

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:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

Pre-technical engagement documents

- 1. Company submission** from Amgen
- 2. Company summary of information for patients (SIP)** from Amgen
- 3. Clarification questions and company responses**
- 4. External Assessment Report** prepared by Kleijnen Systematic Reviews
- 5. External Assessment Report – factual accuracy check**

Post-technical engagement documents

- 6. Technical engagement response** from Amgen
- 7. Technical engagement responses and statements from experts:**
 - a. Dr Qamar Ghafoor – clinical expert, nominated by Amgen
 - b. Dr Toby Talbot – clinical expert, nominated by Amgen
 - c. Jane Scott – patient expert, self-nominated
 - d. Tina Cobb – patient expert, nominated by Oncogene Cancer Research
- 8. Technical engagement responses from stakeholders:**
 - a. Oncogene Cancer Research
 - b. Roy Castle Lung Cancer Foundation
 - c. British Thoracic Oncology Group, incorporating response from Dr Thomas Newsom-Davis – clinical expert, nominated by British Thoracic Oncology Group
- 9. External Assessment Report critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews
 - a. EAG critique of company response to technical engagement
 - b. EAG response to NICE questions around key issues

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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CARE EXCELLENCE**

Single technology appraisal

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

Company evidence submission

June 2025

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Company evidence submission template for sotorasib for previously treated KRAS G12C
mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
A&E	Accident and emergency
ACM	Appraisal committee meeting
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATT	Average treatment effect in the treated
BIC	Bayesian information criterion
BICR	Blinded independent central review
BMI	Body mass index
CAS	Cancer Analysis System
CC	Complications and comorbidities
CDF	Cancer Drugs Fund
CEM	Cost-effectiveness model
CI	Confidence interval
CNS	Central nervous system
COSD	Cancer Outcomes and Services Dataset
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DCR	Disease control rate
DFS	Disease-free survival
DMC	Data monitoring committee
DOR	Duration of response
DSU	Decision Support Unit
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EHR	Electronic health records

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EMA	European Medicines Agency
EOI	Event of interest
EORTC	European Organization for Research and Treatment of Cancer
ERG	Evidence Review Group
ERK	Extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FACT-G GP5	Functional Assessment of Cancer Therapy-General, item 5
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
GDP	Guanosine diphosphate
GEE	Generalised estimating equations
GTP	Guanosine triphosphate
HCRU	Healthcare resource utilisation
HES	Hospital episode statistics
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology appraisal
IA	Investigator assessment
ICD	International Classification of Diseases
IP	Investigational product
IPCW	Inverse probability of censoring weighting
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten ras sarcoma
LoT	Line of therapy
LS	Least squares
LTFU	Long-term follow-up
MAIC	Matching adjusted indirect comparison
MDx	Molecular Diagnostics
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model for repeated measurement

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MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NDRS	National Disease Registration Service
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetics
PP	Post progression
PPS	Per protocol set
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PS	Propensity-score
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1	First quartile
Q3	Third quartile
Q3W	Every three weeks
QD	Once daily
QLQ-C30	Quality of Life Questionnaire 30-Item Core Module
QLQ-LC13	Quality of Life Questionnaire Lung Cancer Module
QoL	Quality of life

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Q-Q	Quantiles-quantiles
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
ROBINS-I	Risk Of Bias In Non-randomised Studies – of Interventions
ROS	Proto-oncogene tyrosine-protein kinase
RPSFT	Rank preserving structural failure time
RTDS	Radiotherapy Data Set
RWE	Real-world evidence
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Standard deviation
SE	Standard error
SFU	Safety follow-up
SLR	Systematic literature review
SMD	Standardised mean difference
SMQ	Standard MedDRA Query
SmPC	Summary of Product Characteristics
SMRW	Standardised mortality ratio weighting
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSE	Two-stage estimation
TTD(D)	Time to treatment discontinuation (or death)
TTNT(D)	Time to next treatment (or death)
TTR	Time to response
VAS	Visual analogue scale

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

Lung cancer is the third most common cancer and the most common cause of cancer death in the UK, accounting for 13% of all new cancer cases and 21% of all cancer deaths (1). This equates to over 49,000 new lung cancer cases and nearly 35,000 deaths from lung cancer in the UK every year. Non-small cell lung cancer (NSCLC) is by far the most common type of lung cancer, accounting for 80%–85% of lung cancers in the UK, with non-squamous cell carcinoma being the predominant sub-type (2).

Specific molecular and genetic tumour characteristics have been identified as key drivers of tumour proliferation and growth in NSCLC (3). This has transformed treatment options for patients with those specific oncogenic mutations for which targeted therapies have been developed. However, there remain other oncogenic mutations that have been recognised as key drivers of tumour proliferation and growth for many years but for which no targeted therapy has previously been successfully developed. These include mutations in the Kirsten rat sarcoma viral oncogene (*KRAS*), of which the most frequently occurring in NSCLC is the *KRAS* G12C mutation (4). This mutation occurs in around 13% of NSCLC cases (5) and, until the advent of sotorasib, was so elusive to effective therapy that it was considered to be “undruggable” (6). Patients harbouring this mutation have historically had a very poor prognosis, especially those who progress on first-line therapies, for whom the only subsequent treatment options were non-targeted, cytotoxic regimens that are associated with off-target toxicities (7, 8). There is therefore a significant need for a highly targeted, effective, tolerable, and convenient treatment that improves clinical outcomes and quality of life (QoL) for patients with *KRAS* G12C-mutated NSCLC.

Sotorasib is an oral, once daily therapy targeted specifically to inhibit the *KRAS*^{G12C} mutated protein in NSCLC. It has been available to patients in England with previously treated *KRAS* G12C-mutated, locally advanced or metastatic NSCLC

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since March 2022 when it was recommended through the Cancer Drugs Fund (CDF) (9). It is the first KRAS^{G12C} inhibitor to receive marketing authorisation in the UK and has previously been granted an Innovation Passport under the Innovative Licensing and Access Pathway, and designated as a Promising Innovative Medicine under the Early Access to Medicines Scheme (10, 11). Sotorasib is therefore recognised as a highly innovative therapy for patients with *KRAS G12C*-mutated NSCLC who currently have no other targeted therapy options available.

