Single Technology Appraisal

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Amgen**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Oncogene Cancer Research
   b. Roy Castle Lung Cancer Foundation

3. **Comments on the Draft Guidance from experts:**
   a. Dr Qamar Ghafoor – Clinical expert, nominated by Amgen
   b. Dr Toby Talbot - Clinical expert, nominated by Amgen

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance** prepared by Kleijnen Systematic Reviews

6. **NHSE SACT Report**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 26 March 2026. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal 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 provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Amgen

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Summary	We thank the Committee for its careful consideration of the evidence submitted for this appraisal. While we are disappointed with the preliminary recommendation, we appreciate the opportunity to respond to the Committee's concerns. We have addressed all issues raised by the Committee, fulfilling the requests outlined in the Appraisal Consultation Document (ACD) as well as additional analyses discussed during the Appraisal Committee Meeting (ACM). We have supplied analyses to mitigate uncertainty surrounding the docetaxel arm of the CAS study, alongside external validation to support the plausibility and generalisability of the survival estimates to NHS clinical practice. We hope that these additional data and clarifications provide reassurance to the Committee in its reconsideration of the evidence, and we urge the Committee to carefully consider the impact on patients as they review.
Severity modifier	Amgen acknowledges that the Committee has not yet reached a preferred conclusion on the appropriate severity modifier for sotorasib, with numerous scenarios presented in the appraisal exceeding and lying close to the 0.95 threshold for a 1.7 weighting. We note that the estimated shortfall is highly sensitive to modelling assumptions, including small changes in baseline

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<table>
<tr><td></td><td>characteristics (e.g. age). Given this sensitivity, and the proximity of several plausible analyses to the decision threshold, reliance on point estimates alone may not adequately reflect the range of plausible outcomes. In such cases, NICE has previously adopted a pragmatic approach where results lie close to severity thresholds.

In this context, Amgen considers it important to highlight that adagrasib, in the same KRAS G12C advanced non-small-cell lung cancer (NSCLC) population following prior systemic therapy, was appraised (TA1076) as meeting the criteria for a 1.7 severity modifier. In the absence of any material change in the treatment pathway and given that the underlying prognosis and disease course for this population remain unchanged, it is not clinically plausible that the severity of the condition has meaningfully reduced between appraisals. The difference in severity categorisation therefore appears more likely to reflect methodological choices and threshold sensitivity rather than a true difference in disease burden. Maintaining consistency in the application of severity modifiers across comparable appraisals is important to ensure transparent and predictable decision making.

A severity categorisation below 1.7 would not align with the high unmet need and poor prognosis associated with this population, raising concerns regarding the face validity of the estimates. Not applying the higher severity weighting risks underrepresenting the health loss experienced by patients and may lead to a decision that is not aligned with NICE’s objective of appropriately weighting treatments for the most severe conditions.

Amgen therefore considers that application of a 1.7 severity modifier represents the most appropriate and methodologically consistent basis for decision making, given the consistency of the indication, the absence of any clinically plausible change in disease severity, and the proximity of the estimated shortfall to the 0.95 threshold across multiple plausible analyses.</td></tr>
<tr><td>Updated base case</td><td>The Amgen base case ahead of ACM 1 is presented in Table 1.

Table 1: Amgen base case cost-effectiveness results
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>Incremental QALYs (x1.7)</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Docetaxel</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sotorasib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£28,172</td></tr>
<tr><td colspan="7">Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.</td></tr>
</table>

Amgen have made several updates to their base case following ACM 1 in an attempt to address the questions raised by the Committee. We have revised the PAS discount and updated our base case, maintaining our position that applying a 1.7 severity modifier is the most appropriate and methodologically consistent basis for decision making. All subsequent base case analyses presented incorporate this updated PAS.

As requested in the ACD, the administration costs for docetaxel have been updated from £394.17 to £435.51 to align with the day case unit costs captured in NHS Reference Costs 2024/25 (Code SB12Z). For completeness, all NHS Reference Costs in the Economic model have been updated using the 2024/25 version, instead of the now outdated 2023/24. . The updated costs are reported in Table 2.</td></tr>
</table>

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Table 2: Updated cost inputs

Input	Updated costs	Source
Drug acquisition and administration		
Price per pack of docetaxel	22.19	eMIT for the period 1 July 2024 to 30 June 2025, weighted average price
Docetaxel administration	435.51	NHS Reference Costs 24/25 Day Case Unit Cost - Code SB12Z
AE management costs		
Anaemia	2,107.54	NHS Reference Costs 24/25 Weighted Average Total Cost HRG codes SA01G-SA01K (Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, CC score 0-8+)
Diarrhoea	4,986.64	NHS Reference Costs 24/25 Weighted Average Total Cost HRG codes FD10E-FD10H (Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, CC score 0-9+)
Dyspnea	4,192.37	NHS Reference Costs 24/25 Weighted Average Total Cost HRG codes DZ19J-DZ19K (Other Respiratory Disorders with Single Intervention, with CC score 0-5+)
Fatigue	2,107.54	NHS Reference Costs 24/25 Weighted Average Total Cost HRG codes SA01G-SA01K (Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, CC score 0-8+)
Febrile neutropenia	5,730.40	NHS Reference Costs 24/25 Weighted Average Total Cost HRG codes WH07C-WH07D (Infections or Other Complications of Procedures, with Single Intervention, CC score 0-2+)
Neutropenia	1,552.59	NHS Reference Costs 24/25 Weighted Average Total Cost HRG codes SA08G-SA08J (Other Haematological or Splenic Disorders, CC score 0-6+)
Pneumonia	5,414.36	NHS Reference Costs 24/25 Weighted Average Total Cost HRG codes DZ11N-DZ11Q (Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-13+)

Key: AE, adverse event; eMIT, electronic market information tool; HRG, healthcare resource group; NHS, National Health Service.

Table 3: Updated Amgen base case cost-effectiveness results with 2024/25 price year

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.

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Following the conclusion by the Committee the base case has also been updated to use utility values derived using EQ-5D-3L data mapped with the Hernandes-Alava algorithm. The cost-effectiveness results of this change applied in addition to the updated price year are presented in Table 4.

Table 4: Updated Amgen base case cost-effectiveness results Hernandes-Alava mapped utility values

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

The Committee concluded in ACM 1 that the baseline characteristics from CAS were the most appropriate for modelling the previously treated KRAS G12C mutated NSCLC population. Amgen has therefore updated its base case to reflect this. The characteristics from the sotorasib arm are used as this group had a confirmed KRAS mutation. The age was updated to [redacted] years, the mean age at index in CAS and the percentage female was updated to [redacted] The resulting change in the Amgen base case is presented in Table 5.

Table 5: Updated Amgen base case cost-effectiveness results with population data from CAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.

Amgen has also updated the approach to overall survival (OS) in their base case. As is described in detail in **additional analysis 2**, Amgen do not believe that the scenario requested in the ACD is methodologically robust. However, we have revised our base case to utilise individually fitted parametric survival models to OS for sotorasib and docetaxel from CAS. Using individually fitted models allows for the application of hazard ratios (HRs) and mixing data sources without having to switch between modelling approaches for the reference arm in those scenarios. The selection of log-logistic models is described in **additional analysis 2**. The results with these models are presented in Table 6.

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Table 6: Updated Amgen base case cost-effectiveness results with log-logistic models individually fitted to CAS OS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.

The Committee also raised concerns related to the specification of the mixed models for repeated measures (MMRM). We have looked to address the uncertainty by conducting the scenario analyses requested by the Committee, described in **additional analysis 6**. Further to this Amgen have explored uncertainty around the utility benefit associated with receiving sotorasib compared to docetaxel. A progression-based model with an interaction term for treatment has been fitted. Amgen believe this addresses two concerns the Committee highlighted in ACM 1. The magnitude of the treatment specific utility benefit, particularly beyond progression, and the use of time-to-death (TTD) utilities. The results with the progression and treatment interaction model are described in Table 7.

Table 7: Updated Amgen base case cost-effectiveness results with progression and treatment interaction utility model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,912

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.

This represents the Amgen base case, all additional analyses requested by the Committee are considered as individual scenario analyses applied to the base case.

Sensitivity analyses around the updated base case are located in Appendix A – Sensitivity analyses around updated base case.

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1	**Additional analyses 1:** more detail about the company's approach to adjusting for treatment switching and about propensity score analysis **Treatment switching – CodeBreaK 200** OS results from CodeBreaK 200 are inherently difficult to interpret due to substantial imbalances in post-progression treatment and the widespread use of treatment switching within the trial. Crossover from the docetaxel arm to sotorasib was permitted following blinded independent central review (BICR)-confirmed disease progression; however, regulatory review highlighted concerns regarding the reliability of BICR-assessed progression-free survival (PFS) as a trigger for crossover, introducing further uncertainty around the timing and appropriateness of switching (Food and Drug Administration, 2023). In practice, a meaningful proportion of patients randomised to docetaxel crossed over to receive sotorasib, with additional patients in the control arm accessing KRAS G12C inhibitors through other routes, while patients in the sotorasib arm also received subsequent active therapies following progression (Alharbi et al. 2024). This asymmetric and intensive use of effective subsequent treatments is well recognised to dilute observable differences in OS, even where a true treatment benefit exists, and is a key driver of the discordance observed in CodeBreaK 200 between the significant PFS benefit and the absence of an OS advantage. Although statistical methods were applied to adjust for treatment switching, these approaches rely on strong and untestable assumptions and cannot fully recover an unbiased treatment effect in the presence of complex and heterogeneous post-progression pathways. In CodeBreaK 200, without appropriate crossover adjustment, the survival in the docetaxel arm is substantially overestimated. Bias occurred due to crossover, with 33.9% of docetaxel subjects either crossing over per protocol (onto sotorasib) or received commercial KRAS-G12C inhibitor. Crossover accounted for 59% of docetaxel patients who progressed (as measured by IA). The sotorasib arm of the trial was unaffected by trial crossover. To account for the bias caused by patient crossover from the docetaxel treatment arm, following the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 16 guidance (Latimer & Abrams, 2014), crossover adjustments were performed. Three crossover adjustment methods were pre-specified: the rank-preserving structural failure time (RPSFT) model, the inverse probability of censoring weights (IPCW), and the two-stage model (TSM). Among these, only the TSM crossover adjustment is appropriate due to the setup of the trial design and the covariates considered for adjustment. The two-stage method is specifically designed for trials in which treatment switching is permitted only after a clearly defined clinical milestone, often referred to as a secondary baseline. In CodeBreaK 200, crossover from docetaxel to sotorasib was permitted only following disease progression, which represents an appropriate and clinically meaningful secondary baseline. The TSM therefore aligns closely with the structure of the trial. Under the TSM framework, patients who cross over after progression are analysed as in the context of an observational study. The effect of receiving sotorasib post-progression is estimated while adjusting for measured confounders at the secondary baseline, and this estimated effect is then used to re-calculate counterfactual survival times for those who switched treatment. This approach is consistent with TSD16, which recommends the TSM when switching occurs after a clearly defined event such as progression and when relevant confounders at that point can be identified and adjusted for. In CodeBreaK 200, potential confounders influencing the decision to switch treatment were identified through consultation with experienced NSCLC clinicians and pre-specified for adjustment in the model. These included factors related to disease status and patient characteristics at progression. By adjusting for these covariates at the time of crossover eligibility, the TSM aims to reduce bias introduced by the non-random nature of treatment switching. The key assumption

underpinning the method is that all relevant confounders are measured, and given the structured clinical input and available trial data, the residual risk of unmeasured confounding is considered limited.

In the first stage of the analysis, HRs were estimated using a stratified Cox proportional hazards model, comparing survival outcomes between crossover and non-crossover patients from the secondary baseline. Then, 95% confidence intervals were estimated using non-parametric bootstrapping (1,000 samples) to appropriately capture uncertainty. In the second stage, to estimate the treatment effect required to adjust survival times, a Weibull accelerated failure time model was fitted to the overall survival data of docetaxel-treated patients from the secondary baseline onwards. The resulting acceleration factor was then applied to reconstruct counterfactual survival times for patients who switched to sotorasib.

The alternative pre-specified approaches were also explored but were considered less appropriate for CodeBreaK 200 for the following reasons:

- The IPCW method censors patients at the time of treatment switching and reweights the remaining observations to account for the censored individuals, but it requires complete and reliably measured time-varying confounders that influence both switching and survival. In CodeBreaK 200, several relevant covariates have substantial missing data over time and key factors such as disease progression were not captured as time-varying covariates. Disease progression is strongly associated with both crossover and mortality; not considering disease progression within the CodeBreaK 200 trial design leads to severe bias to the disfavor of sotorasib. Therefore, an IPCW analysis could lead to unstable or extreme weights and potentially biased estimates.
- The RPSFT model relies on the assumption of a common treatment effect, meaning the effect of sotorasib would need to be the same whether received at randomisation or after progression, which is unlikely given that crossover occurs in patients with more advanced disease. In addition, because the comparator arm received active treatment (docetaxel) rather than placebo and treatment exposure differs over time, the underlying assumptions of the RPSFT counterfactual survival framework are unlikely to hold. RPSFT estimation is also limited when the observed treatment effect is close to null (HR ≈1.0), further reducing the credibility of the adjusted estimates.

Despite adjustment for treatment switching, the cross-over adjusted HR was unable to reliably estimate OS due to the high stochastic uncertainty introduced by the trial design. Prior to disease progression, sotorasib was associated with a substantial reduction in mortality (approximately [redacted] relative reduction; RR ≈ [redacted]), indicating a clear pre-progression survival advantage. The OS HR with and without adjustment suggest that docetaxel patients experience post-progression survival benefits sufficient to counterbalance the pre-progression benefits provided by sotorasib. With limited subsequent treatments available to patients there is no justification for docetaxel patients to have post-progression survival superior to sotorasib. This highlights that the unadjusted result is heavily influenced by crossover, and the confounding within the docetaxel arm heavily limits the ability to apply effective adjustment.

Propensity score analysis – CAS

The Committee requested further detail on the propensity score analysis, including the covariates included in the model, diagnostics (e.g. standardised mean differences), and the distribution of weights. These methodological details are fully documented in the CAS Technical Report (TR) previously submitted to NICE and contained within the supplementary reference pack to the ACD response. For completeness, the requested details are also captured below.

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To address confounding due to non-randomised treatment allocation in the CAS real-world study, propensity score (PS) weighting was used to balance baseline characteristics between patients initiating sotorasib and those initiating docetaxel. The primary estimand was the average treatment effect in the treated (ATT), reflecting the population represented by patients receiving sotorasib in routine NHS practice.

Covariates included in the model

Baseline confounding was addressed using propensity score weighting with standardised mortality ratio weighting (SMRW). Propensity scores were estimated using logistic regression modelling the probability of receiving sotorasib versus docetaxel conditional on clinically relevant baseline variables Covariates included demographic, clinical, and treatment-related variables identified through literature review and clinical input. The following covariates were identified and included in the model:

Table 8: Covariates include in the propensity score analysis

Covariate
Age at index date
Sex
Ethnicity
BMI at index date
Stage at diagnosis
Histologic type at diagnosis
ECOG score at index date
LoT number at index date
CCI at index date
Record of any metastasis prior to index date
Record of brain metastasis prior to index date
Prior treatment with PD-1/PD-L1 targeted immunotherapy
Time from diagnosis to index date

Source: CAS TR. Table 6, Section 8.9.3.1.

Variables with very low prevalence or strong collinearity were excluded (e.g., prior TKI use).

Diagnostics and distributions of weights

Implementation of the method followed diagnostics recommended in NICE DSU TSD17 (Faria et al. 2017).

Weight truncation was applied to limit extreme PS weights. Weights below the 1st percentile of the weight distribution were increased (set) to the value of the 1st percentile, while weights above the 99th percentile were reduced (set) to the value of the 99th percentile Propensity score overlap between treatment groups was assessed using PS distributions before and after weighting. Covariate balance was evaluated before and after weighting on the propensity score using standardised mean differences (SMDs) with a target of SMD < 0.1. See Sections 8.9.3.1.2-8.9.3.1.3 in the CAS TR for more detail.

