NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using adagrasib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: May 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using adagrasib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 2 June 2025
- Second evaluation committee meeting: 12 June 2025
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Adagrasib should not be used to treat KRAS G12C mutation-positive advanced non-small-cell lung cancer (NSCLC) in adults whose cancer has progressed after, or who cannot tolerate, platinum-based chemotherapy or anti-PD-1 or anti-PD-L1 immunotherapy.

1.2 This recommendation is not intended to affect treatment with adagrasib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Adagrasib is not required to be funded in the NHS in England to treat KRAS G12C mutation-positive advanced NSCLC in adults whose cancer has progressed after, or who cannot tolerate, platinum-based chemotherapy or anti-PD-1 or anti-PD-L1 immunotherapy. It should not be used routinely in the NHS in England.

This is because there is not enough evidence to determine whether adagrasib is value for money.

Why the committee made these recommendations

Usual treatment for previously treated KRAS G12C mutation-positive advanced NSCLC includes docetaxel or docetaxel plus nintedanib, and platinum-based chemotherapy. Adagrasib is a treatment targeted to the KRAS G12C mutation.

Clinical trial evidence shows that adagrasib increases how long people have before their cancer gets worse compared with docetaxel. But it is uncertain whether

adagrasib increases how long people live compared with docetaxel. This is because of how the clinical trial was designed and because it is still ongoing.

Adagrasib has not been directly compared in a clinical trial with docetaxel plus nintedanib. Results from an indirect comparison are uncertain.

There are concerns with the economic model. This is because of assumptions made about the effect of adagrasib on quality of life. Because of the uncertainties in the clinical evidence and in the economic model it is not possible to determine the most likely cost-effectiveness estimates for adagrasib.

So, it should not be used.

2 Information about adagrasib

Conditional marketing authorisation indication

2.1 Adagrasib (Krazati, Bristol Myers Squibb) is indicated for 'the treatment of adult patients with advanced non-small cell lung cancer (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'.

Dosage in the conditional marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for adagrasib (pdf only).

Price

2.3 The list price of adagrasib tablets is confidential until published by the Department of Health and Social Care.

2.4 The company has a commercial arrangement, which would have applied if adagrasib had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Bristol Myers Squibb will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Bristol Myers Squibb, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer. The KRAS oncogene is the most commonly mutated gene in lung cancer. The KRAS G12C mutation occurs in 11% of NSCLC tumours in the UK. This mutation is more common in non-squamous NSCLC and does not usually occur with other known mutations such as EGFR, ALK and ROS-1. People with previously treated KRAS G12C mutation-positive locally advanced or metastatic NSCLC usually have chemotherapy, which is a non-targeted treatment associated with adverse effects that affect health-related quality of life. Sotorasib is the only available targeted treatment for the KRAS G12C mutation. It is only recommended for use within the Cancer Drugs Fund (see NICE's technology appraisal guidance on sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer). The patient and professional organisations and clinical expert submissions highlighted that people with KRAS G12C mutation-positive NSCLC have a poor prognosis. They noted that there is an unmet need for effective and tolerable treatments in this population. The patient organisation also highlighted that the lack of targeted treatment options and having symptoms that are difficult to treat, can be distressing for patients and their carers. The company submission also emphasised the psychological and financial impact on patients and their carers. The committee concluded that there is an unmet need for

additional targeted treatments for KRAS G12C mutation-positive locally advanced NSCLC, and that these would have physical, psychological and financial benefits.

