G12C mutation. The economic modelling should include the costs associated with diagnostic testing for KRAS G12C in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related technology appraisals:** Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (2022) NICE technology appraisals guidance 770. Review date to be confirmed. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (2019) NICE technology appraisal 584. Review date June 2022. Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated non-small-cell lung cancer (2021) NICE technology appraisals guidance 683. Review date to be confirmed. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (2018) NICE technology appraisal guidance 531. Review date July 2021. Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer (2021) NICE technology appraisal guidance 705. Review date 2024 Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer

	(2015) NICE technology appraisal guidance 347. Review date to be confirmed Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (2022) NICE technology appraisal guidance 781. Review date 2025 **Related technology appraisals in development:** Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287] Publication to be confirmed **Related NICE guidelines:** Lung cancer: diagnosis and management (NG122) **Related quality standards:** Lung cancer in adults (2019) NICE quality standard 17
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2023) Manual for prescribed specialist services (2023/2024) Chapter 105: Specialist cancer services (adults)

References

1. NHS England. Cancer Registration Statistics, England 2020. Accessed March 2024
2. Royal College of Surgeons of England (2024). National Lung Cancer Audit: State of the Nation Report 2024. Accessed May 2024
3. Reita D, Pabst L, Pencreach E et al (2022) . Direct Targeting *KRAS* Mutation in Non-Small Cell Lung Cancer: Focus on Resistance. Cancers (Basel). Mar 4;14(5):1321
4. Martin P, Leighl NB, Tsao MS and Shepherd FA (2013) KRAS mutations as prognostic and predictive markers in non–small cell lung cancer. Journal of Thoracic Oncology 8(5):530-542.