National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Amgen	NA	-
	British Thoracic Oncology Group	[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?] Yes	Comment noted. No action required.
Timing Issues	Amgen	Amgen believe there is a clear unmet need for a targeted and effective treatment for KRAS G12C mutated NSCLC.	Comment noted. No action required.
	British Thoracic Oncology Group	This oral drug targets the most common driver mutation in the most common form of human cancer, and offers an alternative to intravenous therapy, with a lower risk of toxicities needing inpatient management. In this post-COVID era there is an obvious incentive to introduce such a resource-saving innovation at the earliest opportunity	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Amgen	NA	-
	British Thoracic Oncology Group	This is accurate and it is very important to emphasise that KRAS mutation (the target of sotorasib) is very common in non-small cell lung cancer, and has to date eluded successful in inhibition	Comment noted. No action required.
The technology/ intervention	Amgen	NA	-
	British Thoracic Oncology Group	[Is the description of the technology or technologies accurate?] Yes	Comment noted. No action required.
Population	Amgen	In clinical practice, sotorasib is expected to used in accordance with the anticipated marketing authorisation of adults with previously treated KRAS G12C mutated, locally advanced or metastatic NSCLC.	Comment noted. No action required.
	British Thoracic Oncology Group	[Is the population defined appropriately?] Yes [Are there groups within this population that should be considered separately?] No	Comment noted. No action required.
Comparators	Amgen	• For non-squamous NSCLC with KRAS G12C mutation and no other known targetable genetic alterations (EGFR, ALK, ROS1). Treatment options for these patients depend on the histology of the tumour and the type and molecular markers identified; however, the expression of KRAS and other molecular markers such as EGFR, ROS1, BRAF, ALK1 is generally considered to be mutually exclusive. The prevalence of the KRAS G12C mutation in non-squamous NSCLC is estimated to be 13%.[1] In the NHS, non-squamous NSCLC patients whose tumours express PD-L1 at 50% or above will receive pembrolizumab monotherapy or a combination of pembrolizumab with pemetrexed and platinum chemotherapy in the front line-	Comment noted. No action required. The background section of the scope describes that treatment choices (and so comparators) depend on the presence of biological markers (such as genetic alterations in EGFR-TK, ALK or

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		setting.[2] On progression after pembrolizumab, patients are offered pemetrexed with carboplatin or other platinum doublet chemotherapy.[2] On progression after first-line chemotherapy or pembrolizumab combination, patients are offered docetaxel monotherapy or docetaxel in combination with nintedanib.[2] Non-squamous NSCLC patients whose tumours express PD-L1 below 50% are offered pembrolizumab combination and pemetrexed with cisplatin or pemetrexed with carboplatin or other platinum doublet chemotherapy in the front line-setting.[2] On progression after chemotherapy patients can be offered an immunotherapy and docetaxel monotherapy or docetaxel in combination with nintedanib. [2] On progression after pembrolizumab combination, patients are treated with docetaxel monotherapy or docetaxel in combination with nintedanib [2] Sotorasib is anticipated to primarily displace docetaxel monotherapy following prior treatment with immunotherapy and/or chemotherapy. This positioning is consistent with the Ph2 clinical trial eligibility criteria, the ongoing confirmatory Ph3 clinical trial and NICE Scientific Advice received in February 2020. A secondary comparison versus docetaxel in combination with nintedanib may be considered relevant; however, this is not routinely used across the NHS and is only recommended for patients with adenocarcinoma histology. • For non-squamous NSCLC with KRAS G12C mutation in addition to other known targetable genetic alterations (EGFR, ALK, ROS1) The expression of KRAS and other molecular markers such as *EGFR, ROS1, BRAF* and *ALK1* is generally considered to be mutually exclusive (see response to Q3). Given this, sotorasib is not anticipated to be used within this population. • For squamous NSCLC.	ROS1, or PD-L1 expression), histology (squamous or non-squamous) and prior treatments. The scope aims to include all possible comparators, even if used in a small proportion of patients, including those with KRAS G12C mutation in addition to other known targetable genetic alterations (EGFR, ALK, ROS1). The background section has been adjusted to indicate that co-expression of KRAS and other molecular markers such as EGFR, ROS1, BRAF and ALK1 is very rare.

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		KRAS G12C mutations are relatively rare in squamous NSCLC with an estimated prevalence of <2%[1] and routine molecular testing for other known mutations (ie. *EGFR, ALK, ROS1*) is generally not recommended due to their low incidence.[3] In the NHS, patients with squamous NSCLC whose tumours express PD-L1 at or above 50% are offered pembrolizumab or pembrolizumab in combination with carboplatin and paclitaxel in the front-line setting.[2] On progression of pembrolizumab monotherapy they are offered gemcitabine or vinorelbine and cisplatin or carboplatin.[2] On progression of pembrolizumab combination or chemotherapy, patients are offered docetaxel monotherapy.[2] Patients with squamous NSCLC whose tumours express PD-L1 below 50% are offered pembrolizumab in combination with carboplatin, paclitaxel or gemcitabine or vinorelbine, and cisplatin or carboplatin.[2] On progression of pembrolizumab combination or chemotherapy, patients are offered docetaxel monotherapy.[2] On progression after first-line chemotherapy patients can receive treatment with an immunotherapy or docetaxel monotherapy.[2] Consistent with the non-squamous population, sotorasib is anticipated to displace docetaxel monotherapy following prior treatment with immunotherapy and/or chemotherapy.	
	British Thoracic Oncology Group	The indication being considered is second line. There are several first line options in NSCLC currently, so the diversity of comparators listed is appropriate, if complex. Technology appraisal 374 (gefitinib & erlotinib), and those in development for selpercatinib and tepotinib are out of scope as comparators because they target genetic drivers that are generally mutually exclusive with KRAS activation	Comment noted. No action required.