Clinical management

Treatment pathway and comparators

3.2 According to the conditional marketing authorisation (see section 2.1), people having adagrasib must have previously had, or intolerance to, 'platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy'. The company submission compared adagrasib with docetaxel and docetaxel plus nintedanib in line with the NICE scope. Sotorasib is not a relevant comparator to adagrasib because it is recommended within the Cancer Drugs Fund and so is not considered to be part of routine practice. A clinical expert submission highlighted that people either have first-line platinum-based chemotherapy with immunotherapy, or single-agent immunotherapy based on PD-L1 expression, disease performance status and co-morbidities. People with a poor performance status may have platinum-based chemotherapy only. The clinical expert submission further highlighted that on disease progression after first-line treatment, a KRAS G12C inhibitor treatment can be considered. Sotorasib and adagrasib are KRAS G12C inhibitors. After first-line single-agent immunotherapy, platinum doublet therapy is used before KRAS G12C inhibitor treatment. After platinum-based chemotherapy, people could have docetaxel with or without nintedanib. The clinical experts at the committee meeting agreed that adagrasib would be used instead of docetaxel with or without nintedanib if it was available. They agreed that the company's positioning of adagrasib in the treatment pathway for KRAS G12C mutation-positive NSCLC is broadly reflective of NHS clinical practice. The committee acknowledged that because sotorasib is recommended for use within the Cancer Drugs Fund, it is not available in routine practice and so is not a relevant comparator for this evaluation. The committee concluded that

docetaxel and docetaxel plus nintedanib are the relevant comparators to adagrasib for this evaluation.

Clinical effectiveness

Data sources

3.3 The main clinical-effectiveness evidence for adagrasib came from KRYSTAL-12. This is an ongoing phase 3, multicentre, open-label clinical trial for KRAS G12C mutation-positive advanced NSCLC in adults who have had platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 immunotherapy. It compares adagrasib (n=301) with docetaxel (n=152). People in the trial had up to 4 previous lines of systemic treatments, measurable disease according to RECIST 1.1 criteria and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The company presented KRYSTAL-12 data from the 31 December 2023 data cut. The median duration of follow up was 9.43 months. Adagrasib significantly reduced the risk of progression by 42% (hazard ratio 0.58, 95% confidence interval [CI] 0.45 to 0.76) compared with docetaxel. For the objective response rate, adagrasib was associated with a significantly higher likelihood of response (odds ratio 4.68, 95% CI 2.56 to 8.56) compared with docetaxel. Progression-free survival 2 (PFS2) was also reported as an exploratory outcome in KRYSTAL-12. This provides information in cases when analysis of overall survival could be confounded by subsequent treatments. The results for PFS2 closely overlapped between adagrasib and docetaxel arms following subsequent treatment (the exact results are confidential and cannot be reported here). The company did not present the results of the interim overall-survival analysis because it considered these highly immature and inconclusive.

The company submission also presented evidence from KRYSTAL-1. This is an ongoing phase 1 and 2 multicentre, open-label, single-arm dose-escalation and multiple expansion trial of adagrasib in adults with selected solid-tumour malignancies with the KRAS G12C mutation. Evidence from cohort A (n=116) in phase 2 of KRYSTAL-1 is relevant to

this evaluation. Cohort A included people with NSCLC previously treated with platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 immunotherapy. People in the trial had measurable disease according to RECIST 1.1 criteria and an ECOG performance status of 0 or 1. The company presented KRYSTAL-1 data from the 15 October 2021 data cut for progression-free survival and objective response rate with a median duration of follow up of 12.9 months. The objective response rate was 42.9% (95% CI 33.5 to 52.6) and median progression-free survival was 6.5 months (95% CI 4.7 to 8.4). The median duration of follow up for overall survival was 15.6 months (15 January 2022 data cut). Median overall survival was 12.6 months (95% CI 9.2 to 19.2). The committee concluded that evidence from KRYSTAL-12 shows that adagrasib has a progression-free survival benefit compared with docetaxel.

Brain metastasis

3.4 The committee noted that adagrasib is associated with central nervous system (CNS) penetration and may potentially have some CNS benefits. But it also noted that both KRYSTAL-12 and KRYSTAL-1 excluded people with active brain metastases. The company highlighted that KRYSTAL-12 evaluated intracranial efficacy of adagrasib in people with treated, neurologically stable CNS metastases only (n=78 in the adagrasib arm and n=36 in the docetaxel arm). But phase 1b of KRYSTAL-1 evaluated intracranial efficacy in people with untreated, neurologically stable, asymptomatic CNS metastases (n=25). Adagrasib showed some intracranial response. But the company acknowledged that none of the patients in the trials had active brain metastases. A clinical expert at the committee meeting highlighted that the intracranial response seen with adagrasib from KRYSTAL-1 was consistent with that seen for tyrosine kinase inhibitors penetrating the brain. The NHS England Cancer Drugs Fund clinical lead highlighted that there is good biological plausibility for adagrasib to penetrate the brain because adagrasib is a small-molecule medicine. The committee concluded that adagrasib likely penetrates the

blood-brain barrier and provides some intracranial response in stable brain metastases.