Sotorasib was initially appraised by NICE for this indication in 2021 (appraisal committee meeting [ACM] date: 15th December 2021). The committee acknowledged the high unmet need for targeted treatments for *KRAS G12C* mutation-positive locally advanced or metastatic NSCLC, and that such treatments would have physical and psychological benefits. However, there were recognised uncertainties in the available evidence base for sotorasib at the time and it was recommended for conditional reimbursement via the CDF to allow for additional data collection. These uncertainties related to:

1. The use of an unanchored indirect treatment comparison
2. The utility estimation approach used in the economic model
3. The magnitude of any treatment waning
4. Whether the technology meets the end of life 3-month extension criterion

Sotorasib was therefore recommended for use in the CDF for previously treated *KRAS G12C* mutation-positive advanced NSCLC. It was considered that further follow-up data from CodeBreaK 100 and direct comparative data with docetaxel from CodeBreaK 200, as well as real-world evidence (RWE), would reduce uncertainty in the cost-effectiveness estimates.

In this submission, we address each of the uncertainties highlighted by the committee in the original appraisal, as outlined in Table 1.

Table 1: Uncertainties from TA781

Uncertainty	Mitigation	Section(s) of dossier
1.The use of an unanchored indirect treatment comparison	Data from CodeBreak 200 provides direct head-to-head data versus docetaxel, so an unanchored indirect treatment comparison is not required. In the CAS RWE study, sotorasib is compared with docetaxel using a PS-weighting approach.	CodeBreak 200: Sections 2.3.1, 2.4.1, 2.6.1 CAS RWE: Sections 2.3.3, 2.4.5, 2.6.3
2.The utility values used in the economic model – health state versus time-to-death approach	The ERG preferred the health state approach to utility values given the limited research on the validity of time-to-death utilities at the time. However, since then more research has been published supporting this approach, specifically in NSCLC (12). Additionally, the current submission includes a much larger sample of patients from CodeBreak 200, rather than a small sample from CodeBreak 100 in the original submission, reducing the uncertainty in the estimates. The base case utilises in this submission are time-to-death utilities with a health-state approach explored in a sensitivity analysis.	Section 3.4.4, 3.7.2 (Table 70)
3.The magnitude of any treatment waning	The clinical evidence from the CAS RWE study (the base case of the current submission), CodeBreak 200 and Flatiron (sensitivity analysis) provides more robust evidence base than included in the original submission with the length of follow-up that captures any decline in treatment effectiveness.	Section 3.2.2 (Table 39)
4.Whether the technology meets the end of life 3-month extension criterion	The end-of-life criteria do not apply to the current submission. Instead, the assessment of the severity of the condition is performed and incorporated into the model calculations.	Section 3.6

Abbreviations: CAS, Cancer Analysis System; ERG, Evidence Review Group; PS, propensity score; RWE, real-world evidence.

This evaluation considers the managed access review of sotorasib for previously treated *KRAS G12C* mutation-positive advanced NSCLC. The submission covers the technology's full marketing authorisation for this indication. The decision problem is outlined in Table 2.

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Table 2: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with previously treated <i>KRAS</i> G12C-mutated, locally advanced or metastatic NSCLC	Adult patients with <i>KRAS</i> G12C-mutated locally advanced or metastatic NSCLC, who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy	In line with (conditional) marketing authorisation
Intervention	Sotorasib	Sotorasib	-
Comparator(s)	• Docetaxel • Docetaxel with nintedanib • Adagrasib (subject to NICE appraisal)	• Docetaxel	Docetaxel is considered the only relevant comparator for this submission. RWE from the CAS database shows that from 1st January 2017 to 31st January 2024, across all lines of therapy, only ~5% of patients with <i>KRAS</i>-mutated NSCLC who received chemotherapy (monotherapy or combination) in 2L+ received docetaxel + nintedanib, with fewer than nine recorded patients in 2L (13). While RCT data from the LUME-Lung 1 trial suggested an OS and PFS benefit with the docetaxel + nintedanib combination in 2L treatment of patients with adenocarcinoma, upon which use on the NHS was approved, more recent RWE found poor OS with the combination, raising questions regarding the applicability of the trial data, patient selection and the benefit of this treatment regime (14). NICE guidance for adagrasib is not yet available at the time of submission, and

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			therefore it is not considered a relevant comparator.
Outcomes	• OS • PFS • Response rates • TTD • AEs of treatment • HRQoL	In the cost-effectiveness analysis TTNTD from the CAS RWE study is used as a proxy for PFS. Otherwise, in line with scope.	PFS was not captured in the CAS RWE study. However, in a scenario analysis PFS data from the pivotal CodeBreak 200 is used and produces consistent results (see Section 3.9.3).
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Disease stage • Histology • Previous treatment • Newly diagnosed or recurrent distant metastatic disease	No subgroups included in the economic model.	For disease stage and histology, there were insufficient patient numbers in the smaller subgroups (locally advanced/unresectable, and squamous histology) to perform relevant analyses. Data were not collected with regards to newly diagnosed versus recurrent distant metastatic disease. CAS RWE data showed that results for subgroups with and without previous anti-PD-(L)1 treatment are consistent with the overall population results (see Section 2.8.2). Therefore, these were not included in the economic analysis.

Abbreviations: 2L, second line; AE, adverse event; CAS, Cancer Analysis System; HRQoL, health-related quality of life; NHS, National Health Service; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCT, randomised controlled trial; RWE, real-world evidence; TTD, time to treatment discontinuation; TTNTD, time to next treatment or death.

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1.2 Description of the technology being evaluated

Sotorasib (LUMYKRAS™) was the first KRAS^{G12C} inhibitor to receive (conditional) marketing authorisation in the UK. It is a once daily oral therapy that has been conditionally licensed in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA) since September 2021 as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy and/or anti-programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) immunotherapy, unless contraindicated (15).

Sotorasib is an inhibitor of KRAS^{G12C}, a tumour-restricted, mutant-oncogenic form of the RAS GTPase, KRAS. It forms an irreversible, covalent bond with the unique cysteine of KRAS^{G12C}, locking the protein in an inactive state that prevents downstream signalling, inhibits cell growth, and promotes apoptosis only in *KRAS G12C* tumour cell lines with minimal detectable off-target activity (16); no other wildtype or mutant protein or receptor has been identified to which sotorasib binds, nor has any effect been observed in cells without the *KRAS G12C* mutation. As the *KRAS G12C* mutation has been found only in tumour tissues, and not in normal tissue (17, 18), sotorasib has the potential to be highly tolerable and efficacious compared with standard of care chemotherapy.

Sotorasib was conditionally approved by the MHRA in September 2021 and recommended by NICE via the CDF in March 2022. Prior to this, sotorasib was granted an Innovation Passport under the Innovative Licensing and Access Pathway (10), and was designated as a Promising Innovative Medicine under the Early Access to Medicines Scheme in the UK (11). It received accelerated approval from the US FDA on 28th May 2021 under its Real-Time Oncology Review, a pilot program that aims to explore a more efficient review process that ensures safe and effective treatments are made available to patients as early as possible (19). With clinical evidence indicating meaningful improvements in PFS and OS, sotorasib is highly innovative and provides a step change in therapy for patients with *KRAS G12C*-mutated NSCLC who previously had no targeted therapy options available. Since its availability via the CDF, sotorasib has become embedded in NSCLC

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treatment pathways as the second-line SoC for patients with *KRAS G12C* mutations. A summary description of sotorasib is provided in Table 3, and the SmPC is provided in the reference pack (see Appendix A).