Prior to SMRW, large differences in the PS distributions was observed between treatment groups, and the following covariates were imbalanced: sex, BMI, stage at diagnosis, histology, ECOG score at index date, LoT number at index date, record of any metastasis prior to index date, record

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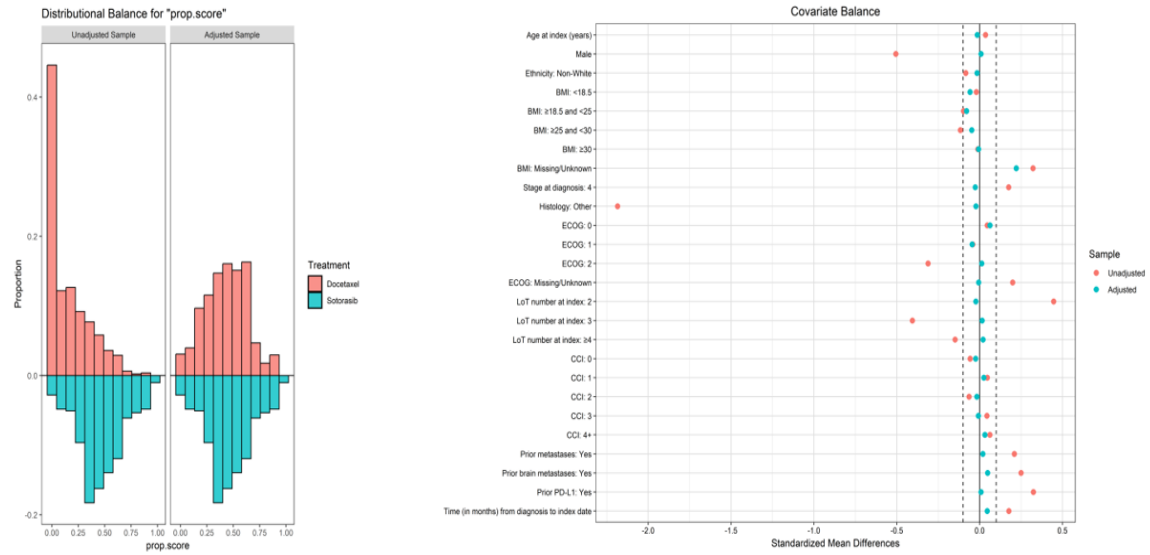
	of brain metastasis prior to index date, prior treatment with PD-1/PD-L1 targeted immunotherapy, and time from diagnosis to index date. Following SMRW, the PS distributions between treatment groups appeared similar, and only BMI remained imbalanced (SMD = 0.221 in the 'missing/unknown' category). Outcomes were analysed using weighted Kaplan–Meier and Cox proportional hazards models, with the proportional hazards assumption assessed using Schoenfeld residuals. The ESS was 394 patients in the sotorasib treatment group and 392 patients in the docetaxel treatment group, indicating good overlap and limited loss of precision. The distribution of propensity scores and weight diagnostics are presented below in Figure 1 and can also be located in Figure 3, Section 9.4.1 in the CAS TR. **Figure 1: Propensity score diagnostics for 2L+ Analysis Set (ATT Estimand)** **a) Distribution of Propensity Scores by Treatment Group Before and After SMRW** **b) Covariate Balance Before and After SMRW**  Source: CAS TR. Figure 3, Section 9.4.1
2	**Additional analyses 2:** to model OS, applying the inverse crossover adjusted relative treatment effect from CodeBreaK 200 to the baseline curves of sotorasib from CAS RWE to generate the docetaxel curves <u>Approach to additional analysis and assumptions</u> In line with the Committee's request, a scenario analysis for OS has been modelled by applying the inverse of the crossover-adjusted OS HR from CodeBreaK 200 to the baseline OS curve for sotorasib derived from the CAS RWE dataset. We hold significant reservations about using the relative effectiveness from CodeBreaK 200 for assessing the OS benefit sotorasib could provide to patients and therefore retain a base case that uses OS data from CAS to model both the sotorasib and docetaxel arm. However, as the Committee wishes to assess a number of scenarios that involve exploring mixed datasets, and utilising HRs we considered it appropriate to revise the Company base case to include CAS OS data extrapolated with individually fitted survival models. The Company base case for ACM 1 utilised jointly fitted models, but using the sotorasib arm of a jointly fitted model then applying a different treatment effect is methodologically erroneous. We believe the revised base case may

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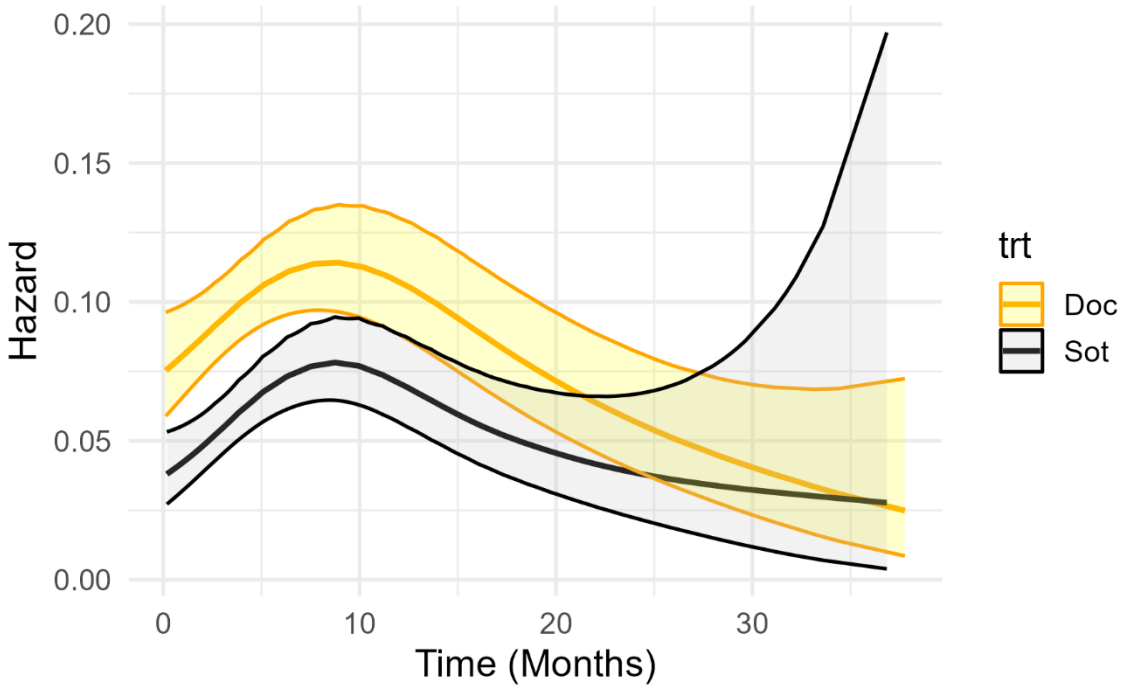
	also address other concerns the EAG or Committee raised in the meeting but not reported explicitly in the ACD. Individually fitted log-logistic models for both the sotorasib and docetaxel arm were identified as the most appropriate pair for extrapolating CAS OS. The smoothed hazard plot (Figure 2) shows that the hazards for both treatments have a single turning point and are then decreasing over time, suggesting an accelerated failure time model is likely to be appropriate. **Figure 2: CAS OS observed hazard**  Key: Doc, docetaxel; OS, overall survival; Sot, sotorasib. When the smoothed hazard for each arm are compared to the hazard profile of each of the fitted models (Figure 3 and Figure 4), only the log-logistic and log-normal closely approximate the profiles observed in CAS for both arms. The generalised gamma does provide a decreasing hazard function for sotorasib in the long-term, however the rate of this decrease is underestimated. The generalised gamma also fails to approximate the initial turning point in the sotorasib hazard.

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Figure 3: Modelled hazards versus observed sotorasib CAS OS smoothed hazard

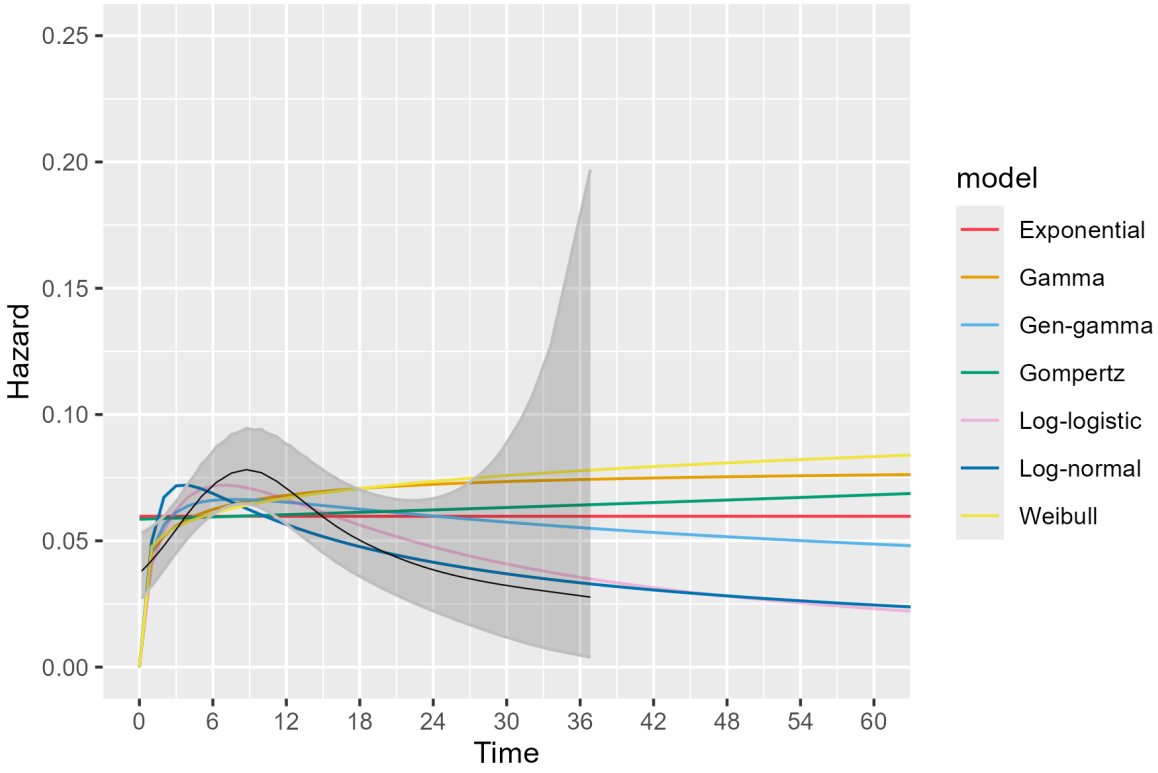

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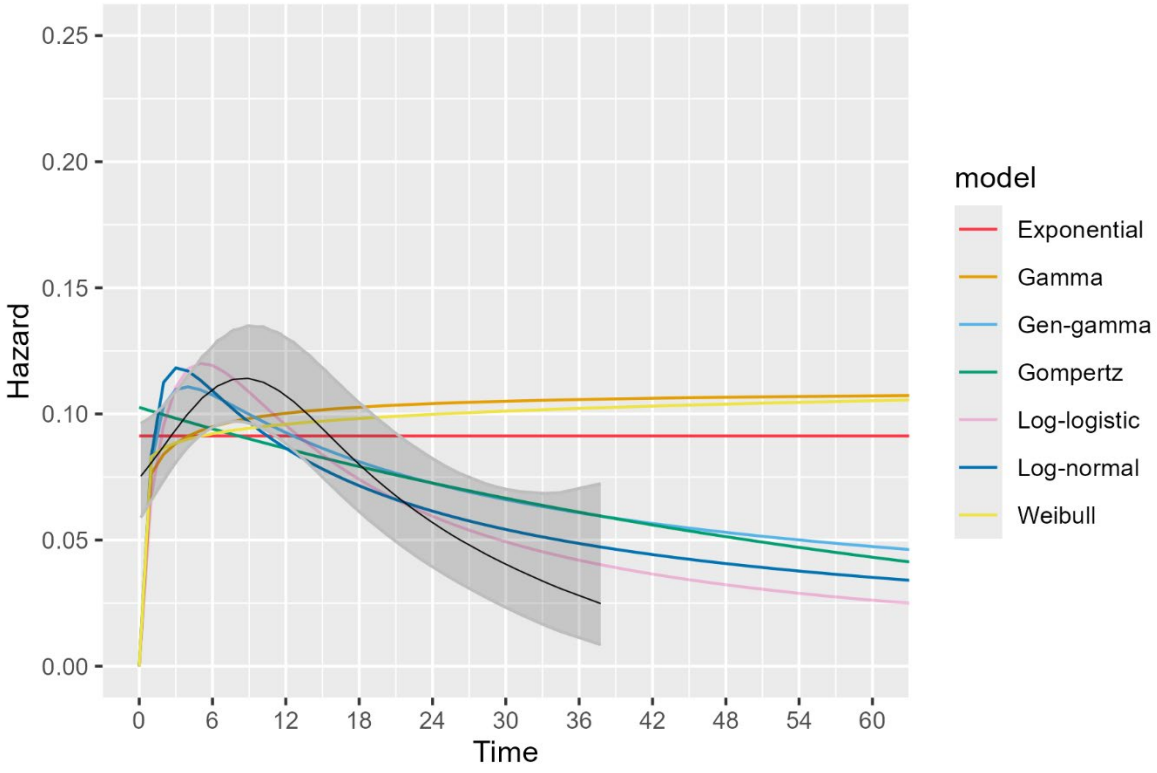
Figure 4: Modelled hazards versus observed docetaxel CAS OS smoothed hazard



When the hazard profiles for the log-logistic and log-normal models for both arms are compared against smoothed hazards (Figure 5), the log-logistic better approximates the relative survival benefit observed in CAS with the hazard rates converging over time.

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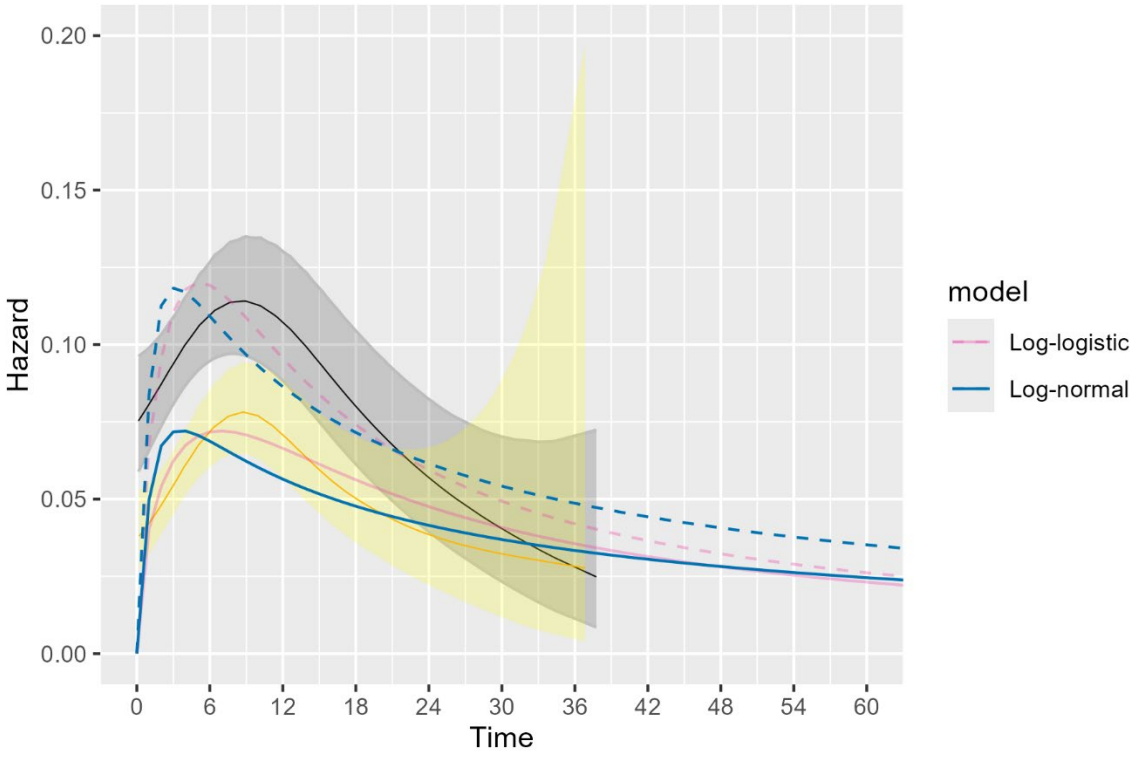
Figure 5: Hazard profiles of log-logistic and log-normal fitted to CAS OS versus smoothed observed hazards



When considering other ways of assessing model fit, the log-logistic models also consistently provide the best statistical fit to the data (Company submission table 43). The log-logistics also provide a good visual fit to the Kaplan-Meier (Figure 6).

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Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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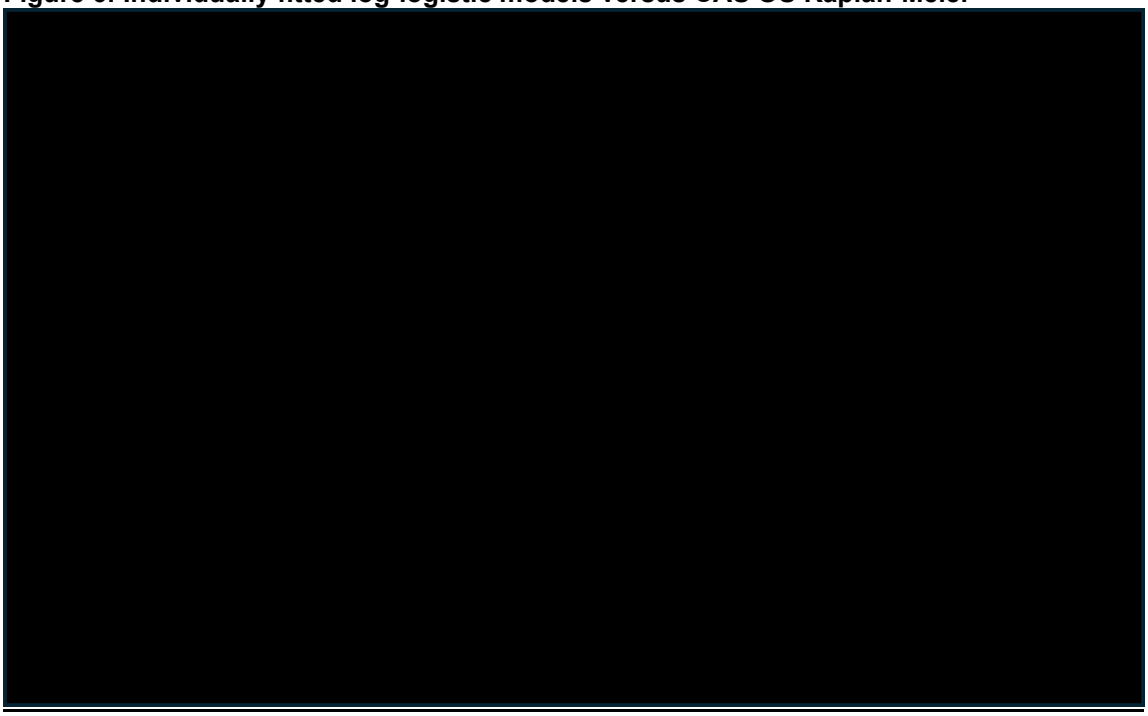
Figure 6: Individually fitted log-logistic models versus CAS OS Kaplan-Meier



Key: KM, Kaplan-Meier.

Requested analysis

The crossover-adjusted HR for OS from CodeBreaK 200 is 0.81. To generate the docetaxel OS curves, the inverse of this HR (1.22) was applied to the parametric baseline hazard function estimated for sotorasib in CAS using a log-logistic distribution. This approach preserves the absolute survival profile observed for sotorasib in CAS, while imposing the relative treatment effect estimated in CodeBreaK 200 onto the RWE baseline.

CE results

Compared to the Amgen base case analysis this scenario reduces the incremental QALYs by [redacted] by increasing the mean undiscounted docetaxel LYs by [redacted]. This has a secondary impact of minorly increasing docetaxel costs, reducing incremental costs by [redacted]. In turn, the ICER increases by £15,667/QALY.