Risk of bias in KRYSTAL-12

3.5 KRYSTAL-12 has an open-label design so people know which intervention they are having. Early withdrawals before having any treatment were significantly lower in the adagrasib arm (n=3, 1.0%) than in the docetaxel arm (n=12, 7.9%), with 11 withdrawals in the docetaxel arm being 'withdrawal by subject'. After treatment initiation, 'withdrawal by subject' was nearly twice as high in the docetaxel arm (n=21, 13.8%) compared with the adagrasib arm (n=21, 7.0%). Some people in both treatment arms also had subsequent treatment before their cancer progressed (the exact numbers are confidential and cannot be reported here). The company assessed a low risk of bias in KRYSTAL-12. It highlighted that the lack of blinding was unlikely to have substantially affected the interpretation of response or progression because these endpoints were assessed by blinded independent central review. The EAG highlighted that people's knowledge of the intervention that they were having (and possible expectation of higher benefit with adagrasib over docetaxel), may have affected patient retention in the docetaxel arm. But the company provided additional sensitivity analyses to explore the potential impact of early asymmetric dropout and informative censoring (people in the docetaxel arm of KRYSTAL-12 who crossed over to adagrasib) on progression-free survival. The results of these analyses are confidential and cannot be reported here. The EAG considered that it is unclear if the prognosis of people who remained in the docetaxel arm was balanced with those remaining in the adagrasib arm. So, it is uncertain if withdrawal in KRYSTAL-12 may have biased overall survival, objective response rates and safety outcomes. Adagrasib was associated with reduced symptom burden and improved health-related quality of life compared with docetaxel. But the EAG said that despite this, the subjective nature of patient-reported outcomes and lack of blinding means that health-related quality-of-life outcomes in KRYSTAL-12 may have

been overestimated. The US Food and Drug Administration (FDA) requested a protocol amendment in KRYSTAL-12, in line with CodeBreaK 200. CodeBreaK 200 was a phase 3, open-label randomised controlled trial of the safety and efficacy of sotorasib compared with docetaxel in people with previously treated KRAS G12C mutation-positive NSCLC. The FDA's protocol amendment permitted crossover to adagrasib in people assigned to the docetaxel arm. At clarification the company reported that a proportion of people in the docetaxel arm had a KRAS G12C inhibitor as subsequent treatment. The subset of people in the docetaxel arm who crossed over to adagrasib or had another KRAS G12C inhibitor had shorter mean time since metastatic diagnosis (11.5 months compared with 15.0 months). The EAG highlighted that it is unclear how many people in the docetaxel arm crossed over to adagrasib or were given another subsequent KRAS G12C inhibitor before confirmed disease progression. The EAG also highlighted that people in both treatment arms may have benefited from adagrasib because of the crossover. They said that a subset of people in the docetaxel arm may also have benefited from subsequent sotorasib or an unlicensed KRAS G12C inhibitor. The committee acknowledged the limitations associated with the design of KRYSTAL-12, including lack of blinding, risk of bias, crossover and subsequent treatments in the docetaxel arm. It noted that this may introduce uncertainty in the overall survival, objective response rates, safety outcomes and health-related quality-of-life outcomes from KRYSTAL-12. But it acknowledged that KRYSTAL-12 is the most robust source of evidence for adagrasib for previously treated KRAS G12C mutation-positive NSCLC. The committee concluded that, despite limitations with the trial design, KRYSTAL-12 provides the best available evidence to inform the clinical effectiveness of adagrasib.