Table 3: Technology being evaluated

UK approved name and brand name	Sotorasib (LUMYKRAS™)
Mechanism of action	Sotorasib is a first-in-class irreversible small molecule inhibitor of KRAS ^{G12C} . It binds specifically to the G12C mutant form of the KRAS protein, locking it in an inactive, GDP-bound conformation. This inactivation of the KRAS protein prevents it from signalling to downstream effectors (including ERK) that control proliferation and mechanisms of cell survival (16).
Marketing authorisation/CE mark status	Sotorasib received conditional marketing authorisation in the UK in September 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The licensed indication is for use as monotherapy for the treatment of adult patients with <i>KRAS G12C</i> -mutated locally advanced or metastatic NSCLC who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy. See SmPC in Appendix A for full details of warnings and contraindications.
Method of administration and dosage	Sotorasib is administered orally at a dose of 960 mg (given as 8 x 120 mg tablets or 4 x 240 mg tablets) once daily until disease progression or unacceptable toxicity.
Additional tests or investigations	As a highly targeted therapy, the presence of <i>KRAS G12C</i> mutation should be confirmed using a validated test prior to initiation of sotorasib. <i>KRAS G12C</i> is now included routinely in the national service for cancer genomic testing. Therefore, no additional tests beyond those used in the routine diagnostic work up and management of patients with NSCLC are required.
List price and average cost of a course of treatment	The list price for sotorasib is £6,907.35 per 30-day supply (pack of 240 tablets of 120 mg or 120 tablets of 240 mg).
Patient access scheme (if applicable)	Sotorasib is currently available through the CDF and via a PAS which provides a confidential discount of [REDACTED] resulting in a cost of [REDACTED] per 30-day supply (pack of 240 tabs of 120 mg or 120 tablets of 240 mg). Based on the modelled drug utilisation and duration of therapy utilised in the economic evaluation, the anticipated average per patient cost of treatment of sotorasib is [REDACTED] (undiscounted).

Abbreviations: CDF, Cancer Drugs Fund; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; PAS, Patient Access Scheme; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SmPC, summary of product characteristics.

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1.3 *Health condition and position of the technology in the treatment pathway*

1.3.1 Disease overview

1.3.1.1 *Lung cancer*

Lung cancer is the third most common cancer, accounting for over 49,000 new cancer cases (13% of all new cancer cases) in the UK. Around 70% of lung cancer cases are diagnosed at an advanced stage, when the cancer has already spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV) (1, 20), which contributes to a disproportionately poor prognosis; despite being the third most common cancer, lung cancer is the most common cause of cancer death in the UK, accounting for around 35,000 deaths (21% of all cancer deaths) each year (1). One-year survival for patients with locally advanced (stage III) lung cancer is 52.5%, whilst 5-year survival is just 16.0% (21). For patients with metastatic (stage IV) lung cancer, 1-year survival is 21.7%, with only 4.3% of patients surviving 5 years (21).

Histologically, lung cancer can be classified into different types and subtypes. These include small cell lung cancer (SCLC); and NSCLC, which includes squamous cell carcinoma, adenocarcinoma and large-cell carcinoma. The latter two, collectively, are referred to as 'non-squamous' lung cancer. NSCLC is by far the most common type, accounting for 80–85% of lung cancers in the UK (2), with non-squamous cell carcinoma the predominant sub-type of NSCLC (adenocarcinoma 66%; large cell 2%; squamous 23%; others 8%) (22).

In addition to histological characteristics, specific molecular and genetic tumour characteristics have been identified as key drivers of tumour proliferation and growth in NSCLC (3). This has transformed treatment options for patients with those specific oncogenic mutations for which targeted therapies have been developed; NSCLC patients with *ALK*, *ROS*, *EGFR*, *BRAF*, and *NTRK* mutations have several highly specific therapy options available. Whilst mutations in the *KRAS* gene, of which the most frequently occurring in NSCLC is the *KRAS G12C* mutation (4), have been recognised as key drivers of tumour proliferation and growth for many years,

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targeted therapies have lagged behind those for other mutations, with sotorasib becoming the first option available to patients in the UK in 2021/2022.

1.3.1.2 *KRAS G12C mutation in NSCLC*

KRAS genes express proteins called GTPases, which regulate cellular proliferation, apoptosis and survival (23). Mutations in *KRAS* genes can therefore disrupt the processes involved in the proliferation and survival of tumour cells. Of the *KRAS* mutations, an estimated 80% occur at codon 12. The *KRAS* gene with a mutation resulting in a *G12C* amino acid substitution (*KRAS G12C* mutation) in codon 12 is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of GTPase-activating proteins, which reduces the normal hydrolysis of guanosine triphosphate (GTP) by the *KRAS* protein. The resulting accumulation of active, GTP bound *KRAS* disrupts the process of apoptosis and promotes tumour proliferation and survival (24). The *KRAS G12C* mutation is therefore an oncogenic driver and *KRAS* mutations are generally acknowledged as negative prognostic factors for treatment response and, hence, survival outcomes in patients with NSCLC and other solid tumours (4, 24, 25).

The *KRAS G12C* mutation occurs in around 13% of NSCLC cases (3, 26). This would equate to an upper estimate of around 5,400 *KRAS G12C*-mutated NSCLC cases in the UK each year, which is well below the prevalence threshold of 5 cases per 10,000 population used by the MHRA to define a disease as an orphan disease (27). Despite NSCLC being a leading cause of cancer death, and *KRAS G12C* being one of the most common types of mutation in NSCLC, *KRAS G12C*-mutated NSCLC is still a rare disease.

Several sources have demonstrated that the *KRAS G12C* mutation rarely occurs concomitantly with other oncogenic mutations for which targeted therapies have been developed (28-30). This has been confirmed in a large Amgen study (Study 20200097) of *KRAS G12C*-mutated NSCLC patients, conducted in the US Flatiron Health-Foundation Medicine Clinico-Genomic Database, who were diagnosed January 2011 to March 2019 (31). Other targeted therapies are therefore rarely an option for patients with the *KRAS G12C* mutation.