Table 9: Deterministic cost-effectiveness results for Additional analyses 2

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,579
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.						

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Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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	Methodological considerations Amgen does not believe that the approach requested by the Committee provides a reliable estimate of sotorasib's benefit, as CodeBreaK 200 is not fit to support decision making on overall survival. As described in response to Additional Request 1, even after cross-over adjustment methods, CodeBreaK 200 provides an unreliable estimate of the treatment effect on OS, due to the high stochastic uncertainty introduced by the trial design. Before and after adjustment for crossover the relative effectiveness of sotorasib versus docetaxel on OS from CodeBreaK 200 does not triangulate with the totality of the available evidence and appears as a clear outlier when compared to the three other evidence bases for sotorasib (Figure 7). The OS HR is also illogical when considered against the treatment effect observed in CodeBreaK 200 prior to progression. During the pre-progression period, CodeBreaK 200 demonstrates a clear and clinically meaningful mortality benefit for sotorasib. Combining the reduction in PFS events (HR 0.66) with the lower probability that a PFS event is fatal yields an estimated pre-progression mortality reduction of approximately [redacted] (HR = 0.41). However, this does not translate into a reliable estimate of overall survival due to the substantial confounding and sparsity of post-progression data. The lack of coherence between pre-progression and overall survival effects, when there are limited treatment options for this population following progression, raises concerns regarding the internal validity of the OS estimates. Amgen also highlights that the estimated docetaxel survival provided by the scenario are out of step with the feedback of all the clinical experts that have been engaged during this process. The 3-year docetaxel OS when using the requested scenario is [redacted]. This is 3% greater than the EAG clinical expert and 2% higher than observed in CAS, which is in a population with unknown KRAS status and therefore anticipated to be a conservative estimate of the population outcomes in clinical practice. Amgen is also concerned that the Committee's request introduces a hybrid evidence structure that increases structural uncertainty in the estimation of overall survival. Specifically, applying a constant HR from CodeBreaK 200 to the CAS baseline assumes comparability in baseline risk, treatment patterns, and post-progression management across fundamentally different data sources. The CAS baseline hazard reflects UK NHS practice, incorporates longer follow-up (39 months), and broader clinical heterogeneity than the CodeBreaK 200 trial population. In contrast, the HR from CodeBreaK 200 is estimated within a controlled trial setting with different eligibility criteria, monitoring, and treatment pathways. Applying this HR to CAS therefore requires strong assumptions, including proportional hazards and absence of effect modification by baseline characteristics. If these assumptions do not hold, the resulting OS estimates may not represent the treatment effect expected in NHS practice. Taken together, applying the inverse of a crossover-adjusted HR derived under these conditions introduces additional structural uncertainty and risks amplifying, rather than resolving, the Committee's concerns regarding the robustness of the OS estimates. This approach combines internally inconsistent evidence sources and results in estimates that are not anchored in a single coherent evidence framework. Overall, the requested approach increases decision-relevant uncertainty rather than reducing it. Company preference The company base case uses CAS to inform both absolute survival and relative efficacy (OS HR = 0.63). This maintains internal consistency within the model and avoids reliance on crossover-adjusted estimates derived from sparse post-progression data.

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Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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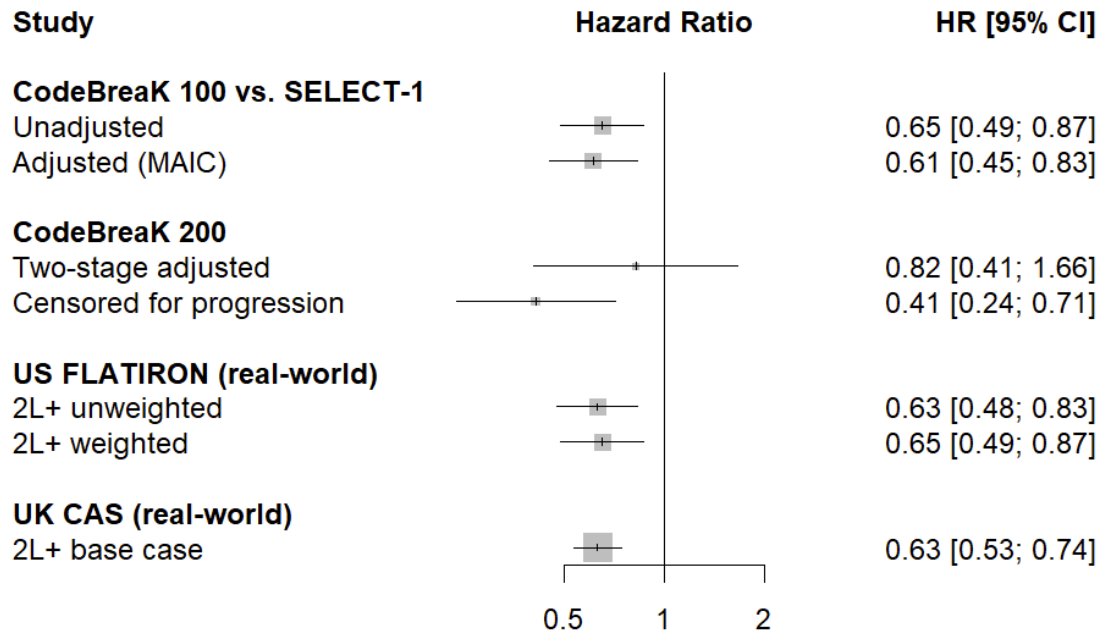
The OS treatment effect estimated using CAS is supported by convergent evidence across multiple independent analyses as demonstrated in Figure 7. HRs derived from a matching-adjusted indirect comparison (MAIC), US real-world evidence and CAS are highly consistent despite differing methodologies and data sources. This consistency provides convergent validation of the treatment effect and reduces the likelihood that the CAS estimate is driven by residual confounding.

Figure 7: OS efficacy overview



Key: CI, Confidence interval; HR, Hazard ratio; MAIC, Matching-adjusted indirect comparison

This consistency provides validation of the treatment effect and reduces the likelihood that the CAS estimate is driven by residual confounding. In contrast, the OS results from CodeBreaK 200 are subject to substantial uncertainty and are not aligned with the totality of available evidence. As noted above, the study was not designed or powered to robustly estimate OS, and the endpoint is heavily influenced by crossover and post-progression treatment dynamics. Accordingly, the OS estimates from CodeBreaK 200 should not be considered decision-relevant for estimating overall survival. Therefore, transporting the treatment effect from CodeBreaK 200 to CAS introduces additional uncertainty without resolving the underlying limitations of the trial data.

Amgen acknowledges that missingness of KRAS G12C mutation status in the docetaxel cohort of the CAS study is a limitation. However, it is important to consider the context in which these data were generated. The design of the CAS study, including the use of historical docetaxel cohorts, was agreed in consultation with NICE and NHS England in recognition of known limitations in the CodeBreaK 200 comparator arm. At the time of data collection, routine KRAS G12C testing was not widely implemented in NHS practice, and targeted treatment with sotorasib was not yet available. In contemporary clinical practice, where a licensed targeted therapy is available, patients with a known KRAS G12C mutation would not ordinarily be treated with docetaxel in preference to sotorasib. As such, constructing a real-world comparator cohort restricted to confirmed KRAS G12C-mutated patients treated with docetaxel would be inherently limited and potentially unrepresentative of routine clinical practice.

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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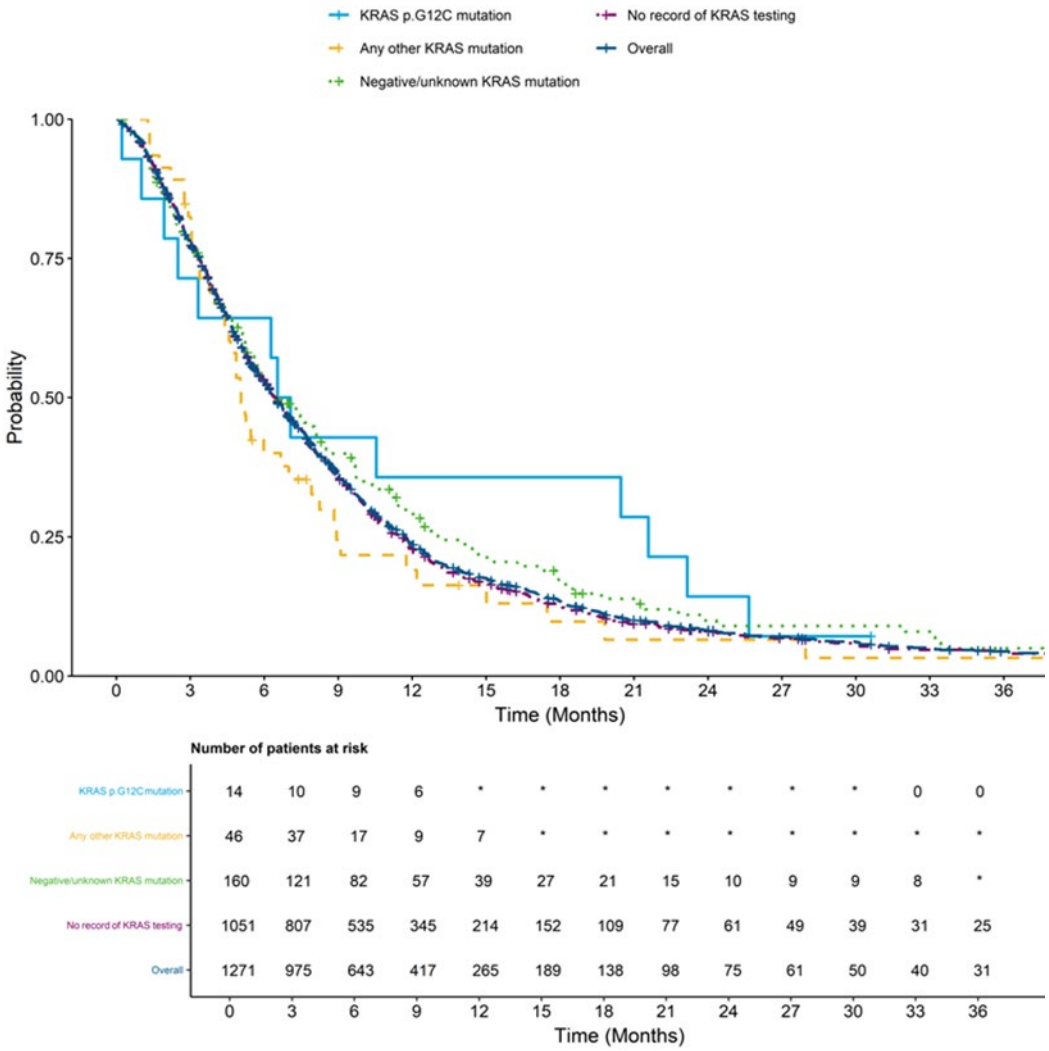
For the Committee's concern to materially affect the conclusion, KRAS G12C mutation status would need to be a strong prognostic factor specifically in patients receiving docetaxel. The available evidence does not support this. Exploratory analyses comparing outcomes by KRAS mutation status among docetaxel-treated patients show no significant differences in overall survival, time to treatment discontinuation, or time to next treatment, with minimal separation observed between Kaplan–Meier curves in Figure 8.

Figure 8: Unweighted KM plot for OS among patients who initiated docetaxel monotherapy, overall and stratified by *KRAS* mutation status



External evidence further supports the conclusion that KRAS mutation status is not a strong prognostic factor for overall survival in patients receiving standard treatments for advanced NSCLC. An analysis presented at ASCO 2022 (Nakajimam 2022) demonstrated highly comparable survival outcomes between KRAS-mutated and KRAS wild-type populations across multiple treatment classes, including chemotherapy. In the chemotherapy-only setting, median overall survival was 17.1 months in KRAS-mutated patients and 14.9 months in KRAS wild-type patients, with a hazard ratio of 1.02 (95% CI: 0.81–1.29), indicating no meaningful difference in outcomes.

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<table>
<tr><td></td><td>
These findings are consistent across immunotherapy-based and chemotherapy-based regimens, with hazard ratios close to 1 and no statistically significant differences observed. This provides external validation that KRAS mutation status does not materially influence survival outcomes in patients treated with docetaxel or similar chemotherapy regimens.

To further contextualise this uncertainty, Amgen sought input from seven UK clinical experts across major oncology centres regarding expected outcomes with docetaxel in KRAS-mutated versus non-mutated NSCLC. Appendix B – Clinical validation of KRASm outcomes contains the exact correspondence and responses received. In summary, consistent clinician feedback indicated no expectation of materially different survival outcomes by KRAS status in this setting.

Taken together, these findings suggest that the inclusion of patients with unknown KRAS mutation status in the CAS docetaxel cohort is unlikely to introduce bias of sufficient magnitude to alter decision making. Overall, Amgen considers that using CAS to inform relative efficacy across endpoints, including OS, provides the most internally consistent, externally valid, and decision-relevant approach. This approach:
• maintains internal consistency within the model
• reflects NHS clinical practice
• avoids compounding uncertainty from crossover-adjusted estimates
• is supported by convergent evidence across multiple independent analyses and clinical expert input

While the requested scenario analysis has been implemented, Amgen’s preferred base case remains the CAS-based comparative effectiveness analysis.
</td></tr>
<tr><td>3</td><td>
Additional analyses 3: to model PFS, using PFS from CodeBreaK 200 to inform PFS directly

This scenario has been implemented using the preferred models for extrapolating CodeBreaK 200 PFS as described in Amgen’s response to technical engagement. An exponential model is used for sotorasib and a log-logistic model for docetaxel. The scenario leads to a small increase in the ICER to £35,949/QALY (Table 10), the absolute QALYs in both arms decrease with a slightly larger decrease in the sotorasib arm. The results are largely insensitive to the distribution used to extrapolate PFS for each arm, PFS from CodeBreaK 200 is mature and thus the different parametric survival models lead to minimal variation in outcomes.

Table 10: Deterministic cost-effectiveness results for Additional analyses 3
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>Incremental QALYs (x1.7)</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>Docetaxel</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sotorasib</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£35,949</td></tr>
<tr><td colspan="7">Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.</td></tr>
</table>
</td></tr>
<tr><td>4</td><td>
Additional analyses 4: to model PFS, exploring the relationship between PFS and TTNTD from CodeBreaK 200 and using this to adjust the TTNTD curve. This should be applied to TTNTD from CAS RWE to produce a better estimate of PFS in CAS RWE. The relative PFS efficacy from CodeBreaK 200 should be applied to the sotorasib baseline curve to get the docetaxel curve
</td></tr>
</table>

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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Amgen have conducted a post-hoc analysis to derive TTNTD for the sotorasib arm of CodeBreaK 200, this analysis is presented against PFS in the sotorasib arm in Figure 9. The HR between PFS and TTNTD was estimated to be [redacted] (95% CI = [redacted] – [redacted]).

Figure 9: CodeBreaK 200 sotorasib Kaplan-Meier for PFS and TTNTD

[redacted]

Key: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TTNTD, time to next treatment or death.

In the Amgen base case TTNTD is modelled using a jointly fitted generalised gamma model, as discussed in **additional analysis 2**, it was considered inappropriate to apply a different HR to one arm of a jointly fitted model. Instead, an individually fitted model is used to extrapolate sotorasib PFS from CAS, the log-logistic model is used as it has the best statistical fit although all the parametric survival models underestimate the tail of the KM. The results of the scenario are presented in Table 11 and the result is largely insensitive to the distribution used to model sotorasib.

Table 11: Deterministic cost-effectiveness results for Additional analyses 4

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,447
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.						

5 **Additional analyses 5:** to model time to discontinuation or death (TTDD), extrapolating data from CodeBreaK 200

The TTDD data from CodeBreaK 200 was included in the cost-effectiveness model, along with parametric survival models fitted to the TTDD data for each arm. For the scenario the log-normal model was preferred for extrapolating the sotorasib arm. The log-normal was the best fitting model, and the other models with close AICs provided similar extrapolations. The best fitting model to the docetaxel CodeBreaK 200 TTDD data was the Gompertz, however this resulted in a small number of patients (2%) remaining on treatment long-term. The Weibull was preferred as it also had a good statistical fit but resulted in less than 1% of patients being on treatment at 2 years and leads to no patients on treatment at 3.5 years. The estimates with the Weibull model are still significantly

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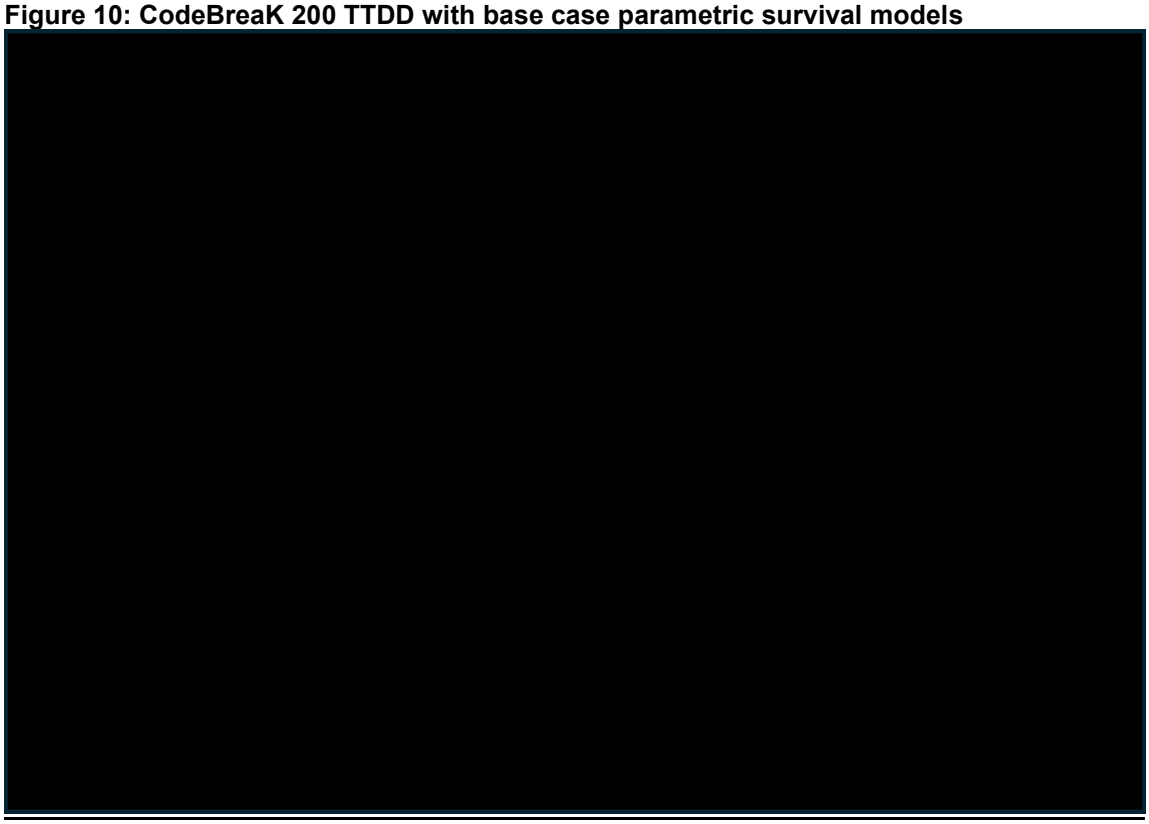
longer than what was observed in UK clinical practice in the UK RWE study, and reemphasis this study providing a more generalisable evidence base for both the sotorasib and docetaxel arm.