Overall survival

3.6 The company did not present the results of the overall-survival analysis in its original submission. This is because it considered the interim overall-survival results from KRYSTAL-12 to be highly immature and

inconclusive, and the presence of the potential confounding effect of crossover had not been adjusted for. But the company did provide the results following a request from the EAG at clarification. The results indicated that adagrasib is associated with a non-statistically significant hazard ratio compared with docetaxel (the exact results are confidential and cannot be reported here). The EAG highlighted that using immature overall-survival data to quantify the treatment effect for adagrasib compared with docetaxel leads to substantial uncertainty in the cost-effectiveness analysis. It advised that in the absence of crossover-adjusted analyses, the potential impact of crossover and subsequent KRAS G12C inhibitors in the docetaxel arm on overall survival is uncertain. The EAG also advised that more mature evidence was needed from KRYSTAL-12 to address the concerns around the overall-survival results from KRYSTAL-12. To explore alternative scenarios around overall survival benefit for adagrasib, the EAG looked at evidence from CodeBreaK 200 (see section 3.5). CodeBreaK 200 showed that sotorasib (a biologically similar treatment to adagrasib licensed for previously treated KRAS G12C mutation-positive advanced NSCLC), had a statistically significant progression-free survival benefit compared with docetaxel (hazard ratio 0.66, 95% CI 0.51 to 0.86). But it did not show a statistically significant overall-survival benefit for sotorasib (hazard ratio 1.01, 95% CI 0.77 to 1.33). CodeBreak 200 allowed for crossover of patients from the comparator arm to the intervention arm upon disease progression. However, when different crossover-adjustment methods were applied, the treatment benefit varied. To explore the uncertainty in the overall-survival results for KRYSTAL-12, the EAG used 2 alternative estimates of overall survival in its base case:

- EAG base case 1 assumed no effect of adagrasib on overall survival compared with docetaxel (hazard ratio 1)
- EAG base case 2 assumed the same effect of adagrasib as sotorasib (the only other KRAS inhibitor with data in the relevant population) on overall survival. This was based on the effect from the 2-step

crossover-adjusted analysis for sotorasib compared with docetaxel from CodeBreaK 200 (hazard ratio 0.89).

The clinical experts explained that despite CodeBreak 200 not demonstrating the expected overall-survival benefit for sotorasib, most healthcare professionals would prefer it to docetaxel. This is because it is a targeted treatment with CNS penetration, has higher response rates for some disease markers including progression-free survival and the convenience of being an oral tablet. They said that healthcare professionals believe that despite the CodeBreaK 200 results, sotorasib is likely to have a benefit. The committee recalled that the decision on choice of treatment in clinical practice is shared between people and their healthcare professionals. The committee also recalled that the KRYSTAL-12 trial design likely introduces uncertainty into the overall-survival estimates, objective response rates, safety outcomes and health-related quality-of-life outcomes (see section 3.5). With the available evidence and uncertainty in the overall-survival estimates for adagrasib from KRYSTAL-12, the committee decided that the EAG's base case 1 that assumes no effect of adagrasib on overall survival compared with docetaxel is the most plausible. But the committee would consider evidence from the company that uses different methods to inform the long-term survival estimates, including:

- interim overall-survival data from KRYSTAL-12 extrapolated for the model time horizon, using methods described in NICE's Technical Support Document 14
- interim overall-survival data from KRYSTAL-12 adjusted for treatment switching using methods described in NICE's Technical Support Document 16, and overall-survival outcomes from each crossover-adjustment method extrapolated for the model time horizon.

Company's surrogacy analysis

3.7 The company did a post-hoc exploratory surrogacy analysis using overall-survival data from KRYSTAL-1 to:

- assess the relationship between time to progression and time to death at the individual patient level for KRAS G12C mutation-positive NSCLC
- predict overall survival for KRYSTAL-12 in censored patients for both adagrasib and docetaxel using the surrogacy relationship derived from KRYSTAL-1 applied to progression data from KRYSTAL-12.