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1.3.1.2.1 Treatment of *KRAS* G12C-mutated NSCLC with non-targeted agents is associated with very poor outcomes

Prior to the availability of *KRAS*^{G12C} inhibitors, therapy options for patients with *KRAS* G12C-mutated NSCLC were limited to non-targeted therapy, and outcomes for patients with advanced NSCLC who are not candidates for currently approved targeted therapy were poor, particularly in the second- or subsequent-line setting. As sotorasib was the first *KRAS*^{G12C} inhibitor to progress in development to the point of marketing authorisation, there is limited RCT evidence on outcomes specifically in NSCLC patients harbouring the *KRAS* G12C mutation. However, randomised controlled trials (RCTs) of second-line non-targeted treatments (e.g. docetaxel, nintedanib plus docetaxel) in advanced NSCLC patients who received first-line platinum-based chemotherapy have demonstrated low objective response rates (ORRs) (complete response [CR] + partial response [PR]) of 5% to 14%, poor progression-free survival (PFS) of 2.8 to 4.2 months and poor overall survival (OS) of 7.9 to 12.6 months) (32, 33).

Literature reviews conducted by Amgen to identify all available trials in NSCLC patients identified with *KRAS* mutations confirmed the sparsity of outcomes data specifically in patients with *KRAS* G12C-mutated NSCLC (see Appendix B). Only three RCTs were identified that assessed *KRAS* G12C-mutated NSCLC exclusively, which investigated sotorasib or adagrasib (both *KRAS*^{G12C} inhibitors) (34-36). Five others were identified which reported subgroup outcomes for the *KRAS* G12C mutation within a broader population (32, 37-40), with the proportion of patients with a G12C mutation ranging from 35% (NCT01362296) (38) to 59% (SELECT-1) (32). Details of the two studies of sotorasib in this population are outlined in Section 2.

Given the limited outcomes data from RCTs specifically in patients with *KRAS* G12C-mutated NSCLC, observational, RWE studies provide a valuable source of data on the natural history and prognosis for these patients. Literature on the prognostic importance of *KRAS* mutations is mixed; while some studies suggest that *KRAS* mutations do not have any effect on OS or PFS compared to *KRAS* wildtype, others suggest a negative prognostic effect in patients with *KRAS*-mutated NSCLC (Table 4). One systematic review and meta-analysis found that DFS was similar for patients with a *KRAS* G12C mutation versus *KRAS* wildtype (hazard ratio [HR]: 2.36,

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$p > 0.05$) but that OS was poorer (HR: 1.42, $p < 0.01$) (41). Goulding et al. (2020) found that *KRAS* mutations did not have any effect on OS or PFS compared to *KRAS* wildtype in RCTs (OS HR: 1.10, 95% confidence intervals [CI]: 0.88, 1.38; PFS HR: 1.03, 95% CI: 0.80, 1.33), but they had a negative prognostic effect in observational studies (OS HR: 1.71, 95% CI: 1.07, 2.84; PFS HR: 1.18, 95% CI: 1.02, 1.36) (25). Finally, Fan et al. (2017) found that *KRAS* mutations predict worse OS and PFS compared to *KRAS* wildtype among chemotherapy-treated patients (OS HR: 2.07, 95% CI: 1.54, 2.78, $p < 0.00001$; PFS HR: 1.83, 95% CI: 1.40, 2.40, $p < 0.0001$) (42).

Although only one of these meta-analyses provided data specifically in *KRAS G12C*-mutated NSCLC (41), several other observational studies in Western (European, Australian and US) populations show that OS in patients with *KRAS G12C*-mutated NSCLC is similarly poor as that in patients with other *KRAS* mutations and in wildtype disease who are not eligible for existing targeted therapies (41, 43-48) (Table 4). One study in 352 patients with *KRAS G12C*-mutated NSCLC diagnosed between 2014 and 2018 in the US observed a median OS of 13 months, and in the subgroup of patients who received first or second-line immunotherapy, the ORR was 24% (43). An analysis of a prospective, multicentre, German (CRISP) registry for patients with stage IV NSCLC also found that 171 patients with *KRAS G12C*-mutated non-squamous tumours had similar survival outcomes to those with other *KRAS*-mutated tumours; following second-line treatment, median PFS was 4.4 months versus 4.8 months and median OS was 10.1 months versus 9.4 months for those with *KRAS G12C*-mutated and other *KRAS*-mutated tumours, respectively (45).

Table 4: Meta-analyses and observational studies on the prognostic effect of *KRAS* and *KRAS G12C* mutations

Study	Number of studies/number of patients	Key results	Key conclusions
Meta-analyses			
Wankhede et al. 2023 (41)	Systematic review and meta-analysis, including 16 studies	<i>KRAS G12C</i>-mutated vs <i>KRAS</i>-wildtype: - OS HR: 1.42; 95% CI: 1.10, 1.84, p=0.007 - DFS HR: 2.36; 95% CI: 0.64, 8.16 <i>KRAS G12C</i>-mutated vs <i>KRAS</i>-mutated - OS HR: 1.03; 95% CI: 0.84, 1.26 - DFS HR: 1.49; 95% CI: 1.07, 2.09, p<0.0001	<i>KRAS G12C</i> -mutated tumours had poor OS but similar DFS compared to <i>KRAS</i> -wildtype tumours. Compared to other <i>KRAS</i> mutations, <i>KRAS G12C</i> -mutated tumours had poor DFS but similar OS. <i>KRAS G12C</i> mutation was a promising prognostic factor for patients with NSCLC, negatively impacting survival
Goulding et al. 2020 (25)	Systematic review and meta-analysis, including 46 publications pertaining to 43 clinical studies	<i>KRAS</i> -mutated vs <i>KRAS</i> -wildtype - Based on RCTs: - OS HR: 1.10, 95% CI: 0.88, 1.38 - PFS HR: 1.03, 95% CI: 0.80, 1.33 - Based on observational studies: - OS HR: 1.71, 95% CI: 1.07, 2.84 - PFS HR: 1.18, 95% CI: 1.02, 1.36	<i>KRAS</i> mutations did not have any effect on OS or PFS compared to <i>KRAS</i> -wildtype in RCTs but they had a negative prognostic effect in observational studies
Fan et al. 2017 (42)	Systematic review and meta-analysis, including 13 studies	<i>KRAS</i> -mutated vs <i>KRAS</i> wildtype - OS HR: 2.07, 95% CI: 1.54, 2.78, p<0.00001 - PFS HR: 1.83, 95% CI: 1.40, 2.40, p<0.0001	<i>KRAS</i> mutations predict worse OS and PFS compared to <i>KRAS</i> -wildtype among chemotherapy-treated patients
Observational studies			
Arbour et al. 2020 (43)	n=1,194 patients with <i>KRAS</i> -mutated NSCLC, 46% (n=352) had <i>KRAS G12C</i> mutation	- Median OS from diagnosis was 13 months for <i>G12C</i> and non-<i>G12C</i> patients (p=0.99) - ORR with anti-PD-(L)1 treatment was 24% vs 28% in <i>G12C</i> vs non-<i>G12C</i> patients (p=0.5)	NR