Figure 10: CodeBreaK 200 TTDD with base case parametric survival models



Key: KM, Kaplan-Meier; TTDD, time to discontinuation or death.

The results of the scenario are presented in Table 12. Using the CodeBreaK 200 data leads to a greater increase in docetaxel acquisition costs than sotorasib acquisition costs compared with CAS RWE. This leads to a reduction in incremental costs and in turn the ICER.

Table 12: Deterministic cost-effectiveness results for Additional analyses 5

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,213
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.						

6

Additional analyses 6: to model utilities, providing a mixed model repeated measures (MMRM) that includes both progression and time-to-death (TTD) covariates. TTD should be limited to 6 months before death. Alternatively, using treatment-independent utilities may also provide a useful estimate

To address Committee uncertainty related to the utility models used to estimate patient quality of life in the cost-effectiveness model, a number of additional analyses have been conducted. As

requested, we have fitted MMRM with progression and TTD covariates and a progression-based model with no treatment covariates. Additionally, we have fitted a progression-based model with an interaction term between progression and treatment. Although not listed in the ACD, it was an analysis suggested by a member of the Committee during the meeting following questions about the plausibility of quality of life benefits for sotorasib patients after disease progression. We describe the fitting and implementation of each model within the cost-effectiveness model.

Progression with treatment interaction term

Although not requested explicitly in the ACD, the plausibility of sotorasib providing a permanent utility benefit compared to those receiving docetaxel, particularly following progression, was questioned in the ACM. We believe that there is clear evidence to support treatment-specific utility values within CodeBreaK 200 and have conducted an additional analysis to address the Committee's uncertainty.

A MMRM was specified with an interaction term between treatment and progression. The estimated utility values from this specification are presented in Table 13. The resulting models estimate a pre-progression utility benefit associated with sotorasib of 0.067, this then decreases to a benefit of 0.042 after progression.

Table 13: Utility values from MMRM by progression and treatment arm

Covariate	Estimate
Sotorasib pre-progression	[redacted]
Sotorasib post-progression	[redacted]
Docetaxel pre-progression	[redacted]
Docetaxel post-progression	[redacted]

The clinical experts that attended the ACM suggested there were justifications for the quality of life of sotorasib and docetaxel patients to differ after progression. They suggested in the ACM that the greater toxicity of docetaxel will lead to acute AEs that will impact a patient's quality of life and this impact may extend beyond the point of disease progression and treatment discontinuation. The quality-of-life impact will reduce over time as the patient recovers from the AEs, but the presence of these AEs at the point of progression may explain the observed benefit in the post-progression responses between arms. The post-progression EQ-5D questionnaire in CodeBreaK200 was conducted within 30 days of progression and would therefore capture the lasting decrement.

Amgen believes that this analysis represents a robust estimate of the quality-of-life benefit associated with sotorasib compared to docetaxel. It also addresses the Committee concerns related to assuming the same benefit before and after progression. Amgen have therefore incorporated the approach into the updated base case, with the result being presented in Table 7.

To fully explore the robustness of our base case utility model we conducted a further scenario analysis exploring waning the docetaxel post-progression utility decrement within the cost-effectiveness model. In the ACM the clinical experts described that part of the utility decrement associated with docetaxel compared to sotorasib would be related to acute AEs. These AEs may result in a quality of life decrement beyond the point of progression but would improve over time. The treatment-related decrement is therefore most likely to apply to those who progress early while still on treatment. Patients who discontinue docetaxel while progression-free may see their AEs alleviate prior to progression and may not be subject to a further decrement. The scenario models the post-progression utility for docetaxel patients increase linearly over the first 12 months of the

model time horizon until it is equivalent with the sotorasib utility value. The results of the scenario are presented in Table 14.

Table 14: Deterministic cost-effectiveness results applying post-progression utility waning

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,858

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.

Progression + TTD model

The Committee requested a model capturing both progression status and a decrement related to TTD within 6 months of death. In all previous analyses the progression based and TTD based models are fitted to different datasets. Progression based models are fitted to the all EQ-5D data from CodeBreaK200. For TTD analyses all questionnaire responses that are ≤184 days old when a patient is censored are excluded from the dataset as it is unknown whether this result is within the 6-month period prior to death. There are limitations to fitting a progression + TTD model to either of these datasets:

- Fitting the model to the full dataset would require making assumptions around the responses within ≤184 days of censoring
- Using the restricted TTD data discards more than half the questionnaire responses and may provide a significantly different estimate of utility by progression status compared to those fitted to the full dataset

It was concluded it would be most appropriate to use the restricted TTD dataset, rather than make assumptions related to responses close to censoring that may bias the results. The outputs of the fitted model are provided in Table 15, the model results in an estimated progression-free utility value of 0.80 and a progressed disease utility value of 0.70. Within the cost-effectiveness model the TTD decrements are then applied to patients regardless of the state they were in prior to death.

Table 15: MMRM by progression and TTD

Covariate	Estimate	p-value
Progression-free (intercept)	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
TTD < 30 days	[redacted]	[redacted]
TTD < 3 months	[redacted]	[redacted]
TTD < 6 months	[redacted]	[redacted]

Key: TTD, time-to-death.

This specification does not consider any difference between treatment arm and thus when it is utilised in the cost-effectiveness model the decrements related to adverse events (AEs) and IV infusions are also included. The results for this scenario are presented in Table 16.

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Table 16: Deterministic cost-effectiveness results for progression + TTD scenario analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,303
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.						

Treatment independent, progression-based model

A MMRM with a single covariate capturing progression was fitted to fulfil the Committee's request for a treatment independent model. The resulting utility values are presented in Table 17 .

Table 17: Utility values from MMRM by progression and TTD

Covariate	Estimate
Progression-free	[redacted]
Progressed disease	[redacted]

Akaike information criterion (AIC) suggests that this model provides a poorer statistical fit to the observed data than other models such as the MMRM specified with progression and treatment (-4099.8 versus -4108.8). This specification also fails to consider any form of utility benefit associated with sotorasib compared to docetaxel. In the progression and treatment MMRM the statistically significant treatment covariate had an estimated coefficient of 0.061. Only considering progression disregards this observed benefit for patients entirely. Including decrements associated with AEs and IV infusion within the cost-effectiveness model still significantly underestimates the benefits of sotorasib to patients. The results for this scenario are presented in Table 18

Table 18: Deterministic cost-effectiveness results for treatment independent utilities

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£39,664
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier.						

Insert extra rows as needed

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.

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- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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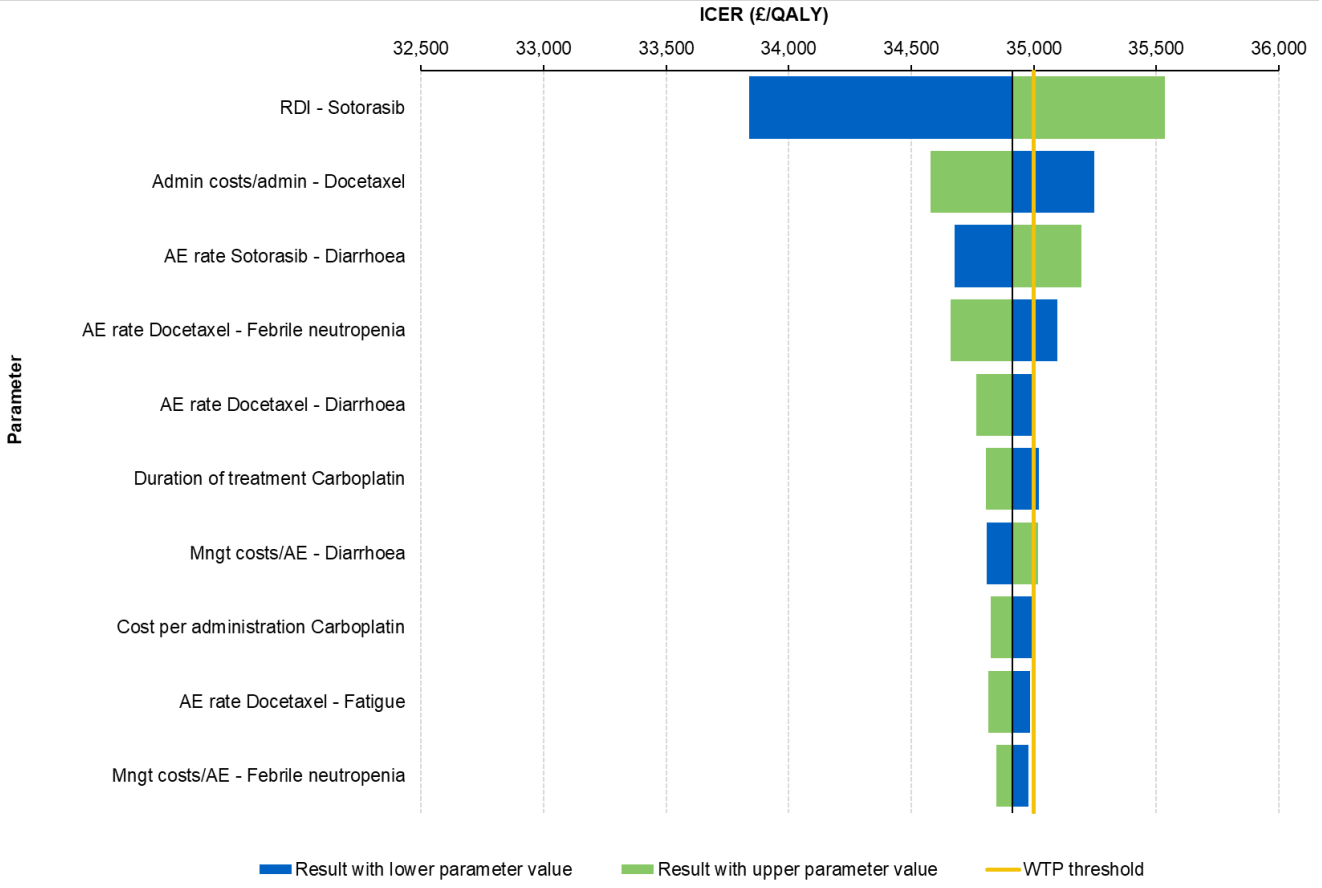
Appendix A – Sensitivity analyses around updated base case

The deterministic and probabilistic sensitivity analyses were rerun incorporating the updated company base case. Figure 11 presents the variation from the 10 most influential parameters on deterministic results.

Figure 11: Deterministic sensitivity analysis tornado diagram



Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; Mngt, management; QALY, quality-adjusted life year; RDI, relative dosing intensity; WTP, willingness-to-pay.

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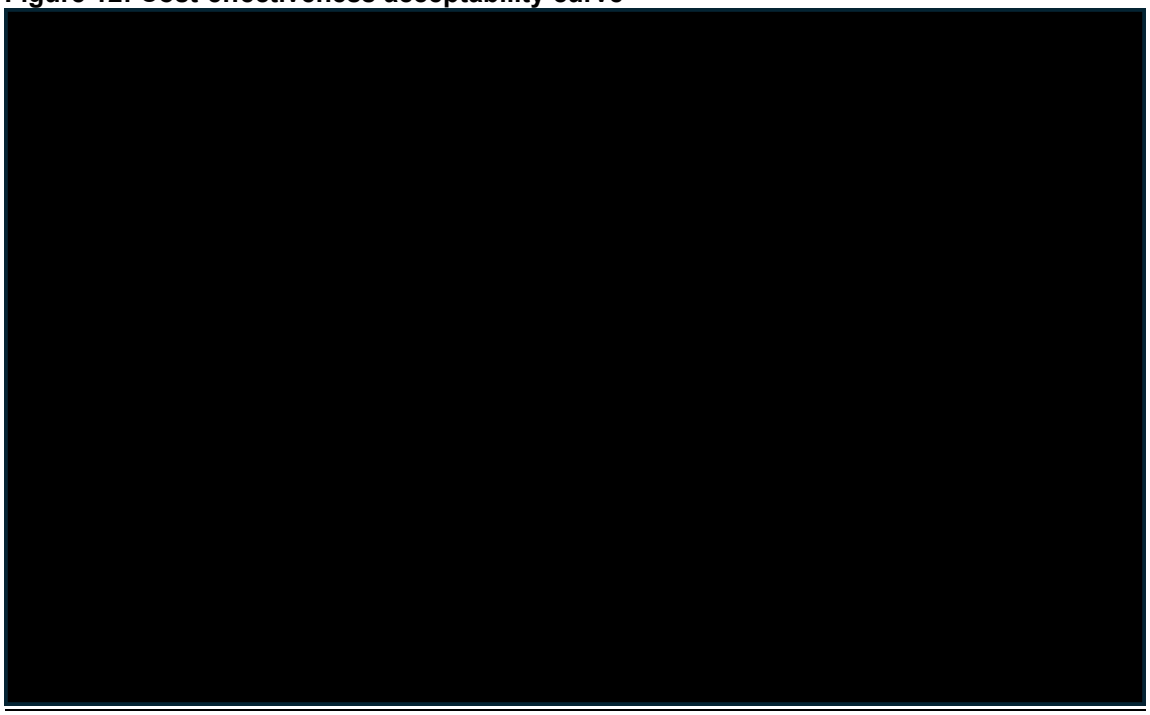
The probabilistic sensitivity analysis was conducted with 1,000 iterations. The mean results are presented in Table 19 and are consistent with the updated deterministic base case results.

Figure 12 presents the cost-effectiveness acceptability plane and the cost-effectiveness plan is presented on Figure 13.

Table 19: Probabilistic cost-effectiveness results with updated company base case

Technologies	Mean probabilistic costs (£)	Mean probabilistic QALYs	Incremental costs (£)	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	[redacted]	[redacted]				
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,217
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SM, severity modifier						

Figure 12: Cost-effectiveness acceptability curve



Key: QALY, quality-adjusted life year; WTP, willingness-to-pay.

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Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 26 March 2026. Please submit via NICE Docs.

Figure 13: Cost-effectiveness plane

Key: QALY, quality-adjusted life year; WTP, willingness-to-pay.

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Appendix B – Clinical validation of KRASm outcomes

1) **Email Survey to HCPs – March 2026**

Email Survey Subject: Amgen request for Clinical Input on Docetaxel Outcomes in NSCLC

Dear Dr [Surname],

I hope you are well.

We are currently preparing the Amgen response to the NICE Appraisal Consultation Document (ACD) for sotorasib in previously treated KRAS G12C-mutated non-small cell lung cancer (NSCLC). During the committee discussion, uncertainty was raised regarding the survival outcomes associated with docetaxel in the CAS real-world evidence study **(**Section 3.6 in Draft Guidance**)**.

To help ensure our response reflects clinical experience in UK practice, we are seeking brief written input from UK oncologists with relevant clinical experience who treat non-small cell lung cancer (NSCLC).

We would be grateful for your perspective on the following question:
Based on your clinical experience, how do survival outcomes for patients with KRAS-mutated NSCLC treated with docetaxel compare with those for patients without a KRAS mutation?

Your participation is entirely voluntary, and there is no obligation to respond. No honorarium is provided for this input.

Please provide your response by email before **Tuesday 24th March**. Any insights you provide will be used in aggregate to contextualise the evidence considered by the NICE committee and support further understanding of expected outcomes with docetaxel in routine care.

Many thanks in advance for your time and consideration.

Best wishes,

[Name]

Responses (Anonymised)

1. From my experience I do not see a difference in outcomes for patients with or without KRAS mutations treated with Docetaxel

2. The data on the predictive (with chemo and IO) and prognostic impact of KRAS G12C is variable. However the biggest data set we have was presented at ASCO 2022 by Eric Nakajima. It was an FDA pooled analysis from the trials and looked at about 1500 patients. There was no statistical difference in outcomes. Consequently the uncertainty about the mutation status of the Docetaxel treated patients is a moot point.

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See slide below:

3. In my view KRAS is a weak prognostic biomarker, in that without treatment they tend to fare less well. However, their response to IO better than KRAS WT. At the point of progression on IO the KRAS phenotype in my view do less well than KRAS wild type on 'standard' chemotherapy like docetaxel. I think there is nuance not captured in the NICE discussions - 1. SOC in well individuals in the UK is Docetaxel + nintedanib - therefore a docetaxel only regimen in RWE is a poorer PS / more co-morbid population and therefore would do less well and 2. One of the greatest strengths of Sotorasib is a chemotherapy-free period - very well received in terms of QoL from patients, pressure of resources and ultimately time to recover from maintenance chemotherapy and a chance to improve for subsequent docetaxel post sotorasib.

4. Based on clinical experience and available evidence, outcomes with docetaxel in previously treated advanced NSCLC are broadly similar between patients with KRAS-mutated disease and those without identifiable oncogenic drivers. KRAS mutation status has not been shown to meaningfully predict response or survival with docetaxel. In this setting, docetaxel is associated with modest outcomes, with median overall survival typically around 7–9 months and progression-free survival of approximately 2–4 months, consistent across molecular subgroups. In current UK practice, outcomes are more strongly influenced by factors such as performance status, disease burden, and prior treatment exposure (particularly prior chemo-immunotherapy), rather than KRAS status itself.

