NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of sotorasib within its marketing authorisation for previously treated KRAS G12C mutated non-small-cell lung cancer.

Background

Lung cancer is the third most common cancer and the most common cause of cancer death in the UK, accounting for 13% of all new cancer cases and 21% of all cancer deaths in 2017.[1] There are around 48,000 new lung cancer cases and 35,000 deaths from lung cancer in the UK every year. The majority of 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 III) or to other parts of the body (metastatic disease; stage IV). Up to 85% of lung cancers are non-small-cell lung cancers (NSCLC).[2] NSCLC may be grouped by tumour histology into squamous cell carcinoma, adenocarcinoma and large-cell carcinoma, with the latter 2 being collectively referred to as 'non-squamous' lung cancer.

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 being responsible for about 12% of NSCLC.[3] It is more common in non-squamous NSCLC, and relatively rare in squamous NSCLC.[4] KRAS G12C mutations do not usually occur in the presence of other known driver mutations (that is, mutations that drive the development of cancer) in NSCLC, including EGFR-TK, ALK or ROS1.[5]

The aims of treatment for advanced NSCLC are to prolong survival and improve quality of life. Currently, treatment choices are influenced by the presence of biological markers (such as genetic alterations in EGFR-TK, ALK or ROS1, or PD-L1 expression), histology (squamous or non-squamous) and prior treatments (NICE Lung cancer pathway, NICE guideline 122). There are currently no treatments available that target KRAS G12C.

The technology

Sotorasib (AMG 510, Amgen Ltd) is a small molecule inhibitor of KRAS G12C protein, which locks it in an inactive state. This may block signalling between tumour cells and stop further growth. Sotorasib is given as an oral tablet.

Sotorasib does not currently have a marketing authorisation in the UK for any indication. It has been studied in clinical trials in adults with previously treated KRAS G12C mutated, locally advanced or metastatic NSCLC.

Intervention(s)	Sotorasib

Population(s)	Adults with previously treated KRAS G12C mutated, locally advanced or metastatic NSCLC

Comparators	Non-squamous NSCLC:
	• pemetrexed with carboplatin
	  o with or without pemetrexed maintenance
	• other platinum doublet chemotherapy
	  o with or without pemetrexed maintenance
	• nintedanib with docetaxel (adenocarcinoma histology)
	• docetaxel monotherapy
	• atezolizumab
	• nivolumab (subject to ongoing CDF review)
	• pembrolizumab (PD-L1-expressing tumours)
	• best supportive care
	Squamous NSCLC:
	• gemcitabine with carboplatin or cisplatin
	• vinorelbine with carboplatin or cisplatin
	• docetaxel monotherapy
	• pembrolizumab (PD-L1-expressing tumours)
	• atezolizumab
	• nivolumab
	• best supportive care
	People with KRAS G12C mutation and another driver mutation (including EGFR-TK, ALK or ROS1):
	Established clinical management without sotorasib Including:
	• atezolizumab combination (after EGFR-TK or ALK-targeted therapies)
	• lorlatinib (after ALK-targeted therapies)
	• brigatinib (after ALK-targeted therapies)
	• ceritinib (after ALK-targeted therapies)
	• osimertinib (EGFR T790M mutation-positive after EGFR-TK targeted therapies)
	• pemetrexed with carboplatin
	• platinum doublet chemotherapy
	  o with or without pemetrexed maintenance
	• nintedanib with docetaxel (adenocarcinoma histology)
	• nivolumab (subject to ongoing CDF review)

	• pembrolizumab (PD-L1-expressing tumours) • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • time to treatment discontinuation • 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 use of sotorasib is conditional on the presence of 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 5.9 of the Guide to the Methods of Technology Appraisals'.
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 and NICE Pathways	**Related Technology Appraisals:** Nivolumab for previously treated squamous non-small-cell lung cancer (2020) NICE technology appraisal guidance 655 Osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer (2020) NICE technology appraisal guidance 653 Lorlatinib for previously treated ALK-positive advanced non-

	small-cell lung cancer (2020) NICE technology appraisal guidance 628 Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer (2019) NICE technology appraisal guidance 584 Brigatinib for treating ALK-positive advanced non-small-cell lung cancer after crizotinib (2019) NICE technology appraisal guidance 571 Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (2018) NICE technology appraisal guidance 520 Nivolumab for previously treated non-squamous non-small-cell lung cancer (2017) NICE technology appraisal guidance 484 [undergoing CDF review] Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (2017) NICE technology appraisal guidance 428 Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer (2016) NICE technology appraisal guidance 403 Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin (2016) NICE technology appraisal guidance 402 Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer (2016) NICE technology appraisal guidance 395 Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (2015) NICE technology appraisal guidance 374 Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (2015) NICE technology appraisal guidance 347 Pemetrexed for the maintenance treatment of non-small-cell lung cancer (2010 updated 2017) NICE technology appraisal guidance 190 **Terminated appraisals** Afatinib for treating advanced squamous non-small-cell lung cancer after platinum-based chemotherapy (terminated appraisal) (2017) NICE technology appraisal 444 **Appraisals in development**

	Amivantamab for treating EGFR Exon 20 insertion-positive non-small-cell lung cancer after platinum-based chemotherapy NICE technology appraisal guidance. Publication date to be confirmed. Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer. NICE technology appraisal guidance. Publication date to be confirmed. Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations. NICE technology appraisal guidance. Publication date to be confirmed. **Related Guidelines:** Lung cancer: diagnosis and management (2019) NICE guideline NG122 **Related Quality Standards:** Lung cancer in adults (2019) NICE quality standard 17 **Related NICE Pathways:** NICE Lung cancer pathway: treating non-small-cell lung cancer
Related National Policy	**National Service Frameworks:** Cancer **Department of Health:** Department of Health, NHS Outcomes Framework 2016-2017: Domains 1, 2, 4, 5. NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 105: Specialist cancer services (adults) **Other policies** Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020

References

1. Lung cancer incidence. Cancer Research UK. Accessed September 2020.
2. Types of lung cancer. Cancer Research UK. Accessed September 2020.
3. Herbst RS and Schlessinger J (2019) Small molecule combats cancer-causing KRAS protein at last. Nature 575(7782):294-295.
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.

5. Zhuang X, Zhao C, Li J, et al. (2019) Clinical features and therapeutic options in non-small cell lung cancer patients with concomitant mutations of EGFR, ALK, ROS1, KRAS or BRAF. Cancer medicine. Jun;8(6):2858-66.

