National Institute for Health and Care Excellence

Single Technology Appraisal

Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer [ID6339]
Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Bristol Myers Squibb (BMS)	Bristol Myers Squibb (BMS) believes that adagrasib for previously treated *KRAS* G12C mutation-positive advanced non-small cell lung cancer (NSCLC) is an appropriate topic for NICE to consider via the single technology appraisal (STA) route given the unmet need in this patient population. Despite *KRAS* being the most prevalent driver mutation in NSCLC and G12C being the most frequent *KRAS* variant, patients with the *KRAS* G12C mutation are underserved relative to those with other driver mutations, for which a broader range of therapies are available. Sotorasib (TA781[1]), currently only commissioned via the Cancer Drugs Fund (CDF), is the only available therapy targeted to *KRAS* G12C mutation-positive NSCLC, leaving patients with limited treatment options.	Thank you for your comment.
	British Thoracic Oncology Group (BTOG)	Yes this is an appropriate topic for review as a health technology evaluation	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
Wording	BMS	BMS believes that in order to reflect the issues of clinical and cost effectiveness of adagrasib, the wording of the remit should align with the wording in the license: as monotherapy for the treatment of adult patients with advanced NSCLC with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.	Thank you for your comment. The wording of the remit has been updated to better reflect the wording of the marketing authorisation.
	BTOG	Yes appropriate background information has been described and quoted TA referenced	Thank you for your comment.
Timing issues	BMS	BMS considers the NICE STA route appropriate to deliver timely guidance to the NHS for this topic. *KRAS* mutations, as a group, are a negative prognostic biomarker vs wild-type NSCLC for progression-free survival[2–4] and for overall survival.[3–10] Some studies suggest that *KRAS* G12C may confer even worse outcomes than other *KRAS* mutations.[8, 11] The poor prognosis for patients with *KRAS* G12C mutation-positive NSCLC is exacerbated by the limited targeted treatment options (as described above) compared with the range of targeted therapies available for patients with other driver mutations. There remains a significant unmet need for targeted treatments for patients with *KRAS* G12C mutation-positive NSCLC. For this reason, BMS is keen to provide access for patients at the earliest possible opportunity.	Thank you for your comment.
	BTOG	Urgent	Thank you for your comment.
	BMS	None	N/A

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	BTOG	None	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BMS	BMS agrees that the background information is accurate in its description of the epidemiology of lung cancer, NSCLC, and *KRAS* G12C mutations in NSCLC. However, the last sentence of the fourth paragraph of the background section should read "If the squamous NSCLC expresses PD-L1 on *over* 50% of its tumour cells…" instead of "*less than* 50%". Additionally, based on recent clinical expert opinion, BMS understands that use of immunotherapy after progression on platinum-based chemotherapy alone is not routine clinical practice for patients with *KRAS* G12C mutation-positive NSCLC. This is because the reasons for not giving immunotherapy initially – namely poor performance status, comorbidity, or contraindication to immunotherapy – typically persist. Patients receiving immunotherapy initially are ineligible to receive it after disease progression. Accordingly, BMS suggests the final background paragraph be amended to read as follows: Docetaxel or docetaxel with nintedanib (TA347) may be offered as a second-line treatment following platinum-based chemotherapy with or without concurrent immunotherapy. For the small proportion of patients who receive chemotherapy without immunotherapy at first line, immunotherapy monotherapy consisting of either nivolumab (TA655; for PD-L1 positive	Thank you for your comment. The background section is intended to give a broad overview of the disease area and treatment options recommended by NICE.

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		disease, TA713), atezolizumab (TA520) or pembrolizumab (for PD-L1 positive disease, TA428) is reimbursed but is rarely used in clinical practice because the reasons for not giving immunotherapy at first line (poor performance status, comorbidity, or contraindication) typically persist at subsequent lines of treatment.	
	BTOG	The background is accurate and complete	Thank you for your comment.
Population	BMS	BMS suggests that the population should be defined according to the wording in the license: adult patients with advanced NSCLC with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.	Thank you for your comment. The population wording has been amended to better reflect the marketing authorisation.
	BTOG	The population stated is appropriate	Thank you for your comment.
Subgroups	BMS	At the time of writing, BMS is not aware of any subgroups in which adagrasib would be more clinically or cost effective.	Thank you for your comment. The subgroups are kept inclusive at this stage to allow committee to consider any subgroups for which there is evidence.

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	BTOG	The technology should be evaluated for the locally advanced and metastatic non-small cell lung cancer population as per the population definition with specifically G12C KRAS mutation. They should have received prior platinum based chemotherapy and anti-PD-1/L1 inhibitors, unless contraindicated.	Thank you for your comment. The subgroups are kept inclusive at this stage to allow committee to consider any subgroups for which there is evidence.
Comparators	BMS	BMS considers several of the comparators listed in the draft scope to be inappropriate based on current clinical practice in England and Wales. BMS considers docetaxel and docetaxel + nintedanib to be the relevant comparators for this appraisal, consistent with (TA781[1]), the only previous appraisal for a therapy for patients with *KRAS* G12C mutation-positive NSCLC. Immunotherapies (nivolumab, atezolizumab, and pembrolizumab) should be removed from the scope. Feedback in early 2024 from five UK-based clinical key opinion leaders (KOLs) is that these are not appropriate comparators for adagrasib as they do not comprise routine clinical practice in England and Wales. Clinical experts consulted by BMS stated that patients receive immunotherapy as their initial treatment unless poor performance status, comorbidity, or contraindication precludes it, and these situations are rare. For this small proportion of patients (<10%), immunotherapy is rarely used after progression on platinum-based chemotherapy because the reasons for not giving immunotherapy as initial treatment typically persist. Patients receiving immunotherapy initially are ineligible to receive it after disease progression.	Thank you for your comments. The scope has been updated to reflect the comparators deemed relevant in TA781.