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Study	Number of studies/number of patients	Key results	Key conclusions
Cui et al. 2020 (44)	n=346 patients with <i>KRAS</i> -mutated NSCLC	<i>KRAS</i> -mutated vs <i>KRAS</i> -wildtype - OS HR: 1.08; 95% CI: 0.83, 1.40, p=0.54 <i>KRAS G12C</i> versus other <i>KRAS</i> -mutations - OS HR: 1.19; 95% CI: 0.78, 1.80 p=0.39	<i>KRAS G12C</i> was not prognostic
Griesinger et al. 2020 (45)	n=3,717 patients with <i>KRAS</i> -mutated advanced non-squamous NSCLC	For <i>KRAS G12C</i> vs non- <i>G12C</i> : - Median PFS: 4.4 months (95% CI: 3.2, 6.4) vs 4.8 (4.3, 5.7) - Median OS: 10.1 months (95% CI: 7.0, 12.3) vs 9.4 (95% CI: 7.1, 10.8)	Survival was similar for pts with <i>KRAS G12C</i> and non- <i>G12C</i> mutations
Yu et al. 2015 (46)	n=677 patients with <i>KRAS</i> -mutated lung cancer	- Median OS for <i>KRAS</i>-mutated advanced lung cancer: 1.2 years (95% CI: 1.2, 1.4) - No significant difference in survival when comparing different <i>KRAS</i> point mutations - Median OS for <i>G12C/G12V</i> mutant tumours was not different from patients with all other point mutations, 1.2 years for both (p=0.74)	<i>KRAS</i> mutation subtype does not appear to be associated with OS from the diagnosis of lung cancer
Noordhof et al. 2023 (47)	n=1,185 patients with <i>KRAS</i> -mutated lung cancer, of which 494 has <i>KRAS G12C</i> mutation	<i>KRAS G12C</i> vs <i>KRAS</i> non- <i>G12C</i> : - Median OS: 15.5 months (95% CI: 13.6, 18.4) vs 14.0 months (95% CI: 11.2, 15.7), (p=0.67) - In multivariable analysis, <i>KRAS</i> subtype was not associated with OS (HR: 0.95, 95% CI: 0.82, 1.10)	There was no influence of <i>KRAS</i> subtype (<i>G12C</i> versus non- <i>G12C</i>) on OS in patients with <i>KRAS</i> -mutated stage IV NSCLC treated with first-line (chemo) immunotherapy

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Study	Number of studies/number of patients	Key results	Key conclusions
Frost et al. 2023 (48)	n=7,440 patients with advanced NSCLC, 11% (n=328) with <i>KRAS</i> G12C mutation	- OS from mutational test result (comparable): <i>KRAS</i> G12C: 7.1 months (95% CI: 5.9, 9.0) - Any <i>KRAS</i> mutation: 7.3 months (6.6, 8.0) - Wildtype: 7.3 months (6.3, 8.1) - OS from first line of therapy (numerical difference only) <i>KRAS</i> G12C: 14.0 months (95% CI: 10.3, 19.8) - Any <i>KRAS</i> mutation: 11.9 months (10.7, 13.4) - Wildtype: 12.0 months (11.1, 13.8)	In patients diagnosed with advanced NSCLC after the implementation of anti-PD-(L)1 therapies, the survival in <i>KRAS</i> G12C-mutated patients is comparable to patients with any <i>KRAS</i> mutation, and all NSCLC patients

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCT, randomised controlled trial.

To provide further outcomes data specifically in *KRAS G12C*-mutated NSCLC, prior to the launch of sotorasib, Amgen conducted two large RWE studies in US advanced NSCLC patients harbouring the *KRAS G12C* mutation (Study 20180277, n=416 and Study 20200097, n=743), and a further study in patients with advanced NSCLC patients with known *KRAS* status, including *KRAS* wildtype, *KRAS G12C*-mutated patients from Study 20200097, and other *KRAS*-mutated patients (Study 20200132, n=7069) (5, 49, 50). These data, which are highly consistent with those observed in Europe (45), confirm that, in the absence of sotorasib, survival was similarly very poor for patients with *KRAS G12C*-mutated NSCLC, other *KRAS*-mutated NSCLC, and other patients who are not candidates for other targeted therapies, irrespective of *KRAS* status. Of note, PFS and OS were particularly poor as patients progressed through lines of therapy, such that by third- or fourth-line therapy, median PFS was 3 months or less and median OS was less than 7 months (Table 5).

Table 5: Real-world outcomes of patients with advanced NSCLC and *KRAS G12C*-mutated advanced NSCLC by line of therapy

	KRAS G12C-mutated NSCLC				KRAS-mutated (non-G12C)		All NSCLC	
	Study 20180277 AACR project GENIE		Study 20200097 Flatiron Health Foundation		Study 20200132 Flatiron Health Foundation			
Median OS (months)								
	N (n)	Median (95% CI)	N (n)	Median (95% CI)	N (n)	Median (95% CI)	N (n)	Median (95% CI)
First-line	150 (87)	14.9 (12.2, 24.3)	288 (174)	12.0 (9.6, 15.3)	480 (283)	12.2 (10.5, 14.4)	2,578 (1,510)	12.9 (11.9, 14.2)
Second-line	113 (70)	10.1 (7.1, 16.9)	154 (106)	9.5 (8.1, 13.1)	292 (188)	9.6 (7.7, 12.4)	1,706 (1,122)	10.2 (9.5, 11.3)
Third-line	47 (27)	6.5 (5.0, NE)	92 (75)	6.7 (5.9, 10.7)	129 (95)	6.6 (5.0, 9.0)	916 (661)	7.9 (6.8, 8.8)
Fourth-line	13 (8)	3.0 (2.2, NE)	42 (34)	5.9 (4.3, 12.9)	52 (43)	5.5 (3.9, 8.6)	406 (300)	7.4 (6.4, 8.6)
Median real-world PFS (months)								
	N (n)	Median (95% CI)	N (n)	Median (95% CI)	N (n)	Median (95% CI)	N (n)	Median (95% CI)
First-line	148 (117)	6.1 (4.4, 9.3)	281 (217)	5.0 (4.4, 5.8)	2,201 (1,660)	5.6 (5.4, 6.0)	2,483 (1,878)	5.6 (5.3, 5.8)
Second-line	111 (86)	3.2 (2.1, 5.3)	145 (121)	4.0 (2.8, 5.3)	1,496 (1,245)	4.1 (3.7, 4.4)	1,644 (1,369)	4.0 (3.7, 4.4)
Third-line	47 (38)	2.3 (1.4, 4.1)	87 (78)	3.1 (2.4, 4.3)	789 (683)	3.5 (3.2, 4.0)	877 (762)	3.5 (3.1, 3.9)
Fourth-line	11 (8)	1.8 (1.4, 15.0)	42 (38)	2.6 (2.1, 4.7)	348 (310)	3.1 (2.7, 3.5)	391 (349)	3.0 (2.7, 3.4)