2) Excerpt from Sotorasib CAS RWE feedback – November 2025 (Amgen, Data on File)

Outcomes for docetaxel treatment in CAS RWE is largely in KRAS unknown patients. Outcomes for patients treated with sotorasib however are all in KRAS G12C positive patients. Is KRAS a prognostic factor for survival in lung cancer treated with standard of care?

Responses - Anonymised

1) Not prognostic, or a negative prognostic factor particularly when KRAS G12C inhibitors not available.

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2) It is not thought that KRAS G12C is a prognostic factor when comparing to the rest of the non-AGA population
3) KRAS can be prognostic but is heavily confounded.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal 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 provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Oncogene Cancer Research.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Company name:** Amgen **Amount:** £25,000 **Purpose of funding:** Amgen is one of four sponsors supporting patient empowerment programmes. This funding supports the development and delivery of long-form written patient stories on our website and the Patient Voices podcast shared via YouTube. The programmes cover a broad range of oncogene-driven lung cancers and are not specific to any single indication or product. Oncogene Cancer Research retains full editorial control over all content. **Status of funding:** Ongoing
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are deeply concerned by the draft recommendation not to make sotorasib routinely available for people with KRAS G12C mutation-positive advanced non-small-cell lung cancer. This has historically been a group with very limited targeted treatment options, as KRAS mutations were long considered “undruggable.” Treatments such as sotorasib represent one of the first advances specifically developed for this population. Without access to sotorasib, patients with a confirmed KRAS G12C mutation are effectively treated the same as those without it, which risks undermining

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Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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	progress in precision medicine and the value of identifying this mutation in the first place. For patients, this feels like a step backwards at a time when treatment should be becoming more personalised.
2	From a patient perspective, it is encouraging that the committee recognises that sotorasib improves progression-free survival compared with docetaxel (1.2), and that available evidence suggests it may also extend overall survival. From a patient perspective, this recognition already demonstrates meaningful benefit. Patients tell us that even small gains in survival are meaningful, and uncertainty in modelling should not outweigh the lived reality of the disease and the lack of alternatives. Uncertainty in economic and clinical modelling should not outweigh the severity of KRAS G12C lung cancer or the lack of alternatives. Patients experience the consequences of these decisions in real time.
3	Many people whose cancer has progressed after chemotherapy or immunotherapy face the prospect of intravenous chemotherapy such as docetaxel, which comes with frequent hospital visits, significant side effects, and major impacts on daily life. In contrast, sotorasib is an oral therapy that can be taken at home, reducing both the physical and emotional burden of treatment. Patients repeatedly describe this as life-changing – allowing them to maintain independence, spend more time with family, and feel less defined by their illness.
4	The committee notes uncertainty around quality-of-life benefits. From a patient perspective, these benefits are real and profound. Avoiding repeated chemotherapy infusions, hospital travel time and costs, and visible side effects such as hair loss has a huge impact on mental wellbeing, dignity, and daily functioning. Patients experience these burdens directly, and they matter.
5	Many people with lung cancer already face stigma and a perception that their disease is self-inflicted. Access to innovative targeted treatments signals that this patient group is equally deserving of modern cancer care and investment in research. Removing access to sotorasib sends the opposite message – that patients with one of the few treatable KRAS G12C lung cancers are left behind.
6	The draft guidance raises uncertainty about which of the two comparative analyses (CAS vs CB200) is most valid. Patients cannot wait for modelling debates. Both analyses indicate that sotorasib offers real benefits over chemotherapy. From the patient perspective, uncertainty about the precise magnitude of benefit should not close the door to treatment. Patients experience the impact on quality of life and independence firsthand.
7	The committee notes that the CB200 study is non-randomised. Patients value real-world evidence because it reflects what happens outside trials in the NHS. Even if not randomised, these data show how sotorasib works for people like them – improving tolerability, convenience, and quality of life. These experiences are critical to understanding the value of the treatment. The trial also allowed patients to switch from docetaxel to sotorasib. From a patient perspective, this reflects compassionate, responsive care: when a treatment is not working or is poorly tolerated, patients are offered an alternative that may provide benefit with fewer side effects. Importantly, this switching may actually underestimate the benefit of sotorasib in the trial, because patients initially assigned to docetaxel may not respond well before switching. Patients find it difficult to understand why this standard of care feature is framed as uncertainty rather than evidence of real-world value.
8	The draft guidance questions whether a severity weighting of 1.2x or 1.7x is appropriate. From a patient perspective, KRAS G12C advanced lung cancer is devastating and life-limiting. Patients experience rapid disease progression, severe symptoms, and a heavy treatment burden. The

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	higher weighting of 1.7x more accurately reflects the severity of the disease and the urgent need for effective, tolerable treatment. We note that NICE previously applied a 1.7 severity modifier for adagrasib (TA1076) for the same condition. The condition has not become less severe since that decision; patients' lived experiences remain the same. Using a lower weighting now risks underestimating the real-world impact on patients' lives and could unjustly restrict access to one of the few targeted options available.
9	The managed access period has generated valuable real-world evidence. Patients hope that this evidence will be fully considered. For many, sotorasib is the first therapy designed specifically for their cancer, and removing access would mean returning to older chemotherapy with heavier burdens. Uncertainty in modelling should be weighed against this urgent need.
10	The draft guidance notes concerns about treatment switching from docetaxel to sotorasib. From a patient perspective, this flexibility is a real benefit: it allows people to move to a therapy that is better tolerated, more effective, or less disruptive to daily life. Patients often describe the ability to switch as a sign that their treatment can be more responsive to their needs, reducing physical and emotional burden while maintaining hope and dignity.
11	The committee states that the recommendation "does not restrict access to treatment for some people over others" and therefore is not considered an equalities issue. From a patient perspective, we are concerned that this does not fully reflect how treatment decisions are experienced in real life. Even if a recommendation applies equally to all patients, its impact is not experienced equally. Intravenous chemotherapy such as docetaxel requires frequent hospital visits, time off work, travel, and support from others. For people in less secure employment, including manual or zero-hours roles, this can mean lost income, job insecurity, and significant additional stress. Oral treatment taken at home can reduce this burden considerably and allow patients to maintain more stability in their daily lives. We also note the committee's recognition that not everyone is tested for KRAS mutations, which may already create inequalities in access to targeted treatments. Removing access to a targeted therapy such as sotorasib risks compounding this issue by limiting options even when a mutation is identified. In addition, if sotorasib is not routinely available on the NHS, some patients may seek access privately or in other countries. This risks creating a two-tier system, where access to a targeted treatment is determined by financial means rather than clinical need. Finally, we note that the UK's National Cancer Plan places strong emphasis on improving quality of life and expanding access to targeted and personalised treatments. From a patient perspective, restricting access to one of the first targeted therapies for KRAS G12C lung cancer appears to be at odds with this aim. From a patient perspective, these are meaningful equality considerations. We encourage the committee to consider not only whether access is restricted in principle, but how the real-world impact of the recommendation may be experienced differently across patient groups.
12	From a patient perspective, it is also important to recognise that not all patients will accept further chemotherapy. People who have had a difficult experience with previous treatment, or who are concerned about the side effects of docetaxel, may choose to decline treatment altogether. For these patients, the availability of an oral targeted therapy can make the difference between continuing treatment or stopping entirely. Without this option, some patients may face the prospect of going without further active treatment, which can have a direct impact on both length and quality of life. We urge the stakeholders to consider this real world consideration.

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Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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13	For people living with KRAS G12C advanced lung cancer, this is not abstract. It determines whether future patients will have access to one of the first treatments developed specifically for their cancer, or whether they will be limited to older chemotherapy options. We respectfully ask the committee to continue working with stakeholders to address uncertainties so patients are not left without access to this important therapy.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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Response to the National Institute for Health and Care Excellence's Draft Guidance Consultation Document - Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (review of TA781) [ID6287]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are disappointed that the Committee's preliminary decision is not to recommend sotorasib in this indication.

- Sotorasib is the only targeted therapy currently available, in any indication, for patients in England, with KRAS G12C mutations. **There is massive unmet need in this patient population.**

- We note in paragraph 3.20, the Committee's acknowledgement, that the clinical effectiveness evidence suggests that sotorasib improved key outcomes for people with KRAS G12C mutation positive locally advances or metastatic NSCLC, whose disease has progressed on, or who cannot tolerate, platinum based chemotherapy or anti-PD-1/PD-L1 immunotherapy.

- We note that with uncertainty in the clinical effectiveness and economic modelling, the Committee has concluded that it is unable to determine the most likely cost effectiveness estimate.

- We are pleased to note in paragraph 3.18, additional analysis and information which the Committee would like to see, to make further assessment. We hope that this additional analysis will be undertaken and made available by the manufacturer and that with greater clarity, this therapy will be recommended and will be available for patients in this indication.

Roy Castle Lung Cancer Foundation
March 2026

Response to Draft Guidance Consultation
Single Technology Appraisal: Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

I am a consultant clinical oncologist specialising in thoracic malignancies and routinely treat patients with advanced non-small-cell lung cancer (NSCLC). I therefore have direct clinical experience managing patients with KRAS G12C-mutated disease and have treated patients with sotorasib through the managed access arrangement.

Unmet clinical need

There remains a significant unmet clinical need for patients with KRAS G12C mutation-positive locally advanced or metastatic NSCLC whose disease has progressed following platinum-based chemotherapy and anti-PD-1/PD-L1 immunotherapy. In routine NHS clinical practice, treatment options in this setting are extremely limited.

The principal systemic option remains docetaxel chemotherapy. However, docetaxel is associated with significant toxicity, including neutropenia, infection, fatigue and treatment-related hospitalisation. Many patients progressing after chemo-immunotherapy are older and have declining performance status, meaning that the tolerability of further cytotoxic chemotherapy is often poor. In practice, a substantial proportion of patients are either unable to receive docetaxel or experience considerable treatment-related morbidity.

As a clinical service lead for a service that manages 1/3rd of the UK lung cancer cases, I have seen the ability to deliver an oral, less toxic treatment had reduced hospital admissions for this patient population and impacted on the resource burden this costs the NHS.

The availability of a targeted therapy addressing a defined oncogenic driver represents an important therapeutic advance for this patient population.

Use of clinical trial data compared with real-world evidence

While I recognise that clinical trial data form the foundation of evidence assessment within technology appraisals, my interpretation of the draft guidance is that a significant proportion of the modelling and clinical interpretation relies heavily on data derived from the Codebreak trial.

Although this trial provides important evidence, I believe that the real-world evidence generated during the managed access period should be given substantial weight in the committee's considerations. Real-world data reflect how sotorasib is used in routine UK clinical practice, including the patient demographics, performance status, comorbidities and treatment patterns encountered in the NHS.

In my experience, this real-world evidence better reflects the population we treat in clinical practice and demonstrates that sotorasib can be delivered safely and effectively in this setting.

Clinical benefit observed in routine practice

During the managed access period, clinicians across the UK have gained meaningful experience using sotorasib in routine care. In my own practice, I have observed patients achieving tumour responses, disease stabilisation and symptomatic improvement while receiving treatment.

Importantly, the tolerability of sotorasib has been favourable compared with chemotherapy. As an oral targeted therapy, it is generally better tolerated and more manageable for patients who may already be significantly burdened by previous treatments and the symptoms of advanced lung cancer.

These clinical benefits often translate into improved symptom control, better functional status and meaningful improvements in quality of life for patients.

Interpretation of the economic modelling

I am not a health economist and therefore cannot comment in detail on the technical aspects of the economic model. However, from my interpretation of the draft guidance, I am concerned that the modelling may underestimate the overall clinical benefit that sotorasib provides in routine practice.

In particular, I believe that the modelling may not fully capture the real-world improvements in tolerability, symptom control and quality of life that clinicians observe when treating patients with this therapy. These factors are highly meaningful for patients with advanced NSCLC and may not always be adequately reflected in trial-derived modelling assumptions.

Importance of maintaining access to targeted therapies

The development of targeted therapies has transformed the management of lung cancer over the past decade. Identifying actionable molecular drivers and treating them with targeted therapies has become a central principle of modern oncology.

KRAS G12C represents a defined molecular subgroup of patients with historically limited targeted treatment options. The availability of sotorasib has therefore been an important step forward in addressing this unmet need.

Removing access to sotorasib after the managed access period would represent a significant step backwards in the treatment landscape for this patient population.

Impact on patients

From a clinical perspective, the most important consideration is the impact on patients. Since the introduction of sotorasib, many patients with KRAS G12C-mutated NSCLC have experienced meaningful benefits in terms of disease control, quality of life and hope for additional time with acceptable tolerability.

For a group of patients with otherwise limited options, the availability of a targeted therapy provides an important alternative to further chemotherapy or best supportive care.

Conclusion

In summary, there remains a clear unmet need for effective and tolerable treatments in patients with KRAS G12C mutation-positive advanced NSCLC following chemo-immunotherapy. Based on my clinical experience and the evidence generated during the managed access period, I believe that sotorasib provides meaningful benefit for this patient population.

I therefore encourage the committee to carefully consider the clinical experience and real-world evidence accumulated during the managed access period, and to reconsider the draft recommendation that sotorasib should not be used in the NHS for this indication.

Dr Qamar Ghafoor
Consultant Clinical Oncologist
University Hospitals Birmingham

NICE National Institute for Health and Care Excellence

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal Cornwall Hospitals NHS Trust

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Toby Talbot

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	There are limited treatment options for non-small cell lung cancer in the second line setting. Whilst Docetaxel remains standard of care and the control arm for most second line studies, including

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	CodeBreak200, the reality is that it is a treatment commonly avoided due to risk of toxicity and erosion of quality of life and patients are managed with supportive care (palliative) care alone.
2	Patients are generally aware of their mutation status and given that Sotorasib is a second line treatment, many patients will be aware that their tumour carries a KRAS G12C mutation whilst undergoing first line treatment in the expectation that they would be able to receive Sotorasib upon first line treatment failure. Removal of this option will cause significant emotional distress in that cohort of patients currently still receiving first line treatment.
3	The apparent lack of overall survival gain seen in CodeBreak200 does not match clinical experience – Sotorasib is generally well tolerated and easy to administer (oral treatment) and in my experience disease control (progression free survival) is better that we might have expected had we used Docetaxel. This leads to the conclusion that real world data will have a contribution to make when considering efficacy of Sotorasib.
4	Treatment crossover was allowed in CodeBreak200 which is widely recognised as a factor that can erode possible overall survival analysis in clinical trials.
5	The oncology community and NHS in general continues to develop genomic analysis/molecular diagnostics in the pursuit of precision medicine. Losing access to Sotorasib would mean some loss of momentum of this important and ongoing development of treatment for cancer.
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
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Single Technology Appraisal

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	ICAN – The International Cancer Advocacy Network
Conflict	N/A
Comments on the DG:	

- **Has all of the relevant evidence been taken into account?**

Although the relevant evidence may have been taken into account, we respectfully submit that it has not been weighted fairly. We would ask the Committee members to reconsider the provisional negative recommendation for sotorasib (Lumykras) in NICE TA ID6287 because:

a) Sotorasib is clearly superior to docetaxel—the current standard of care—by statistical measures such as PFS and OS, and by quality of life measures.

b) Regarding quality of life measures, sotorasib is easier to take—an oral tablet taken at home as opposed to a hospital or clinic-infused medicine requiring a trip by the patient to the office for the treatment. This is an additional burden on already burdened patients and can mean time off work just to take the medicine, not to mention the difficulties of travel if the patient is in bad shape.

c) Additionally, sotorasib is "easier to take" in the sense of fewer and less severe side effects that are easily manageable in contrast to the prolonged toxicity of docetaxel.

Our organization, ICAN, International Cancer Advocacy Network, is a US-based non-profit charitable organization serving late-stage cancer patients around the world, including throughout the United Kingdom. We have a particular specialty in rare lung cancers, including KRAS G12C lung cancer. ICAN's KRAS G12C lung cancer patients have consistently expressed relief and gratitude that sotorasib has the convenience of being an oral medication with manageable side effects.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Not at all. In fact, the evidence not only refutes the recommendations, but the language in the recommendations itself refutes the conclusions. Here is the relevant section:

"Clinical trial evidence shows that sotorasib increases how long people have before their condition gets worse compared with docetaxel. Clinical trial and real-world evidence suggest that sotorasib may increase how long people live

compared with docetaxel. But this is uncertain because of the limitations in the evidence and how the data was analysed.

“There are uncertainties with the economic model, including:

• which clinical evidence should be used in the model
• how the long-term benefits of sotorasib are modelled
• sotorasib's quality-of-life benefits.

“Because of the uncertainties in the clinical evidence and economic model, it is not possible to determine the most likely cost-effectiveness estimates for sotorasib. Further analyses are needed. So, sotorasib should not be used.”

The very language of the first two sentences in the Recommendations quoted above indicates that sotorasib is superior to docetaxel. Those unequivocal statements are then followed by language (“But this is uncertain….”) that does not in the least refute the evidence that the first two sentences were based on—PFS and OS derived from clinical trial and real world evidence—but rather raise questions regarding “limitations in the evidence and how the data was analysed.” That is followed by raising concerns regarding “uncertainties with the economic model.”

If the evidence is limited, and the economic model is uncertain, that argues for gathering additional evidence and fixing the economic model. It does not argue for denying sotorasib to the new patients who will need it. Indeed, the case of sotorasib’s superiority to docetaxel is made by the overwhelming evidence presented in the supporting documents that NICE has displayed, including that the company’s cost-effectiveness estimates were within NICE’s acceptable range of £20,000 to £30,000 per QALY gained. Although we argue below against the use of QALYs as inherently discriminatory against people with disabilities—in this case, cancer—it is notable that the economic data, along with the medical data, makes the case for the continued use of sotorasib for new patients.

- **Are the recommendations sound and a suitable basis for guidance to the NHS?**

Not at all. For the reasons elaborated upon immediately above (and immediately below regarding discrimination based on disability) we believe that the evidence would lead one to exactly the opposite conclusion than that reached in the Recommendations, namely that sotorasib should continue to be used, both for existing patients and for new patients, because it is clearly superior to docetaxel, the current standard of care. Further, while sotorasib is continuing to be used for both existing and new patients, NICE should gather the additional evidence and fix the economic model.