The company then used the predicted KRYSTAL-12 overall-survival data from this surrogacy analysis to inform its network meta-analysis and cost-effectiveness analysis. The NICE technical team referred to NICE's manual on health technology evaluations in the committee meeting. The manual states that for a surrogate endpoint to be considered validated, there needs to be good evidence that the relative effect of a technology on the surrogate endpoint is predictive of its relative effect on the final outcome. The EAG advised that the company did not follow recommendations in the manual. This was because the company used a within-study relationship based on analysis of the KRYSTAL-1 single-arm phase 1 and 2 trial to predict absolute overall survival rather than surrogacy based on relative effect. The EAG further highlighted several limitations with the surrogacy analysis, including that:

- There was no evidence to suggest that progression-free survival benefits translate to overall-survival benefits, or that progression-free survival is a reliable surrogate for overall survival in KRAS G12C NSCLC at second line and beyond. A single-arm study cannot determine whether the relative effect of adagrasib on progression is predictive of relative overall survival.
- The surrogacy analysis had not been externally validated in the KRAS G12C NSCLC population. The surrogacy relationship was unlikely to be exchangeable between KRAS-targeted and non-targeted treatments

because the strength of the association can vary by treatment class and line of treatment.

- Predicting overall survival for the same follow-up time as KRYSTAL-1, but with data from KRYSTAL-1 censored when 5% or fewer people are still at risk of progression suggests predicted overall-survival estimates are overly precise. This means that the predicted overall survival estimates are less certain than the data suggests because of a small number of people at risk at later time points and this uncertainty needs to be reflected in the estimates.

  The committee acknowledged that the company's surrogacy-analysis approach does not follow NICE's recommendations and has serious limitations. It recognised that surrogacy analysis is recommended in the absence of clinical trial endpoints. But it noted that interim overall-survival data was available from KRYSTAL-12 (see section 3.6). The committee concluded that the company's surrogacy analysis using overall-survival data from KRYSTAL-1 to predict overall survival for KRYSTAL-12 is not appropriate for decision making.

Indirect treatment comparison

3.8 In the absence of a direct comparison between adagrasib and docetaxel plus nintedanib, the company did an indirect treatment comparison. For progression-free survival and safety outcomes it used available data from the most recent data cut-offs from KRYSTAL-12 (adagrasib), LUME-Lung1 (docetaxel plus nintedanib) and CodeBreaK 200 (sotorasib). For overall-survival outcomes, the company used the most recent data cut-off from LUME-Lung1 and CodeBreaK 200. It also used overall survival estimates from the surrogacy analysis of KRYSTAL-1 to provide estimates of overall survival for KRYSTAL-12. For both progression-free survival and overall survival, the company used the fixed-effects time-varying network meta-analysis using the gamma curve in its base case. The EAG raised several concerns with the validity of the network meta-analysis results because of limitations in the clinical evidence, including:

- the validity of the overall-survival data from the company's surrogacy analysis (see section 3.7).
- the risk of bias in KRYSTAL-12 (see section 3.5).
- the population from LUME-Lung 1, which had limited comparability with KRYSTAL-12 and CodeBreaK 200, most notably in prior immunotherapy exposure and histology. People in LUME-Lung 1 were recruited between 2008 and 2011, so may not have benefited from the improvements in treatment and managing tolerability and safety over the past decade. So, it was uncertain whether prior immunotherapy exposure may affect the relative overall-survival benefits of docetaxel plus nintedanib compared with docetaxel monotherapy. Also, adenocarcinoma histology might be a treatment-effect modifier for network meta-analysis comparisons between docetaxel plus nintedanib and adagrasib or docetaxel monotherapy, although the evidence is limited and uncertain.
- Adagrasib, docetaxel plus nintedanib and sotorasib were only directly compared with docetaxel, so the absence of loops in the network and the limited number of studies prevents any assessment of consistency and heterogeneity.
- substantial quality issues with CodeBreaK 200 because of concerns with early asymmetric dropout, censoring and crossover, the duration of interval between assessments, and lack of blinding.