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Outcomes	Amgen	NA	-
	British Thoracic Oncology Group	[Will these outcome measures capture the most important health related benefits (and harms) of the technology?] Yes	Comment noted. No action required.
Economic analysis	Amgen	NA	-
	British Thoracic Oncology Group	-	-
Equality and Diversity	Amgen	NA	-
	British Thoracic Oncology Group	KRAS mutation is less common in lung cancer from East and South Asian populations (reviewed by Burns et al J Clin Onocol (2020) 38;4208 and refs there in), but nevertheless relevant in all NSCLC populations	Comment noted as potential equality consideration.
Other considerations	Amgen	NA	-
	British Thoracic Oncology Group	The alternatives especially IV therapy require visits to overcrowded cancer day units	Comment noted. No action required.
Innovation	Amgen	Lung cancer is the third most common cancer and remains the leading cause of cancer death in the UK (accounting for 21% of all cancer deaths) with 35,300 deaths per annum.[5] More than 80% of all lung cancer cases worldwide are classified as NSCLC and the prognosis is extremely poor with a 5-year survival rate of stage III and stage IV disease in the UK of 5.65%.[5] There are currently no treatments available that target KRAS G12C, a prevalent driver mutation in NSCLC, with patients typically receiving toxic chemotherapy regimens following front-line treatment. Given the low response	Comment noted. No action required.

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		rates to chemotherapy regimens and poor survival outcomes of patients with NSCLC in second-line or later treatment, new biomarker-driven anticancer therapies are urgently needed in this patient population. Sotorasib is a first-in-class, targeted treatment with once-daily dosing that selectively and irreversibly targets the KRAS G12C mutation and provides a step-change in the management and outcomes of NSCLC. Furthermore, as an oral therapy, it provides greater convenience to patients and reduced burden on the health care system. Sotorasib has received a Promising Innovative Medicine (PIM) designation by the MHRA.	
	British Thoracic Oncology Group	Highly innovative – no approved KRAS-targeting therapy yet approved Sotorasib offers potentially significant health-related benefit due to the prevalence of the drug's target, and the efficacy and safety reported to date Likely to be straightforward to implement, as this is a relatively well-tolerated oral therapy. The resource utilisation of parenteral comparators, especially those with the potential to cause myelosuppression, is highly relevant in a post-COVID context Hong D et al. New Engl J Med (2020) DOI: 10.1056/NEJMoa1917239	Comment noted. No action required.
Questions for consultation	Amgen	How frequently KRAS G12C mutation coexists with other known targetable genetic alterations (EGFR, ALK, ROS1)? Is there any published evidence to support this estimate?	Comment noted. The background section has been adjusted to

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		Clinical experts consulted by Amgen and feedback received during the NICE Scientific Advice process indicated that the expression of KRAS and other molecular markers such as *EGFR, ROS1, BRAF, ALK1* is generally considered to be mutually exclusive. This is supported by a large retrospective analysis of the Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-FMI CGDB) which includes approximately 29,000 patients from over 289 oncology practices in the United States. Based an analysis of co-mutation profiles, KRAS G12C was found to be nearly mutually exclusive across most established driver mutations in NSCLC, including very low co-mutation rates with *EFGR* (1.2%), *ROS1* (0.3%) and *ALK* (0%).[4] Are the outcomes listed appropriate? Are any key outcomes missing? Amgen consider the outcomes listed in the scope to be appropriate for this appraisal. Are there any subgroups of people in whom sotorasib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Amgen are not aware of any subgroup that would be considered more clinically effective or cost-effective.	indicate that co-expression of KRAS and other molecular markers such as EGFR, ROS1, BRAF and ALK1 is very rare.

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	British Thoracic Oncology Group	KRAS expression is almost entirely mutually exclusive with other driver mutations such as EGFR, ALK and ROS1; it is uncommon in combination with BRAF mutations (Nature 2014 511:543, El Osta J Thoracic Oncol 2019 14:576; Alredo et al. Lung Cancer 2019 133:144)	Comment noted. The background section has been adjusted to indicate that co-expression of KRAS and other molecular markers such as EGFR, ROS1, BRAF and ALK1 is very rare.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

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Additional References from Amgen:

1. Amgen Data on File. Prevalence of KRAS G12C – NSCLC. AACR Genie 2020
2. NICE, Guideline Updates Team UK. "Lung cancer: diagnosis and management." (2019).
3. Hirsh FR,et al. 2018 Molecular and Immune Biomarker Testing in Squamous-Cell Lung Cancer: Effect of Current and Future Therapies and Technologie Cinical Lung Cancer 19 94):331-9
4. Aggarwal S, et al.Clinicopathological Characteristics, Treatment Patterns, and Outcomes in Patients with KRAS p.G12C Mutant Advanced Non-Small Cell Lung Cancer in the Flatiron Health-Foundation Medicine Clinico-Genomic Database. Poster presented at the European Society for Medical Oncology (ESMO); Virtual Congress, 2020. Poster Number: 1339P)
5. Cancer Research UK; Lung cancer statistics.. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer Accessed Jan 2021