- **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?**

Yes. Since the recommendations are ultimately based on the use of the metric known as Quality Adjusted Life Years (QALYs), the recommendations are inherently discriminatory toward people with disabilities—in this case, cancer.

ICAN, International Cancer Advocacy Network, is opposed to QALYs in whatever form they are used precisely because they discriminate against those with cancer and other life-threatening or chronic diseases. Although we are an international organization, and have helped patients in every region of the United Kingdom, we are based in the United States where QALYs have been outlawed by majorities of our two major parties in Congress and legislation outlawing QALYs has been signed into law by Presidents of both parties—specifically, President George H.W. Bush who signed the Americans with Disabilities Act (ADA) in 1990 and President Barack Obama who signed the Affordable Care Act in 2010 (ACA, aka "Obamacare"). Both outlaw QALYs.

Thank you for your consideration of our comments. They are based on decades of experience dealing with cancer medicines and dealing with the side effects of those drugs on our patients—since our founding in 1996, ICAN has helped over 20,000 late-stage cancer patients around the world. The introduction of sotorasib has been a godsend to our KRAS G12C lung cancer patients and we hope that the great benefits of this drug will continue to be available to the patients that NICE serves.

Respectfully submitted,

ICAN, International Cancer Advocacy Network

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287] – EAG critique of company response to draft guidance

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. EAG critique of company response to draft guidance

This document contains the EAG critique of the company response to technical engagement.

1.1 Comment 1. Additional analyses 1: more detail about the company's approach to adjusting for treatment

1.1.1 Treatment switching – CodeBreaK 200

The company provided its rationale for preferring the two stage estimation (TSE) method, which was already provided in the company submission (CS). The company also restated the conclusion that the adjustment was insufficient to reduce the bias due to crossover:[1] *"Despite adjustment for treatment switching, the cross-over adjusted HR was unable to reliably estimate OS due to the high stochastic uncertainty introduced by the trial design. Prior to disease progression, sotorasib was associated with a substantial reduction in mortality (approximately [redacted] relative reduction; RR ≈ [redacted]), indicating a clear pre-progression survival advantage. The OS HR with and without adjustment suggest that docetaxel patients experience post-progression survival benefits sufficient to counterbalance the pre-progression benefits provided by sotorasib. With limited subsequent treatments available to patients there is no justification for docetaxel patients to have post-progression survival superior to sotorasib. This highlights that the unadjusted result is heavily influenced by crossover, and the confounding within the docetaxel arm heavily limits the ability to apply effective adjustment."*

EAG comment: As stated in the EAG report, the EAG continue to consider the TSE method to be valid.[2] As the company state, it is likely that switching post-progression improves survival. However, the company have provided no explanation as to why the adjustment is insufficient to address the bias. It might be that missing data on confounders, despite the company's attempts to identify all relevant ones, causes insufficient adjustment. It is also possible that most of the survival advantage due to sotorasib is pre-progression.

1.1.1 Propensity score analysis – CAS

The company provided the results of diagnostic tests for the standardised mortality ratio weighting (SMRW) method, which was already provided in the CAS technical report provided with the CS.[1] The company concluded that there was adequate adjustment for difference in baseline characteristics:[1] *"Following SMRW, the PS distributions between treatment groups appeared similar, and only BMI remained imbalanced (SMD = 0.221 in the 'missing/unknown' category)."* They also stated:[1] *"The ESS was 394 patients in the sotorasib treatment group and 392 patients in the docetaxel treatment group, indicating good overlap and limited loss of precision."*

EAG comment: The EAG continue to agree with the company that covariate balance was generally achieved. As stated in the EAG report, there might still be bias due to missing data on confounders, which the EAG expanded on in the critique of the technical engagement response by quoting the CAS technical report:[3] *"The company themselves in the Technical Report for the CAS RWE study identify the potential for residual confounding as a limitation: "The primary limitation of the study relates to two key eligibility criteria from the Managed Access Agreement for sotorasib that could not be replicated in the docetaxel cohort due to data source limitations: (a) evidence of KRAS G12C-mutated NSCLC at index date, and (b) no known brain metastases or symptomatically stable at index date if brain metastases were present. This could lead to bias in the estimated treatment effects if such criteria are prognostic of study outcomes and create systematic or uncontrolled differences between treatment*

cohorts" The EAG agreed with the company that:[3] "*... there is no clear evidence of an effect of mutation status on prognosis on docetaxel, but the evidence is sparce."* In the Technical report the company also state that any bias due to the presence of brain metastases might be mitigated by the exclusion of patients with ECOG > 2, and that there was adjustment for prior metastases. Nevertheless, these two characteristics, KRAS status and presence of brain metastases, which the company state could be cofounders, were not adjusted for, which could mean that there is residual bias.

1.2 Comment 2. Additional analyses 2: to model OS, applying the inverse crossover adjusted relative treatment effect from CodeBreaK 200 to the baseline curves of sotorasib from CAS RWE to generate the docetaxel curves

As requested by the committee in the draft guidance, the company provided a scenario analysis modelling OS by applying the inverse of the crossover-adjusted OS HR from CodeBreaK 200 to the baseline OS curve for sotorasib derived from CAS RWE. Nevertheless, the company presented various arguments against this approach and remains using CAS RWE to inform both absolute survival and relative efficacy in their updated base-case, including individually fitted log-logistic models (instead of jointly fitted generalised gamma models in their previous base-case).

EAG comment: While acknowledging that CAS RWE may better reflect absolute OS, the EAG continues to prefer randomised comparisons for estimates of relative treatment effects, because observational data typically remain at risk for unmeasured confounding (particularly unknown KRAS G12C mutation status and presence of brain metastases in the current appraisal). The EAG therefore updated its base-case by incorporating the baseline OS curve for sotorasib based on CAS RWE and by subsequently applying the inverse of the relative treatment effect derived from CodeBreaK 200 to estimate the relative effectiveness versus docetaxel.

The company preferred the individually fitted log-logistic curve to inform the baseline OS curve for sotorasib, based on the fit of its hazard profile to the observed hazard in CAS RWE. It also provided the best statistical fit to the observed data and good visual fit (CS Table 43 and company's DG response Figure 6). Although the EAG agrees on these arguments, it noted that the individual log-logistic resulted in higher 3-year ([redacted]) and 5-year OS ([redacted]) estimates for sotorasib compared to the company's initial base-case (i.e. 3-year OS [redacted] and 5-year OS [redacted]). Applying the inverse of the relative treatment effect derived from CodeBreaK 200 to the individually fitted log-logistic curve also resulted in higher 3-year ([redacted]) and 5-year OS ([redacted]) estimates for docetaxel compared to the company's initial base-case (i.e. 3 year OS [redacted] and 5-year OS [redacted]). This is particularly relevant because the clinical experts during the first appraisal committee meeting stated that the expected 3-year and 5-year OS estimates would be similar to those from the company's initial base case. The EAG therefore selects the individually fitted generalised gamma in its updated base-case to inform the baseline OS curve for sotorasib, as its 3-year and 5-year OS estimates for sotorasib ([redacted] and [redacted]) and docetaxel ([redacted] and [redacted]) were more closely aligned with the expected estimates of the clinical expert present at the meeting. The hazard profile of the generalised gamma also reasonably fitted the observed hazard in CAS RWE and it was amongst the better fitting curves in terms of statistical fit. The EAG explores the company's preferred individually fitted log-logistic curve to inform the baseline OS curve for sotorasib in a scenario analysis.

1.3 Comment 3. Additional analyses 3: to model PFS, using PFS from CodeBreaK 200 to inform PFS directly

As requested by the committee in the draft guidance, the company provided a scenario analysis informing PFS based on CodeBreaK 200. Individually fitted exponential and log-logistic models were

selected for sotorasib and docetaxel respectively to extrapolate PFS beyond the observed CodeBreaK 200 data.

EAG comment: The EAG appreciates the scenario analysis provided by the company, but maintains the approach of informing PFS using individually fitted log-logistic models fitted to the observed CodeBreaK 200 data for both sotorasib and docetaxel in its base-case.

1.4 Comment 4. Additional analyses 4: to model PFS, exploring the relationship between PFS and TTNTD from CodeBreaK 200 and using this to adjust the TTNTD curve.

As requested by the committee in the draft guidance, the company provided a scenario analysis informing PFS by first adjusting the sotorasib TTNTD from CAS RWE based on the relationship between PFS and TTNTD from CodeBreaK 200, and subsequently applying the inverse of the relative treatment effect for PFS in CodeBreaK 200 to the sotorasib baseline curve to estimate docetaxel PFS.

EAG comment: The EAG appreciates the scenario analysis provided by the company. Although acknowledging that using different evidence sources to inform the sotorasib baseline curves for PFS (CodeBreak 200) and OS (CAS RWE) may be suboptimal, the EAG maintains informing PFS by directly using PFS data from CodeBreaK 200 in its base-case as the company's scenario analysis is conditional on the questionable assumption that the relationship between PFS and TTNTD would be similar in CodeBreaK 200 and CAS RWE. The EAG explored the company's scenario analysis conditional on its updated base-case. Notably, contrary to the relatively small impact on the company's base-case, this scenario analysis substantially increased the ICER conditional on the EAG base-case.

1.5 Comment 5. Additional analyses 5: to model time to discontinuation or death (TTDD), extrapolating data from CodeBreaK 200

As requested by the committee in the draft guidance, the company provided a scenario analysis informing TTDD by extrapolating data from CodeBreaK 200. The company preferred the log-normal model for extrapolation of TTDD for sotorasib and the Weibull model for docetaxel.

EAG comment: The EAG reiterates that it questions the suitability of CAS RWE to inform TTDD for the reasons highlighted in section 4.2.5 of the EAG report, and prefers informing TTDD directly by fitting parametric survival curves to the observed TTD(D) data in CodeBreaK. However, it noted that, apart from the company's arguments for selecting their preferred parametric survival models for the extrapolation of TTDD from CodeBreaK 200, no details (i.e. NICE DSU TSD 19) were provided for the EAG to assess which models would be the most appropriate. In absence of these details, the EAG adopted the company's scenario analysis using the log-normal model for sotorasib and the Weibull model for docetaxel in its updated base-case.

1.6 Comment 6. Additional analyses 6: to model utilities, providing a mixed model repeated measures (MMRM) that includes both progression and time-to-death (TTD) covariates. TTD should be limited to 6 months before death.

Alternatively, using treatment-independent utilities may also provide a useful estimate.

The company provided an additional analysis including a MMRM specified with an interaction term between treatment and progression to assess the plausibility of a HRQoL benefit for sotorasib patients after disease progression. This analysis was included in their updated base-case. Additionally, the company explored scenario analyses including 1) waning of the docetaxel post-progression utility decrement, 2) a MMRM including both progression status and time to death, and 3) a treatment independent progression-based MMRM.

EAG comment: The EAG appreciates the various analyses provided by the company. It considers the MMRM including both progression status and TTD to be suboptimal for informing HRQoL in the economic model, as the limitations highlighted by the company (i.e. fitting the model to either of the datasets: the full CodeBreaK 200 dataset for progression or the restricted TTD dataset) likely negatively impact the credibility of the estimated utility values. Further, based on evidence provided by the company during technical engagement and following the committee discussion, the EAG agrees that the use of treatment-dependent utility values for the progression-free health state would be appropriate. The appropriateness of using treatment-dependent utility values post-progression is, however, unclear to the EAG. Based on the limited information provided by the company to justify their updated base-case approach of estimating utility values based on progression status, treatment arm and an interaction term (i.e. no full model specification or regression diagnostics were provided), it is difficult for the EAG to assess the adequacy of the underlying MMRM. The company's base-case MMRM does have the better statistical fit compared to other MMRMs explored. However, compared to the MMRM including progression status only, it seems slightly better in terms of AIC, whereas it seems slightly worse in terms of BIC. Additionally, clinical experts during the appraisal committee meeting suggested that the greater toxicity impact of docetaxel may extend beyond the point of disease progression and treatment discontinuation, but that no post-progression utility difference between treatments would be expected once the side effects stopped. Taking these considerations all together, the EAG prefers using the best statistically fitting MMRM in its updated base-case, including progression status, treatment and an interaction term (in line with the company's base-case). In addition, it adopts the company's analysis including linear waning of the docetaxel post-progression utility decrement over a period of 12 months in its base-case, as this is considered a reasonable reflection of what was mentioned by the clinical experts during the appraisal committee meeting.

1.7 Updated deterministic and probabilistic company and EAG base-case

Table 1: Updated deterministic and probabilistic company and EAG base-case

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Deterministic results								
Company's updated base-case								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£59,351	-1.07	-0.53
				1.2	[redacted]	£49,459	-0.96	-0.42
				1.7	[redacted]	£34,912	-0.69	-0.15
EAG_1: use the individually fitted generalised gamma from CAS RWE to inform sotorasib OS, and the inverse HR from CodeBreaK 200 to inform docetaxel OS.								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£118,018	-1.31	-0.79
				1.2	[redacted]	£98,348	-1.26	-0.73
				1.7	[redacted]	£69,422	-1.12	-0.60
EAG_2: use the individually fitted log-logistic from CodeBreaK 200 to inform sotorasib and docetaxel PFS								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£60,804	-1.08	-0.54
				1.2	[redacted]	£50,670	-0.97	-0.44
				1.7	[redacted]	£35,767	-0.71	-0.17
EAG_3: use the individually fitted log-normal from CodeBreaK 200 to inform sotorasib TTDD, and the individually fitted Weibull from CodeBreaK for docetaxel TTDD								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£59,862	-1.09	-0.54
				1.2	[redacted]	£49,885	-0.98	-0.43
				1.7	[redacted]	£35,213	-0.71	-0.16
EAG_4: use treatment dependent pre- and post-progression utilities, including post-progression utility waning								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£60,959	-1.09	-0.55
				1.2	[redacted]	£50,799	-0.98	-0.44
				1.7	[redacted]	£35,858	-0.72	-0.18
EAG_5: include treatment waning starting at 2 years with gradual decline over 5 years								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£62,190	-1.10	-0.56
				1.2	[redacted]	£51,825	-0.99	-0.45
				1.7	[redacted]	£36,583	-0.73	-0.19
EAG base-case								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£127,824	-1.16	-0.70
				1.2	[redacted]	£106,520	-1.12	-0.66
				1.7	[redacted]	£75,190	-1.01	-0.55
Probabilistic								
Company's updated base-case								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£59,869	-1.10	-0.55
				1.2	[redacted]	£49,891	-0.99	-0.44

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
				1.7	[redacted]	£35,217	-0.71	-0.16
EAG's updated base-case								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£123,023	-1.13	-0.68
				1.2	[redacted]	£102,519	-1.08	-0.64
				1.7	[redacted]	£72,367	-0.98	-0.53
CAS = Cancer Analysis System; CS = company submission; EAG = Evidence Assessment Group; FV = fixing violation; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MJ = matters of judgement; MMRM = mixed models for repeated measures; NHB = net health benefit; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RWE = real-world evidence; TTD = time to treatment discontinuation; WTP = willingness-to-pay								

1.8 Updated deterministic and probabilistic scenario analyses

Table 2: Updated deterministic and probabilistic scenario analyses (conditional on updated EAG base-case)

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Deterministic results								
Updated EAG base-case								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£127,824	-1.16	-0.70
				1.2	[redacted]	£106,520	-1.12	-0.66
				1.7	[redacted]	£75,190	-1.01	-0.55
EAG_6: use the individually fitted log-logistic from CAS RWE to inform sotorasib OS								

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£98,319	-1.11	-0.64
				1.2	[redacted]	£81,932	-1.05	-0.59
				1.7	[redacted]	£57,834	-0.91	-0.45
EAG_7: use the adjusted TTNTD from CAS RWE to inform sotorasib PFS, and use the inverse HR from CodeBreaK 200 to inform docetaxel PFS.								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£142,156	-1.38	-0.84
				1.2	[redacted]	£118,464	-1.33	-0.80
				1.7	[redacted]	£83,621	-1.22	-0.68
Probabilistic								
Updated EAG base-case								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£123,023	-1.13	-0.68
				1.2	[redacted]	£102,519	-1.08	-0.64
				1.7	[redacted]	£72,367	-0.98	-0.53
EAG_6: use the individually fitted log-logistic from CAS RWE to inform sotorasib OS								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£98,730	-1.10	-0.64
				1.2	[redacted]	£82,275	-1.04	-0.58
				1.7	[redacted]	£58,076	-0.90	-0.44
EAG_7: use the adjusted TTNTD from CAS RWE to inform sotorasib PFS, and use the inverse HR from CodeBreaK 200 to inform docetaxel PFS.								
Docetaxel	[redacted]	[redacted]	-		-	-	-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£151,872	-1.36	-0.84

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
				1.2	[redacted]	£126,560	-1.32	-0.79
				1.7	[redacted]	£89,337	-1.21	-0.69

CAS = Cancer Analysis System; CS = company submission; EAG = Evidence Assessment Group; FV = fixing violation; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MJ = matters of judgement; MMRM = mixed models for repeated measures; NHB = net health benefit; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RWE = real-world evidence; TTD = time to treatment discontinuation; WTP = willingness-to-pay

2. References

[1] National Institute for Health and Care Excellence. *Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]: Draft comments guidance form*. London: NICE, 2026. 31p.

[2] Armstrong N, Witlox W, Ramaekers B, Holly T, Sugden B, Katsipataki M, et al. *Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]: a Single Technology Assessment [PostFAC]*. York: Kleijnen Systematic Reviews Ltd., 2026. 126p.

[3] Armstrong N, Witlox W, Ramaekers B, Holly T, Sugden B, Katsipataki M, et al. *Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]: EAG critique of company response to technical engagement*. York: Kleijnen Systematic Reviews Ltd., 2026. 16p.