So, the EAG advised that the results of the network meta-analysis should be interpreted with caution. It also highlighted that incorporating results from the subgroup of people with adenocarcinoma from LUME-Lung 1 may partially address concerns about the comparability of this trial. For progression-free survival and safety outcomes, the committee acknowledged that there was little the company could do to improve its approach to doing these network meta-analyses. So, the committee concluded that this was acceptable for decision making. But the committee noted the uncertainty introduced by using the overall-

survival data from the company's surrogacy analysis. It concluded that the overall-survival results from the company's network meta-analyses to inform the economic model were not suitable for decision making.

Adverse events

3.9 In KRYSTAL-12, the safety population was defined as everyone who had any part of a dose of study medication. This was 298 people in the adagrasib arm and 140 people in the docetaxel arm. Everyone in the adagrasib arm and 98.6% of people in the docetaxel arm experienced treatment-emergent adverse events. Fatal treatment-emergent adverse events occurred in 48 (16.1%) people in the adagrasib arm and 10 (7.1%) people in the docetaxel arm. Grade 3 or higher treatment-emergent adverse events occurred in 213 (71.5%) people in the adagrasib arm and 93 (66.4%) people in the docetaxel arm. Serious treatment-emergent adverse events occurred in 149 (50.0%) people in the adagrasib arm and 50 (35.7%) people in the docetaxel arm. Treatment-emergent adverse events led to treatment discontinuation for 40 (13.4%) people in the adagrasib arm and 25 (17.9%) people in the docetaxel arm. Treatment-emergent adverse events that led to dose reductions or interruptions were reported in 237 (79.5%) people in the adagrasib arm and 67 (47.9%) people in the docetaxel arm.

In KRYSTAL-1, the safety population was defined as everyone who had had at least 1 dose of adagrasib (n=116). Everyone experienced treatment-emergent adverse events. Twenty (17.2%) people died. The most common cause of death was malignant neoplasm progression (8 people, 6.9%). Grade 3 or more treatment-emergent adverse events occurred in 94 (81.0%) people. Ninety-five (81.9%) people had dose reductions or interruptions because of treatment-emergent adverse events and 17 people (14.7%) discontinued adagrasib because of treatment-emergent adverse events. Seventy (60.3%) people experienced serious treatment-emergent adverse events.

The clinical experts at the committee meeting acknowledged that KRAS G12C inhibitors have a different level of toxicity compared with targeted treatments for EGFR and ALK mutations. They highlighted that with increasing knowledge of KRAS G12C inhibitors, there is increasing recognition that immunotherapy washout likely affects the toxicity profile, in particular liver and gastrointestinal toxicities, of KRAS G12C inhibitors. This has been seen with an increase in the use of corticosteroid treatments to manage these toxicities earlier in the treatment pathway when the corticosteroids would otherwise be used for grade-3 adverse events. The committee was aware of the number of people in the adagrasib arm of KRYSTAL-12 who experienced fatal treatment-emergent adverse events, and this is similar to trials in other KRAS G12C inhibitors. The committee noted that a proportion of people had not completed the EQ-5D questionnaire in KRYSTAL-12, and that it would be useful to understand why this was the case and to see data on questionnaire completion rates for grade 2 and above treatment emergent adverse events. The committee concluded that there are serious adverse events associated with KRAS G12C inhibitors that will be factored into the decision making on its clinical effectiveness and costs in the model and would like to see the impact of grade-2 or above adverse events adequately captured in the economic modelling.

Economic model

Company's modelling approach

3.10 The company used a partitioned survival model with 3 health states:

- progression-free
- progressed
- death.