Abbreviations: *KRAS G12C*, *KRAS* gene with a mutation resulting in a G12C amino acid substitution; n, number with event; N, total number of patients; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

Retrospective Studies 20200097 and 20200132 were conducted using the United States Flatiron Health - Foundation Medicine Clinico-Genomic Database in 743 patients with *KRAS G12C*-mutated advanced NSCLC and 7069 patients with advanced NSCLC (i.e. regardless of *KRAS G12C* mutation), respectively. Retrospective Study 20180277 was conducted using the American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange database in 416 patients with *KRAS G12C*-mutated advanced NSCLC (5, 49, 50)

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1.3.1.2.2 Non-targeted treatment for *KRAS G12C*-mutated NSCLC is associated with frequent toxicities and impaired quality of life

As NSCLC is diagnosed at an advanced stage in most patients, it is particularly important to consider the impact of treatment on symptom burden and health-related quality of life (HRQoL) (51, 52). Patients whose disease progresses following first-line treatment are often already fatigued, anorexic and in pain. It is therefore important that further treatment does not worsen these symptoms or add to the symptom burden (53).

Prior to the launch of sotorasib, there were no targeted therapies available for patients with advanced *KRAS G12C*-mutated NSCLC that had progressed on first-line therapy, so treatment often consisted of intravenous (IV) myelosuppressive, cytotoxic chemotherapy such as docetaxel, which as a non-targeted therapy is associated with a number of off-target toxicities, including neutropenia and febrile neutropenia, dyspnoea, fatigue, infection, anaemia, diarrhoea, stomatitis and nausea and vomiting that can lead to hospitalisation and severely compromise HRQoL (7, 8). Approximately 50% of patients with previously treated *KRAS*-mutated advanced NSCLC experience symptom progression one month after initiating treatment with docetaxel (32).

Febrile neutropenia (fever in the presence of neutropenia) is a particularly concerning complication of myelosuppressive chemotherapy such as docetaxel (54). Patients who develop febrile neutropenia are more susceptible to potentially fatal infections, such as severe sepsis or septic shock, that may necessitate chemotherapy dose modification, delays, or discontinuation, jeopardising treatment response and clinical outcomes and compromising QoL (55, 56).

1.3.1.3 *There is a critical need for targeted therapy with sotorasib in *KRAS G12C*-mutated NSCLC*

Sotorasib has been available to patients in England under the CDF since March 2022. In contrast to other driver mutations, for which there are several targeted treatment options available, sotorasib is the only targeted treatment option recommended by NICE for patients with NSCLC harbouring the *KRAS G12C* mutation. Adagrasib, another *KRAS*^{G12C} inhibitor, received conditional marketing authorisation from the MHRA in November 2023, however, guidance from NICE is Company evidence submission template for sotorasib for previously treated *KRAS G12C* mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

still in development at the time of this submission. With the earlier use of immunotherapy in the NSCLC pathway, treatment options for patients with *KRAS G12C*-mutated NSCLC who progress to second- and subsequent-line therapy are otherwise limited to cytotoxic, IV chemotherapy that is associated with a number of severe, off-target toxicities (7, 8). As well as impacting QoL for patients, these toxicities require additional attention from clinicians and impose additional costs for the NHS. There is, therefore, a particularly high unmet need for effective and tolerable therapies for *KRAS G12C*-mutated NSCLC, in particular targeted treatments, that can improve outcomes without compromising HRQoL for patients who have progressed to second- or subsequent-line therapy.

With the advent of sotorasib as a specifically targeted therapy for the *KRAS G12C* mutation, *KRAS G12C* is now an important predictive biomarker for one of the most common types of lung cancer.

As a specifically targeted oral therapy for the *KRAS G12C* mutation, sotorasib offers the potential for improved clinical outcomes, tolerability, convenience and HRQoL compared with existing highly toxic, non-targeted, standard of care therapy. Its early use in line with its licensed indication as a second- or subsequent-line therapy can delay the need to use less effective, IV cytotoxic chemotherapy.

It is therefore of crucial importance to ensure continued access to sotorasib in this patient population.

1.3.2 NSCLC clinical care pathway

1.3.2.1 *Diagnosis of NSCLC and KRAS G12C-mutated NSCLC*

The importance of molecular biomarker testing has increased with the development of a range of highly targeted therapies for NSCLC. The latest National Comprehensive Cancer Network (NCCN) guidelines call for broad molecular profiling as a key component of care for patients with NSCLC, with the goal of identifying driver alterations that can guide use of available targeted therapies (57). Molecular testing for key oncogenic drivers, including *KRAS*, is recommended in all patients with advanced or metastatic non-squamous NSCLC and NSCLC not otherwise specified (57). Similarly, the latest guidelines from the European Society for Medical Oncology (ESMO) call for molecular testing in all patients with advanced or metastatic NSCLC (58). The company evidence submission template for sotorasib for previously treated *KRAS G12C* mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

Oncology (ESMO) provide separate guidance for patients with ‘oncogene-addicted’ and ‘non-oncogene-addicted’ metastatic NSCLC, and stipulate mandatory testing for oncogenic drivers for which drugs are approved for routine usage, including *KRAS G12C* (58). Broader testing may also be used to support early drug access or clinical trials (58).

NICE Guideline 122 – Lung cancer: diagnosis and management (59) outlines the approach to diagnosis and staging of lung cancer, emphasising the need for rapid assessment of suspected cases, and appropriate use of sputum cytology, bronchoscopy, computed tomography (CT) and magnetic resonance imaging (MRI) scans and X-rays. Regarding the use of biomarkers, the guidance is limited, noting only the need to ensure that biopsy samples are adequate (without unacceptable risk to the person) to permit pathological diagnosis, including tumour subtyping and assessment of predictive markers (59)

The National Optimal Lung Cancer Pathway produced by NHS England (60) provides the diagnostic standards of care for lung cancer, detailing the sequence and timing of investigations. This specifies that, where a pathological diagnosis could influence treatment, biopsy results providing the subtype of cancer should be available within 3 working days, and results of testing for molecular biomarkers should be available within 10 working days from the point of referral (60).