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS England

Sotorasib for previously treated KRAS G12C mutation-positive, locally advanced or metastatic non-small-cell lung cancer – data review

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS England. Its purpose is to collect, collate and analyse data on patients with cancer, congenital anomalies, and rare diseases. It provides robust surveillance to monitor and detect changes in health and disease in the population. NDRS is a vital resource that helps researchers, healthcare professionals and policy makers make decisions about NHS services and the treatments people receive.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

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1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of sotorasib in treating KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer. The appraisal committee highlighted clinical uncertainties in the evidence submission. As a result, they recommended the commissioning of sotorasib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England have evaluated the real-world treatment effectiveness of sotorasib in the CDF population, during the managed access period. This report presents the results of the use of sotorasib in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The collection and follow up of real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99% of patients and 95% of patient outcomes reported in the SACT dataset. NHS England are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

The NHS England Blueteq® system was used to provide a reference list of all patients with an application for sotorasib for previously treated KRAS G12C mutation-positive, locally advanced or metastatic non-small-cell lung cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to NDRS' routinely collected SACT data to provide SACT treatment history.

Between 3 March 2022 and 30 June 2023, 420 applications for sotorasib were identified in the Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 347 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

347/350 (99%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 5.6 months [95% CI: 4.8, 6.4] (170 days) (N=347). 47% of patients were still receiving treatment at 6 months [95% CI: 41%, 53%], 26% of patients were still receiving treatment at 12 months [95% CI: 21%, 32%] and 18% of patients were still receiving treatment at 18 months [95% CI: 12%, 25%].

At data cut off, 61% (N=213) of patients were identified as no longer being on treatment. Of these 213 patients:

- 49% (N=104) of patients stopped treatment due to disease progression
- 20% (N=42) of patients died not on treatment
- 14% (N=29) of patients stopped treatment due to acute toxicity
- 8% (N=16) of patients died on treatment
- 6% (N=13) of patients chose to end their treatment
- 2% (N=4) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 2% (N=4) of patients were treated palliatively and did benefit from the treatment they received
- Less than 1% (N=1) of patients were treated palliatively and did not benefit from the treatment they received

The median OS was 10.2 months [95% CI: 8.9, 12.1] (310 days) (N=347). OS at 6 months was 69% [95% CI: 63%, 73%], 12 months OS was 44% [95% CI: 38%, 50%] and OS at 18 months was 34% [95% CI: 28%, 41%].

Sensitivity analyses were conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with sotorasib for previously treated KRAS G12C mutation-positive, locally advanced or metastatic non-small-cell lung cancer in the CDF. It evaluated treatment duration, OS and treatment outcomes for all patients treated with sotorasib for this indication.

Introduction

Lung cancer (ICD-10: C34) accounts for 8% of all cancer diagnoses in England. In 2021, 39,605 patients were diagnosed with lung cancer (males 20,301, females 19,304)[2].

- sotorasib is recommended for use within the Cancer Drugs Fund as an option for treating KRAS G12C mutation-positive locally advanced or metastatic non-small-cell lung cancer in adults whose disease has progressed on, or who cannot tolerate, platinum-based chemotherapy or anti-PD-1/PD-L1 immunotherapy
    - it is recommended only if the conditions in the managed access agreement for sotorasib are followed[3]

2. Background to this report

Using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England's ambitions of monitoring cancer care and outcomes across the patient pathway. NHS England produces routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access using Systemic Anti-Cancer Therapy (SACT) data collected by the National Disease Registration Service (NDRS).

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHS England analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NDRS.

NICE Appraisal Committee review of sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer [TA781]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of sotorasib (Amgen Limited) in treating KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer [TA781] and published guidance for this indication in March 2022[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of sotorasib for the treatment of KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer through the CDF for a period of 19 months, from March 2022 to September 2023. The drug will be funded through the CDF until NICE publish their final guidance.

During the CDF funding period, results from ongoing clinical trials (CodeBreaK100 (CB100)[7] and CodeBreaK 200 (CB200)[8]) evaluating sotorasib in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the CB100 and CB200 clinical trials is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the CB100 and CB200 clinical trials[7,8].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection:

- the use of an unanchored indirect treatment comparison
- the utility and disutility values used in the economic model
- the magnitude of any treatment waning
- whether the technology meets the end of life (EoL) 3-month extension criterion

Overall survival and treatment duration were not an area of clinical uncertainty but have been included in this report.

Other uncertainties listed above will be included in the CB100 and CB200 clinical trial results.

Approach

Upon entry to the CDF, representatives from NHS England, NICE and the company (Amgen Limited) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA sets out the real-world data to be collected and analysed to support the NICE re-appraisal of sotorasib. It also detailed the eligibility criteria for patient access to sotorasib through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for sotorasib, approved through Blueteq® and followed up in the SACT dataset collected by NDRS in NHS England.

3. Methods

CDF application – identification of the cohort of interest

NHS England collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NDRS has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS England, through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England.

NDRS in NHS England collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Sotorasib clinical treatment criteria

- the application for sotorasib is being made by and the first cycle of systemic anti-cancer therapy with sotorasib will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- the patient has locally advanced or metastatic non-small cell lung cancer
- the patient has a histologically or cytologically confirmed diagnosis of non-small cell lung cancer that has been shown to exhibit a KRAS G12C mutation using a validated assay and determined on a tumour tissue biopsy or a plasma specimen (liquid biopsy) or both
- completion of the checklist regarding the status of the patient's lung cancer with respect to other actionable mutations in NSCLC and if present that all commissioned targeted therapies have been fully explored
- the patient has been treated with platinum doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy
- the patient has not been previously treated with a drug specifically targeting the KRAS G12C mutation unless the patient has received sotorasib via a company early access scheme and the patient meets all the other treatment criteria on this form
- the patient has an ECOG performance status (PS) score of 0 or 1
- the patient either has no known brain metastases or if the patient does have brain metastases then the patient is symptomatically stable before staring sotorasib
- sotorasib will be used as monotherapy
- the clinician is aware of the side-effects of sotorasib including the risks of developing interstitial lung disease and hepatotoxicity
- the clinician is aware that proton pump inhibitors and H2 receptor antagonists reduce absorption of sotorasib and should not be co-administered with sotorasib but if an acid-reducing agent cannot be avoided, sotorasib should be administered >4hrs before and >10hrs after a local antacid
- the patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment whichever is the sooner
- a formal medical review as to how sotorasib is being tolerated will be done before the start of the second month of treatment and the next review to determine whether treatment with sotorasib should continue or not will be scheduled to occur at least by the end of the second month of therapy
- when a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, I will complete a treatment break approval form to restart treatment, including as appropriate if the patient has had an extended break on account of Covid-19
- sotorasib will be otherwise used as set out in its Summary of Product Characteristics (SPC)

CDF applications – de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

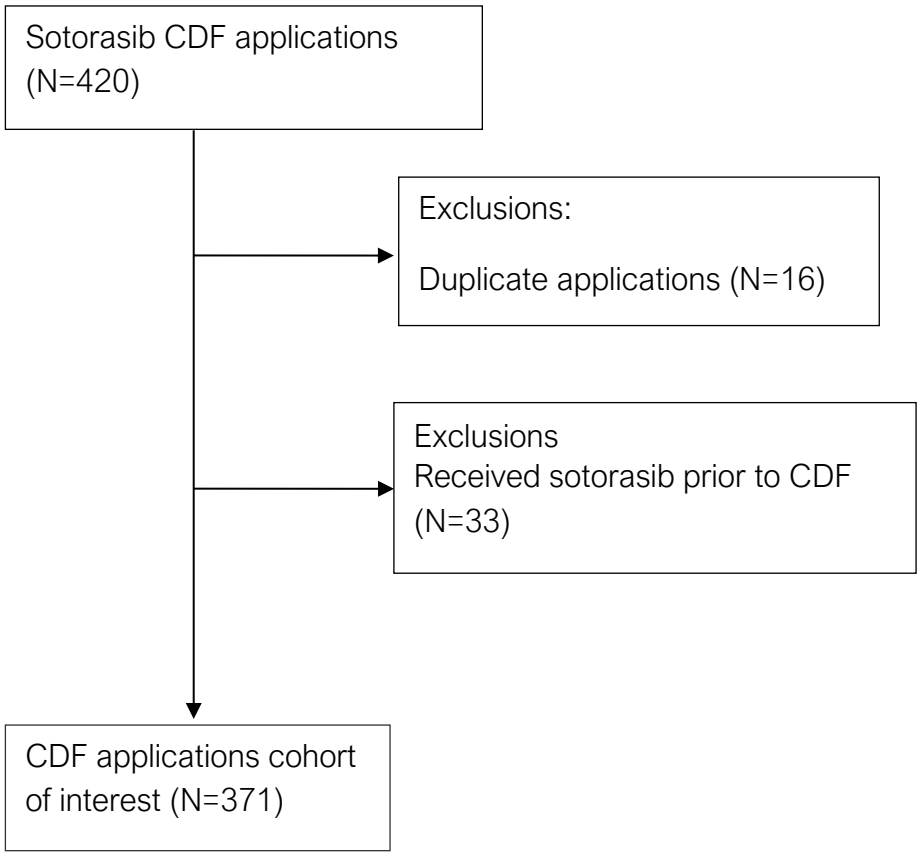
Initial CDF cohorts

The analysis cohort is limited to the date sotorasib entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 3 March 2022 to 30 June 2023. A snapshot of SACT data was taken on 7 October 2023 and made available for analysis on 16 October 2023 and includes SACT activity up to 30 June 2023. Tracing the patients' vital status was carried out on 14 November 2023 using the Personal Demographics Service (PDS)[1].

There were 420 applications for CDF funding for sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer between 3 March 2022 and 30 June 2023 in the NHS England Blueteq database. Following de-duplication this relates to 404 unique patients. Thirty-three of these patients were excluded as they received sotorasib prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer between 3 March 2022 and 30 June 2023



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for sotorasib in the Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[9] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[9] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Sotorasib is administered orally. As such, treatment is generally administered in a healthcare facility and healthcare professionals can confirm that the prescribing of treatment has taken place on a specified date. A duration of 28 days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next. Sotorasib is a 28-day cycle consisting of one administration of 28 tablets.

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patient's censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patient's date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61
- there is no further SACT records for the patient following a three-month period

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

At the date patients were traced for their vital status as patients are confirmed as alive on this date.

Lost to follow-up:

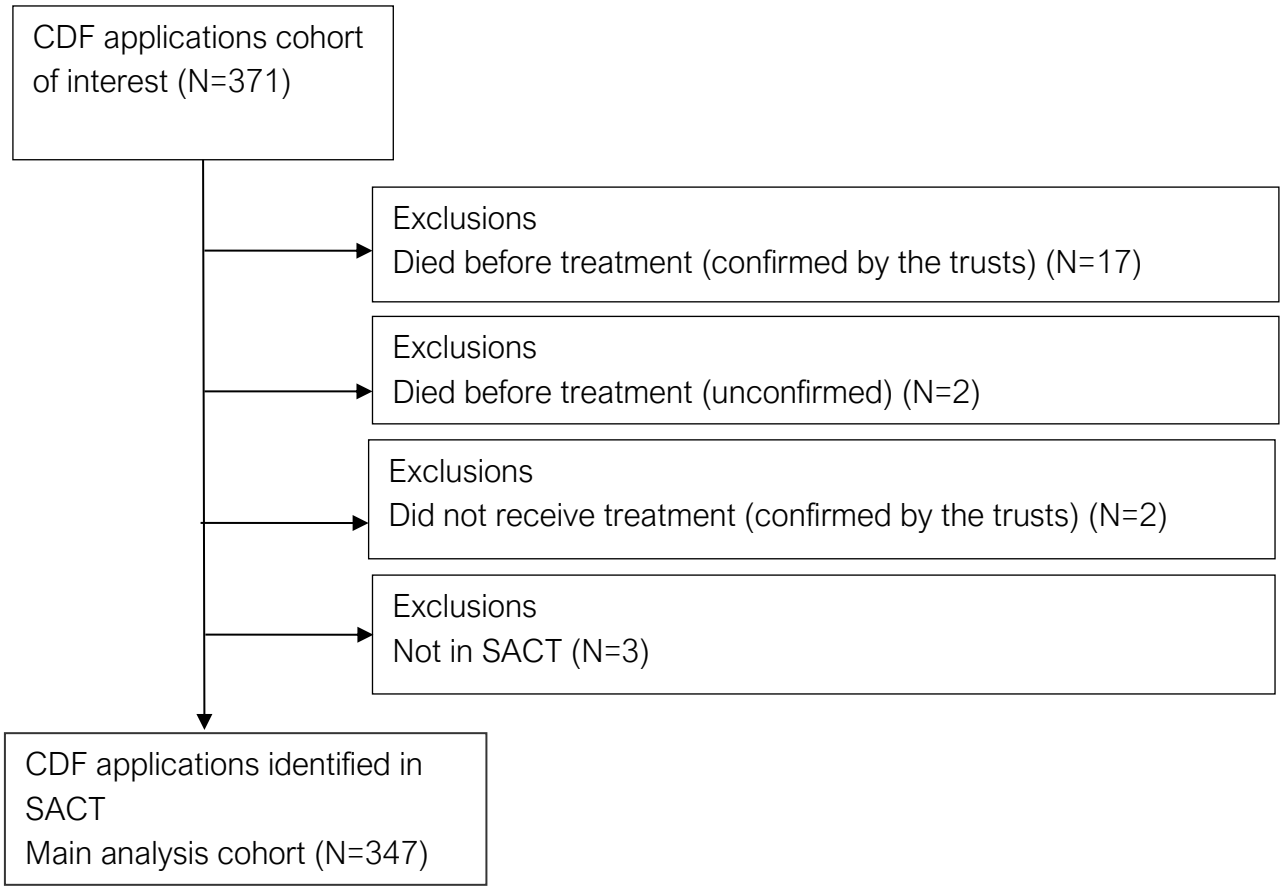
Where we cannot determine whether a patient is alive or not on the censor date; this happens when a patient cannot be successfully traced, for example, because they have emigrated or because important identifiers such as NHS number or date of birth contain errors, the patient's record will be censored at their last known treatment date in SACT. This is the date the patient was last known to be alive.

4. Results

Cohort of interest

Of the 371 applications for CDF funding for sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer, two patients did not receive treatment, 19 patients died before treatment and three patients were missing from SACT[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer between 3 March 2022 and 30 June 2023



[a] Of the two patients that did not receive treatment, both were confirmed by the relevant trust. Of the 19 patients that died before treatment, 17 were confirmed by the relevant trust as deaths before treatment by the SACT data liaison team.

A maximum of 350 sotorasib records are expected in SACT for patients who were alive, eligible, and confirmed to have commenced treatment (Figure 2). 99% (347/350) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 74% complete.

Table 1: Completeness of key SACT data items for the sotorasib cohort (N=347)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	74%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with sotorasib in at least three months[10]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 213 patients. Of these, 202 (95%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=213)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	95%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. All Blueteq fields are 100% complete.

Table 3: Completeness of Blueteq key variables (N=347)

Variable	Completeness (%)
Histological or cytological confirmed diagnosis of NSCLC, shown to exhibit a KRAS G12C mutation	100%
Mutations in NSCLC	100%
KRAS G12C treatment criteria	100%
Brain/CNS metastases	100%
Platinum doublet chemotherapy and/or PD-1, PD-L1 targeted therapy	100%

Patient characteristics

The median age of the 347 patients receiving sotorasib for the treatment of previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer was 69 years; the median age was 70 years and 69 years for males and females respectively.

Table 4: Patient characteristics (N=347)

Patient characteristics[b]			
		N	%
Gender	Male	127	37%
	Female	220	63%
Age	<40	2	1%
	40 to 49	15	4%
	50 to 59	49	14%
	60 to 69	112	32%
	70 to 79	140	40%
	80+	29	8%
Performance status at the start of regimen	0	29	8%
	1	213	61%
	2	16	5%
	3	0	0%
	4	0	0%
	Missing	89	26%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items.

Table 5: Distribution of key Blueteq data items (N=347)

Blueteq data items[c]		N	%
Histological or cytological confirmed diagnosis of NSCLC, shown to exhibit a KRAS G12C mutation	Tumour tissue biopsy only	329	95%
	Plasma specimen (liquid biopsy) only	12	3%
	Both tumour tissue and plasma specimen	6	2%
Mutations in NSCLC	No other actionable mutation is known to be present	343	99%
	The NSCLC has an EGFR mutation and all appropriate targeted therapies have been explored	2	1%
	The NSCLC has a BRAF mutation and appropriate targeted therapies have been explored if available	2	1%
	The NSCLC has a ROS1 gene rearrangement, and all appropriate targeted therapies have been explored	0	0%
	The NSCLC has an ALK gene rearrangement, and all appropriate targeted therapies have been explored	0	0%
	The NSCLC has a MET exon 14 skipping alteration and appropriate targeted therapies have been explored if available	0	0%
	The NSCLC has a RET gene fusion rearrangement and appropriate targeted therapies have been explored if available	0	0%

[c] Figures may not add to 100% due to rounding.

Blueteq data items		N	%
Platinum doublet chemotherapy and/or PD-1, PD-L1 targeted therapy	the patient has received 1st line combination treatment of platinum doublet chemotherapy and immunotherapy for locally advanced or metastatic NSCLC with or without 2nd line cytotoxic chemotherapy	145	42%
	the only treatment that the patient has received is platinum based cytotoxic chemotherapy for locally advanced or metastatic NSCLC with or without 2nd line cytotoxic chemotherapy	82	24%
	the only treatment that the patient has received is 1st line immunotherapy monotherapy for locally advanced or metastatic NSCLC	79	23%
	the patient has received 1st line platinum based cytotoxic chemotherapy for locally advanced or metastatic NSCLC followed by 2nd line immunotherapy with or without further cytotoxic chemotherapy	26	7%
	the patient has received 1st line immunotherapy monotherapy for locally advanced or metastatic NSCLC followed by 2nd line cytotoxic chemotherapy with or without 3rd line cytotoxic chemotherapy	15	4%
KRAS G12C treatment criteria	The patient has not been previously treated with a drug specifically targeting the KRAS G12C mutation	347	100%
	The patient has received sotorasib via a company early access scheme and the patient meets all the other treatment criteria on this form	0	0%
Brain/CNS metastases	The patient has never had known brain/CNS metastases	271	78%
	The patient has had brain/CNS metastases treated before with surgery/radiotherapy and is currently symptomatically stable	54	16%
	The patient has brain secondaries which have not been treated with surgery/radiotherapy and is currently symptomatically stable	22	6%

Treatment duration

Of the 347 patients with CDF applications, 213 (61%) were identified as having completed treatment by 30 June 2023 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with sotorasib in at least three months (see Table 10). The median follow-up time in SACT was 4.2 months (127 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 19 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 20 months. SACT follow-up ends 30 June 2023.