The cycle length was 1 week, and the time horizon was 20 years. Health-state occupancy for adagrasib, docetaxel and docetaxel plus nintedanib was informed by overall-survival and progression-free

survival estimates from the company's time-varying network meta-analysis. For adagrasib and docetaxel, the company's surrogacy analysis used KRYSTAL-1 individual patient data to predict KRYSTAL-12 overall survival that was used in the overall-survival network meta-analysis. Treatment discontinuation was informed from extrapolated progression-free survival curves for each treatment and adjusted to reflect the relationship between time to treatment discontinuation and progression-free survival. The EAG advised the company's base-case model structure is consistent with previous NICE evaluations on advanced or metastatic NSCLC at the second line of treatment. The committee noted the uncertainty in the overall-survival data. It recalled its conclusion on overall survival that the EAG's base case 1 which assumes no effect of adagrasib on overall survival compared with docetaxel is the most plausible. But it would consider the company trying different methods to inform the long-term survival estimates (see section 3.6). Overall, the committee agreed the company's model was similar to previous models used in NSCLC. It concluded that the model structure was appropriate for decision making.

Utility values

3.11 The company used EQ-5D-5L data from KRYSTAL-12 mapped to EQ-5D-3L to inform the utility values for progression-free and progressed-disease health states grouped by treatment arm and disutilities for adverse events. The company applied utility values to time spent in the progression-free and progressed-disease health states to calculate quality-adjusted life years (QALYs) that reflect the improvement in quality of life. It used higher utility values for the adagrasib arm compared with docetaxel or docetaxel plus nintedanib. This was based on the company's mixed models for repeated measures analysis of EQ-5D responses from KRYSTAL-12. This was done while controlling for treatment arm. This demonstrated a positive co-efficient for the adagrasib arm, suggesting that people in the adagrasib treatment arm have a higher quality of life even when taking into account progression status, age and sex. The company highlighted

the quality-of-life benefit with adagrasib in the progression-free and progressed-disease health states. It said that this was because of the convenience of adagrasib being an oral treatment taken at home, compared with docetaxel's intravenous administration in hospital. The exact utility values are confidential and cannot be reported here. The EAG disagreed with a utility increment associated with adagrasib in the progressed-disease health state because the treatment is discontinued upon disease progression. It also highlighted that people in the docetaxel arm of KRYSTAL-12 who crossed over to adagrasib were censored from the company's utility analysis resulting in potential selection bias in the post-progression analysis. So, the EAG used the same treatment-independent utility value for adagrasib in the progressed-disease health state as for docetaxel and docetaxel plus nintedanib. The committee did not agree with a quality-of-life benefit attributed to administration mode accruing when the treatment is no longer taken. It said that it would like further justification for different utility values between treatment arms in the progressed-disease health state. The committee concluded that it prefers the same health-state utility value for all treatments (based on the confidential value of the docetaxel arm) in the progressed-disease health state. But it said that it would also consider scenarios using the same progressed-disease health-state utility value (based on the confidential value reported for the adagrasib arm) and scenarios with differential utility values. The committee would also like to see further justification of any utility values used in the progressed-disease health state.

Severity

3.12 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company and the EAG agreed that it was appropriate to apply a severity

weight of 1.7 to the adagrasib QALYs in the comparison with docetaxel. The company did not provide severity weighting analysis for adagrasib compared with docetaxel plus nintedanib. But the EAG did the analysis and advised that it was appropriate to apply a severity weighting of 1.7 to the adagrasib QALYs in the comparison with docetaxel plus nintedanib. So, the committee concluded that the severity weight of 1.7 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.13 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will consider the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also consider other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically, the:

- limitations of KRYSTAL-12 and uncertainty in the overall survival, objective response rates, safety outcomes and health-related quality-of-life outcomes (see section 3.5)
- effect of adagrasib relative to docetaxel or docetaxel plus nintedanib on overall survival (see section 3.6)
- company's surrogacy analysis to predict overall survival for KRYSTAL-12 from overall survival from KRYSTAL-1 (see section 3.7)
- uncertainty in the company's network meta-analysis results, in particular overall survival (see section 3.8)
- serious adverse events associated with adagrasib that were factored into the decision making on the clinical effectiveness (see section 3.9)
- insufficient justification of the different utility values in the progressed-disease health state between the treatment arms (see section 3.11).

The committee concluded that given the considerable uncertainties, and to minimise risks posed by opportunity cost of other treatments and services being displaced, an acceptable cost-effectiveness estimate would not be higher than £20,000 per QALY gained.