Previous UK Governments have highlighted ambitions to create the most advanced genomic healthcare system in the world, incorporating the latest genomics advances into routine healthcare to improve the diagnosis, stratification and treatment of illness (61). The NHS Long Term Plan, published in 2019, outlined the strategy to expand the molecular diagnostics and to offer genomic testing routinely to all people with cancer for whom it would be of clinical benefit (61, 62). To achieve this aim, NHS England established a national service for cancer genomic testing to replace all local testing. This involved the setting up of seven genomic laboratory hubs across England to do testing by next generation sequencing when locally advanced or metastatic solid tumours are first diagnosed (63). *KRAS* mutation testing is confirmed and listed on the National Test Directory (64), meaning that no additional tests beyond those that will be used in the routine diagnostic work and management

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of patients with NSCLC are anticipated to be required to determine eligibility for sotorasib.

1.3.2.2 Current treatment guidelines

With the conditional approval of the first KRAS^{G12C} inhibitors (sotorasib and adagrasib) in multiple markets, national and international guidelines have been updated to reflect the availability of targeted therapies for patients with *KRAS G12C*-mutated NSCLC.

NICE Guideline 122 (59) provides varying treatment pathways depending on histology (squamous versus non-squamous), presence of specific targetable mutations, and PD-L1 expression (less than 50% versus 50% or higher). An overview of the treatment pathway is shown in Figure 1. For patients with *KRAS G12C*-mutated NSCLC and PD-L1 expression $\geq 50\%$, anti-PD-1/PD-L1 immunotherapies are recommended as first-line treatment, either alone or in combination with platinum-based chemotherapy. Subsequent treatment options depend on the first-line treatment (monotherapy or combination) and histology, but include sotorasib, docetaxel, docetaxel in combination with nintedanib (for those with adenocarcinoma), and platinum-based chemotherapy, if not given in first-line. For patients with PD-L1 expression $< 50\%$, the same treatment options are recommended, though platinum-based chemotherapy alone is also an option at first-line, allowing for anti-PD-1/PD-L1 immunotherapy at subsequent lines.

Similarly, ESMO (58), NCCN (57), and American Society of Clinical Oncology (ASCO) guidelines (65), all updated in 2023/24, recommend platinum-based chemotherapy and immunotherapy as first-line treatment for patients with *KRAS*-mutated NSCLC. Sotorasib and adagrasib are recommended as subsequent therapy options for patients who experience disease progression after treatment with first-line systemic therapy.

1.3.3 Positioning of sotorasib within the NSCLC clinical pathway

In line with the current treatment guidelines, clinical experts at an advisory board held by Amgen in February 2021 confirmed that an increasing majority of patients in the UK with NSCLC without current actionable mutations now receive

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anti-PD-1/PD-L1 immunotherapy alone or in combination with platinum-based chemotherapy as first-line therapy; few patients receive immunotherapy as second-line therapy and re-challenge with immunotherapy is not routine practice (66). RWE from the Cancer Analysis System (CAS) database in the UK shows that only approximately 5% of patients with *KRAS G12C*-mutated NSCLC treated with chemotherapy (monotherapy or combination) in second- or subsequent-line therapy from 1st January 2017 to 31st December 2024 received docetaxel in combination with nintedanib (13). While RCT data from the LUME-Lung 1 trial suggested an OS and PFS benefit with the docetaxel + nintedanib combination in 2L treatment of patients with adenocarcinoma, upon which use on the NHS was approved, more recent RWE found poor OS outcomes with the combination. Of the 60 patients identified at the Clatterbridge Cancer Centre who received docetaxel + nintedanib between 2016 and November 2021, 59 had stopped treatment at the time of data cut-off and 57 deaths had occurred. The median length of time taking nintedanib was 63 days and only 24 (40%) of patients proceeded to maintenance monotherapy. If patients proceeded to maintenance, the median time on treatment was 203 days. Median OS was 224 days. Of the 35 patients (58%) who had a grade 3/4 toxicity, there were seven grade 3/4 events specifically attributable to nintedanib. As a result, the applicability of the trial data, patient selection and the benefit of this treatment regime has been brought into question (14).

The proposed positioning of sotorasib is in line with its licensed indication, as a second- or subsequent-line therapy following prior treatment with platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy (see Figure 1). This positioning is aligned with the pivotal clinical trial data and data collected via the CDF (see Section 2.3.1). Whilst available through the CDF, sotorasib has become a key treatment option for these patients.

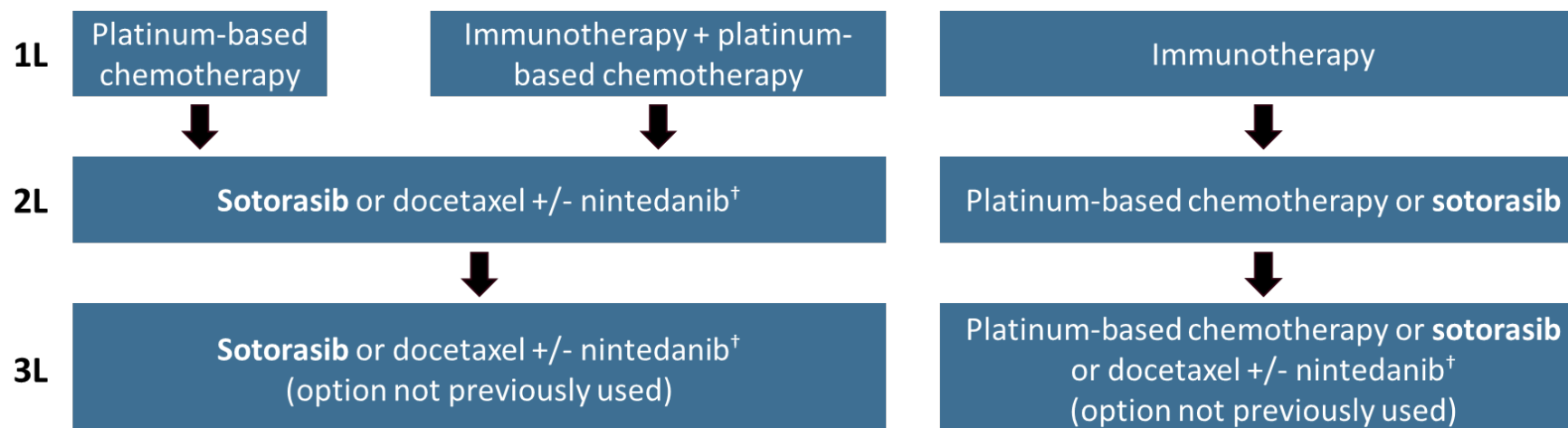
As docetaxel monotherapy is recognised in the NICE lung cancer guideline (NG122) and pathway as a key second- and subsequent-line option in NSCLC across non-squamous and squamous disease and across PD-L1 expression scores (59), this is the only appropriate comparator for this appraisal. Whilst nintedanib in combination with docetaxel is recommended for use in patients with adenocarcinoma (67), given the limited number of patients receiving this treatment in 2L (13, 66), it is Company evidence submission template for sotorasib for previously treated *KRAS G12C* mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

not considered a relevant comparator in UK clinical practice. Docetaxel is the only routinely used, guideline-relevant treatment option and the comparator in this submission.