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		Given their limited use in routine clinical practice in *KRAS* G12C mutation-positive advanced NSCLC, BMS suggests that immunotherapies are not appropriate comparators for this appraisal. BMS also notes that sotorasib is undergoing managed access review by NICE and is currently only available via the CDF. At the time of writing, BMS intends to exclude it as a comparator based on NICE's position statement that therapies only available via the CDF are not relevant comparators. In summary, BMS considers docetaxel and docetaxel + nintedanib to be the appropriate comparators for this appraisal, consistent with the comparators presented in the only previous submission (TA781[1]) of a therapy for *KRAS* G12C mutation-positive NSCLC.	
	BTOG	Appropriate comparators are Docetaxel, Docetaxel and Nintedanib for adenocarcinoma population. Also Sotorasib currently on CDF which carries the same indication for the previously treated KRAS G12C population. Note patients should have received Nivolumab, Atezolizumab or Pembrolizumab hence not comparators. Likewise they should have received platinum base chemotherapy and therefore not a comparator.	Thank you for your comments. The scope has been updated to reflect the comparators deemed relevant in TA781.
	Roche Products Limited	Atezolizumab in combination (TA584) is noted in the background section, but not included in the PICO table.	Thank you for your comments. The background section of the scope aims to give a broad overview of the condition and the treatment pathway. The scope has been updated to reflect the

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			comparators deemed relevant in TA781.
Outcomes	BMS	BMS agrees that the outcomes listed in the draft scope are appropriate for capturing important health-related benefits of adagrasib. BMS will also report duration of response and intracranial efficacy.	Thank you for your comment.
	BTOG	The outcomes listed are appropriate	Thank you for your comment.
	Roche Products Limited	In-line with TA781, include time to treatment discontinuation	Thank you for your comment. The outcomes listed in the scope are not intended to be exhaustive. The appraisal committee can consider other outcomes if appropriate.
Equality	BMS	BMS is unaware of any potential impacts of the draft remit and scope on the equality of opportunity or discrimination against people with protected characteristics.	Thank you for your comment.
	BTOG	There are no foreseen equality issues.	Thank you for your comment.
	BMS	None	N/A

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Other considerations	BTOG	Given the similarities in efficacy to comparator Sotorasib and target population, if poor tolerance in first 3 months due to side effects (without progression), should consider allowing patient to try alternate drug in case of better tolerability as is allowed with ALK inhibitors for example	Thank you for your comment.
Questions for consultation	BMS	**Where do you consider adagrasib will fit into the existing care pathway for the disease?** The licensed indication for adagrasib is monotherapy for the treatment of adult patients with advanced NSCLC with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy. The proposed positioning for adagrasib, in line with its licensed indication, is as a second- and later-line therapy following prior treatment with (1) immunotherapy as monotherapy, (2) platinum-based chemotherapy alone, or (3) immunotherapy in combination with platinum-based chemotherapy. **Is the *KRAS* G12C mutation tested for as part of routine practice in advanced or metastatic NSCLC care?** Yes. BMS has been advised by clinical KOLs that routine testing for driver mutations prior to initiation of first-line therapy always includes tests for variants in *KRAS*, often as part of next-generation sequencing panels. **Would the technology be a candidate for managed access?** BMS anticipates that the evidence for adagrasib from the ongoing phase 3 KRYSTAL-12 trial and the completed phase 1/2 KRYSTAL-1 trial will enable NICE to recommend adagrasib funding via routine commissioning. However, if the NICE committee feels unable to make a positive recommendation for routine NHS funding on the basis of this evidence, then BMS would be open to discussions with NICE and NHS England around potential inclusion in the CDF.	Thank you for your responses to the consultation questions. The scope has been updated to reflect the comparators deemed relevant in TA781..

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		Do you consider that the use of adagrasib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? BMS believes that all substantial health-related benefits are likely to be captured in the QALY calculation. **Are the comparators suggested above appropriate? Would immunotherapy checkpoint inhibitors be offered to patients with previously treated *KRAS* G12C mutation positive NSCLC?** As described above in comments on the draft scope (comparators section), feedback elicited from five UK-based clinical KOLs is that immunotherapies are not appropriate comparators for adagrasib because their use at second line is not routine clinical practice for patients with *KRAS* G12C mutation-positive NSCLC in England and Wales. This is because the reasons for not giving immunotherapy initially (poor performance status, comorbidity, or contraindication) typically persist. Given the very limited use of second-line immunotherapy in routine clinical practice in *KRAS* G12C mutation-positive advanced NSCLC, BMS suggests that nivolumab, atezolizumab, and pembrolizumab should not be included as comparators for this appraisal. **Are the subgroups suggested above appropriate and complete?** **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** At the time of writing, BMS is not aware of any subgroups in which adagrasib would be more clinically or cost effective. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in**	

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		order to meet these aims. In particular, please tell us if the proposed remit and scope: • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which adagrasib will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** As described above, BMS has not identified any equality issues.	
	BTOG	N/A	N/A
Additional comments on the draft scope	BMS	None	N/A
	BTOG	This should be considered for the cancer drug fund pending full NICE review	Thank you for your comment.

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

Roy Castle Lung Cancer Foundation