Company and EAG cost-effectiveness estimates

3.14 Because of confidential commercial arrangements for adagrasib and some of the comparators, the exact cost-effectiveness results are confidential and cannot be reported here.

Committee's preferred assumptions

3.15 The committee's preferred assumptions included:

- Assuming no effect of adagrasib on overall survival compared with docetaxel (hazard ratio of 1). Alternatively, the committee would consider the company trying different methods to inform the long-term survival estimates including:
  - interim overall survival from KRYSTAL-12 extrapolated for the model time horizon, using methods described in NICE's Technical Support Document 14
  - interim overall survival from KRYSTAL-12 adjusted for treatment switching using methods described in NICE's Technical Support Document 16, and overall-survival outcome from each crossover-adjustment method extrapolated for the model time horizon (see section 3.6).
- In the progressed-disease health state, using the same health-state utility value for all treatments (based on the confidential value of the docetaxel arm). The committee would consider scenarios using the same progressed-disease health-state utility value (based on the confidential value reported for the adagrasib arm) and scenarios with differential utility values with further justification (see section 3.11).

The exact ICERs are confidential and cannot be reported here. The company's base case incorporated the surrogacy analysis, which the committee found unsuitable for decision making (see section 3.7). The EAG's base case 1 assumed there is no effect of adagrasib on overall survival (hazard ratio of 1) compared with docetaxel and docetaxel plus nintedanib. It also used the same progressed-disease health-state utility value for all treatments using the value in the adagrasib arm (which is confidential so cannot be reported). Using the EAG's base case 1, the ICER for adagrasib compared with docetaxel was above the range that NICE considers a cost-effective use of NHS resources. The EAG's base case 2 assumed that adagrasib has the same effect on overall survival as sotorasib (hazard ratio 0.89). It also used the same progressed-disease utility value for all treatments using the value in the adagrasib arm (which is confidential so cannot be reported). Using the EAG's base case 2, the ICER for adagrasib compared with docetaxel was above the range that NICE considers a cost-effective use of NHS resources. In both the EAG's base cases, docetaxel with nintedanib provided fewer health benefits at higher cost compared with a combination of adagrasib and docetaxel monotherapy. So, the committee concluded that adagrasib could not be recommended for routine commissioning.

Managed access

Recommendation with managed access

3.16 Having concluded that adagrasib could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed-access period for treating KRAS G12C mutation-positive advanced NSCLC. But the committee noted that the company had not made a managed-access proposal for adagrasib for inclusion in the Cancer Drugs Fund. The committee noted that for it to be considered for the Cancer Drugs Fund adagrasib needs to have plausible potential to be cost effective. But the committee recalled the uncertainties

in the clinical evidence and economic model. It also noted that the most likely cost-effectiveness estimates using its preferred assumptions are uncertain but are most likely above the range that NICE considers a cost-effective use of NHS resources. So, the committee concluded that, in the absence of a managed-access proposal, adagrasib could not be considered for use with managed-access. The committee also considered that if a managed-access proposal was made during consultation, adagrasib would still not be considered for use with managed-access because currently it is not plausibly cost effective.

Other factors

Equality

3.17 The committee did not identify any equality issues.

Uncaptured benefits

3.18 The committee considered whether there were any uncaptured benefits of adagrasib. It did not identify additional benefits of adagrasib not captured in the economic modelling. So, the committee concluded that all additional benefits of adagrasib had already been taken into account.

Conclusion

Recommendation

3.19 The clinical-effectiveness evidence for adagrasib is uncertain because of the design of KYSTAL-12, immature interim overall-survival results and uncertainties in the company's surrogacy analysis. There are uncertainties in the economic model, including with the utility values for adagrasib and the comparators used in the modelling. The most likely cost-effectiveness estimates for adagrasib are substantially above the range that NICE considers an acceptable use of NHS resources. So, adagrasib should not be used.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Megan John

Chair, technology appraisal committee D.

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Zain Hussain

Technical lead

Rufaro Kausi

Technical adviser

Kate Moore

Project manager

Christian Griffiths

Principal technical adviser

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