Table 6: Breakdown by patients' treatment status [d,e,f]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	165	48%
Patient died – on treatment	16	5%
Treatment stopped	32	9%
Treatment ongoing	134	39%
Total	347	100%

Table 7: Treatment duration at 6, 12 and 18-month intervals

Time period	Treatment duration (%)
6 months	47% [95% CI: 41%, 53%]
12 months	26% [95% CI: 21%, 32%]
18 months	18% [95% CI: 12%, 25%]

[d] Figures may not sum to 100% due to rounding.
[e] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[f] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

The Kaplan-Meier curve for treatment duration is shown in Figure 3. The median treatment duration for all patients was 5.6 months [95% CI: 4.8, 6.4] (170 days) (N=347).

Figure 3: Kaplan-Meier treatment duration (N=347)

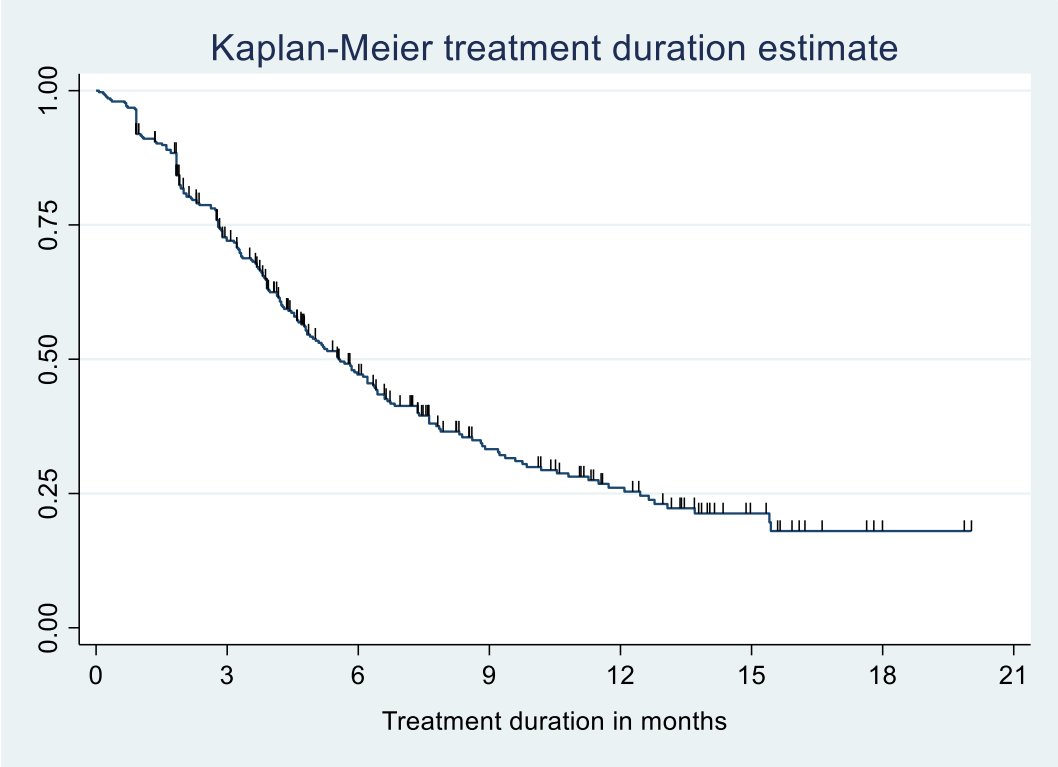


Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 15.9 months (483 days). SACT contains more follow-up for some patients.

Table 8: Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	347	223	117	60	36	14	2

Table 9 shows that for all patients who received treatment, 134 were still on treatment (censored) at the date of follow-up and 213 had ended treatment (events).

Table 9: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	134	103	67	40	28	12	2
Events	213	120	50	20	8	2	0

Table 10 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 61% (N=213) of patients had ended treatment at 30 June 2021.

Table 10: Treatment outcomes for patients that have ended treatment (N=213)[g,h]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	104	49%
Stopped treatment – died not on treatment[i]	42	20%
Stopped treatment – acute toxicity	29	14%
Stopped treatment – died on treatment	16	8%
Stopped treatment – patient choice	13	6%
Stopped treatment – no treatment in at least 3 months	4	2%
Stopped treatment – palliative, patient did benefit	4	2%
Stopped treatment – palliative, patient did not benefit	1	Less than 1%
Total	213	100%

[g] Figures may not sum to 100% due to rounding.
[h] Table 10 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[i] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 11: Treatment outcomes and treatment status for patients that have ended treatment (N=213)

Outcome[j]	Patient died [k] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	88	16	
Stopped treatment – died not on treatment	42		
Stopped treatment – acute toxicity	19	10	
Stopped treatment – died on treatment			16
Stopped treatment – patient choice	13		
Stopped treatment – no treatment in at least 3 months		4	
Stopped treatment – palliative, patient did benefit	3	1	
Stopped treatment – palliative, patient did not benefit		1	
Total	165	32	16

j Relates to outcomes submitted by the trust in Table 10.
k Relates to treatment status in Table 6 for those that have ended treatment.

Overall survival (OS)

Of the 347 patients with a treatment record in SACT, the minimum follow-up was 4.5 months (136 days) from the last CDF application. Patients were traced for their vital status on 14 November 2023. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time was 7.3 months (222 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 12: OS at 6, 12 and 18-month intervals

Time period	OS (%)
6 months	69% [95% CI: 63%, 73%]
12 months	44% [95% CI: 38%, 50%]
18 months	34% [95% CI: 28%, 41%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 14 November 2023. The median OS was 10.2 months [95% CI: 8.9, 12.1] (310 days) (N=347).

Figure 4: Kaplan-Meier survival plot (N=347)

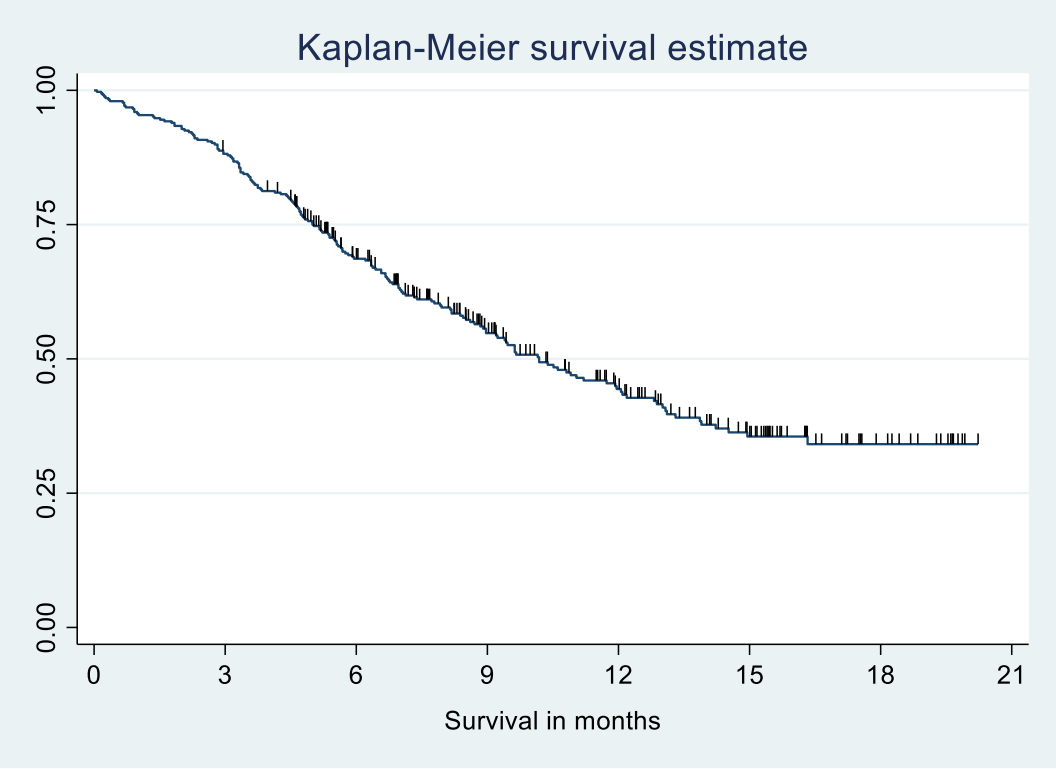


Table 13 and Table 14 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 20.4 months (620 days), all patients were traced on 14 November 2023.

Table 13: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	347	305	206	130	82	44	15

Table 14 shows that for all patients who received treatment, 166 were still alive (censored) at the date of follow-up and 181 had died (events).

Table 14: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	166	165	131	93	67	43	15
Events	181	140	75	37	15	1	0

5. Sensitivity analyses

6-months follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 3 March 2022 to 31 December 2022 and SACT activity was followed up to 30 June 2023.

Following the exclusions above, 211 patients (61%) were identified for inclusion. The median follow-up time in SACT was 5.8 months (176 days). The median follow-up time in SACT is the patients' median observed time from the start of their treatment to their last treatment date in SACT plus the prescription length.

The Kaplan-Meier curve for treatment duration is shown in Figure 5. The median treatment duration for patients in this cohort was 5.8 months [95% CI: 4.8, 7.4] (176 days) (N=211).

Figure 5: Kaplan-Meier treatment duration plot (N=211)

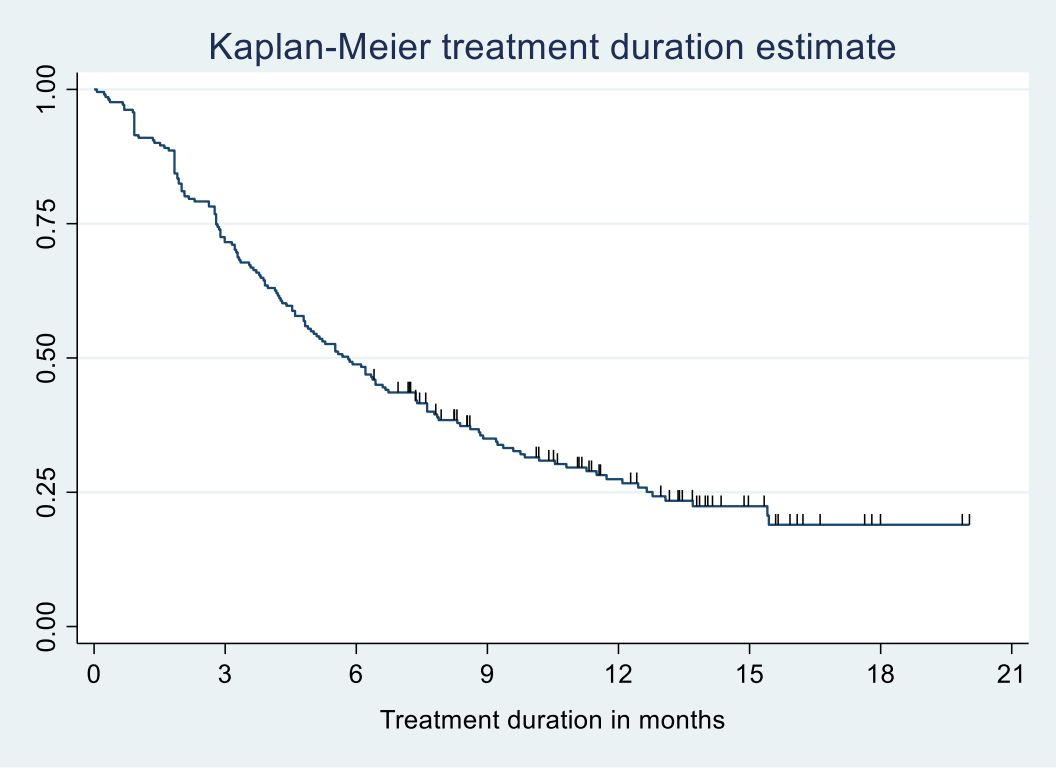


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 15.9 months (483 days).

Table 15: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	211	151	103	60	36	14	2

Table 16 shows that for all patients who received treatment, 56 were still on treatment (censored) at the date of follow-up and 156 had ended treatment (events).

Table 16: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	56	56	56	40	28	12	2
Events	155	95	47	20	8	2	0

Overall survival

Sensitivity analysis was also carried out for OS on a cohort with at least six months follow-up. To identify the cohort, CDF applications were limited from 3 March 2022 to 14 May 2023 and patients were traced for their vital status on 14 November 2023.

Following the exclusions above, 308 patients (89%) were identified for inclusion. The median follow-up time was 8.2 months (249 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 6. The median OS for patients in this cohort was 10.2 months [95% CI: 8.8, 12] (310 days) (N=308).

Figure 6: Kaplan-Meier survival plot (N=308)

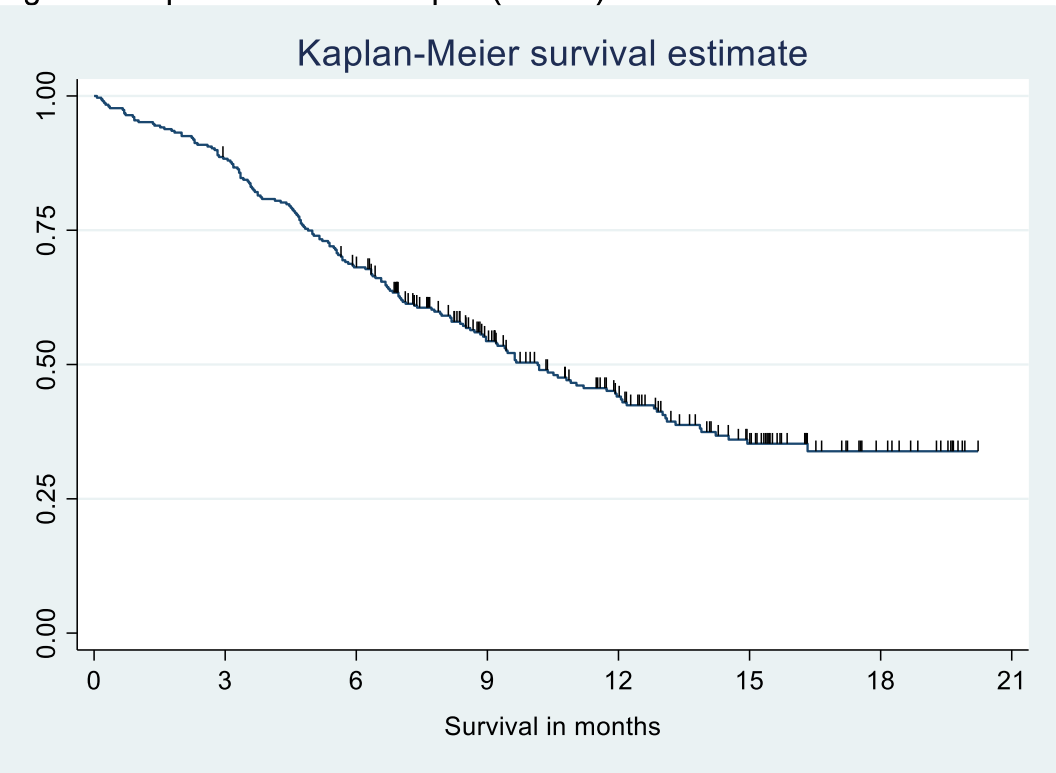


Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 20.4 months (620 days), all patients were traced on 14 November 2023.

Table 17: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	308	271	206	130	82	44	15

Table 18 shows that for all patients who received treatment, 135 were still alive (censored) at the date of follow-up and 173 had died (events).

Table 18: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	135	134	131	93	67	43	15
Events	173	137	75	37	15	1	0

Table 19: Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: overall survival
N	347	211	308
Median treatment duration	5.6 months [95% CI: 4.8, 6.4] (170 days)	5.8 months [95% CI: 4.8, 7.4] (176 days)	
OS	10.2 months [95% CI: 8.9, 12.1] (310 days)		10.2 months [95% CI: 8.8, 12.0] (310 days)

6. Conclusions

350 patients received sotorasib for the treatment of sotorasib for KRAS G12C mutation-positive, locally advanced or metastatic non-small-cell lung cancer [TA781] through the CDF in the reporting period (3 March 2022 and 30 June 2023). 347 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99%. An additional two patients with a CDF application did not receive treatment and 19 patients died before treatment. Both patients who did not receive treatment and 17 of the 19 patients identified as a death before treatment were confirmed by the trust responsible for the CDF application by the team at NHS England.

Patient characteristics from the SACT dataset show that 37% (N=127) of patients that received sotorasib for KRAS G12C mutation-positive, locally advanced or metastatic non-small-cell lung cancer were male, 63% (N=220) of patients were female. Most of the cohort were aged 50 and over 95%, (N=330) and 70% (N=242) of patients had a performance status between 0 and 1 at the start of their regimen.

At data cut off, 61% (N=213) of patients were identified as no longer being on treatment. Of these 213 patients:

- 49% (N=104) of patients stopped treatment due to disease progression
- 20% (N=42) of patients died not on treatment
- 14% (N=29) of patients stopped treatment due to acute toxicity
- 8% (N=16) of patients died on treatment
- 6% (N=13) of patients chose to end their treatment
- 2% (N=4) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 2% (N=4) of patients were treated palliatively and did benefit from the treatment they received
- Less than 1% (N=1) of patients were treated palliatively and did not benefit from the treatment they received

Median treatment duration was 5.6 months [95% CI: 4.8, 6.4] (170 days) (N=347). 47% of patients were still receiving treatment at 6 months [95% CI: 41%, 53%], 26% of patients were still receiving treatment at 12 months [95% CI: 21%, 32%] and 18% of patients were still receiving treatment at 18 months [95% CI: 12%, 25%].

The median OS was 10.2 months [95% CI: 8.9, 12.1] (310 days) (N=347). OS at 6 months was 69% [95% CI: 63%, 73%], 12 months OS was 44% [95% CI: 38%, 50%] and OS at 18 months was 34% [95% CI: 28%, 41%].

Sensitivity analysis was carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration showed a very slight difference that was not statistically significant (full cohort = 5.6 months; sensitivity analysis cohort = 5.8 months).

7. References

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