1.4 *Equality considerations*

No specific equality considerations are anticipated.

Figure 1: Current treatment pathway for *KRAS* G12C-mutated NSCLC, and positioning of sotorasib



Abbreviations: NSCLC, non-small cell lung cancer.

† Nintedanib is only reimbursed for patients with adenocarcinoma. Other histologies will receive docetaxel monotherapy.

Note: Different immunotherapies (e.g. nivolumab, pembrolizumab, atezolizumab) are recommended in different patient groups (i.e. squamous vs non-squamous, and PD-L1 ≥50% vs <50%), however, for simplicity, these have been grouped in the schematic. Similarly, in some instances, the exact platinum-based chemotherapy is specified (e.g. carboplatin + paclitaxel). For detailed treatment pathways, please refer to NICE Guideline NG122.

2 Clinical effectiveness

Summary of clinical effectiveness

The available clinical effectiveness data for sotorasib come from the CodeBreak 200 and CodeBreak 100 trials, and CAS RWE study, as outlined below.

CodeBreak 200

CodeBreak 200 was highlighted as a key source of data for sotorasib when entering the CDF

- CodeBreak 200 is an ongoing Phase 3, multicentre, randomised, open-label, active-controlled study comparing sotorasib with docetaxel in patients with locally advanced/ unresectable or metastatic *KRAS G12C*-mutated NSCLC (68)
- As of the data cut-off for the primary analysis of PFS (2nd August 2022), the full analysis set (FAS) population included 174 patients in the sotorasib arm and 171 in the docetaxel arm (68)
- CodeBreak 200 met its primary endpoint. Treatment with sotorasib resulted in a 34% reduction in the hazard of progression or death when compared with docetaxel (HR: 0.66 [95% CI: 0.51, 0.86], $p=0.002$), equating to a 1.1 month improvement in PFS, in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with the *KRAS G12C* mutation (68)
- More than twice as many subjects in the sotorasib group were alive without progression at a 1-year landmark compared with subjects in the docetaxel group (1-year PFS was 24.8% for sotorasib vs 10.1% for docetaxel) (68)
- The PFS benefit observed with sotorasib treatment was consistent across all relevant subgroups, including history of CNS involvement and liver metastasis at baseline (68)
- In addition, ORR, duration of response (DOR), time to response (TTR), and disease control rate (DCR) were all improved for sotorasib versus docetaxel, with statistically significant improvements observed in ORR and DCR (68)
- Due to challenges arising from crossover between treatment groups, in the primary analysis, OS was not significantly different between the sotorasib group (median 10.6 months) and the docetaxel group (median 11.3 months). However, adjusted analyses accounting for crossover (including off-protocol crossover) yielded an OS HR of 0.820 (95% CI: 0.315, 1.309). These adjusted results, although not statistically significant due to limited statistical power, support a favourable OS trend for sotorasib and align with CAS RWE findings (68)
- Treatment with sotorasib demonstrated better QoL and reduced symptom burden compared with docetaxel. While QoL measurements for subjects in the sotorasib group remained stable, for subjects in the docetaxel group, QoL

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measurements significantly worsened, both directly after administration and long-term treatment (68). Patients treated with sotorasib reported less severe symptoms and were less bothered by treatment side effects than those receiving docetaxel (69)

- The most common adverse events (AEs) reported in the sotorasib and docetaxel groups of CodeBreak 200 were consistent with those previously observed with the individual study treatments or with events expected to occur in the study population independent of drug exposure. Crude subject incidences of grade ≥ 3 AEs, serious events, and fatal events were higher in the sotorasib group compared with the docetaxel group. However, ad hoc analyses of exposure-adjusted event rates were lower in the sotorasib group for all event categories, except for dose interruption (68)

CodeBreak 100

CodeBreak 100 was the key source of clinical evidence supporting the original submission of sotorasib in this indication. Upon entering the CDF, long-term data from CodeBreak 100 were anticipated to help reduce uncertainty in the cost-effectiveness estimates

- CodeBreak 100 is a single-arm open-label Phase 1/2 trial of sotorasib in patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC after progression on prior therapies
- As of 22nd February 2022, 174 patients (Phase 1, N=48; Phase 2, N=126) received sotorasib
- 2-year follow-up analysis of CodeBreak 100 showed that sotorasib treatment provided long-term efficacy and was well tolerated, with no new safety signals detected (70)
 - ORR was 41% (95% CI: 33.3, 48.4), with a median DOR of 12.3 months (95% CI: 7.1, 15.0) (70)
 - Median PFS was 6.3 months (95% CI: 5.3, 8.2) (70)
 - Median OS was 12.5 months (95% CI: 10.0, 17.8), with Kaplan-Meier (KM) estimates of OS of 51% (95% CI: 42.8, 58.2) and 33% (95% CI: 25.0, 40.2) at 12 and 24 months, respectively (70)
 - Across 172 efficacy-evaluable patients, 40 (23%) had long-term clinical benefit (PFS ≥ 12 months) (70)

CAS RWE study

*The CAS RWE study provides key clinical evidence to demonstrate the OS benefit of sotorasib in patients with *KRAS* G12C-mutated NSCLC. The study was designed taking into account input from NICE and NHS England, to support a robust evidence package and validation of real-world outcomes with sotorasib.*

- After accounting for differences in baseline confounders using standardised mortality ratio weighting (SMRW) (average treatment effect in the treated

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[ATT] estimand), CAS RWE study results indicated that sotorasib is more effective than docetaxel monotherapy in 2L+ for prolonging OS, time to next treatment or death (TTNTD), and time to treatment discontinuation or death (TTDD)

- Compared with patients treated with docetaxel, patients treated with sotorasib had:
 - a 36.7% lower risk of death (HR: 0.633; 95% CI: 0.536, 0.749; $p < 0.001$)
 - a 43.3% lower risk of death or new line of therapy (LoT) initiation (HR: 0.567; 95% CI: 0.485, 0.663; $p < 0.001$)
 - a 74.8% lower risk of death or treatment discontinuation (HR: 0.252; 95% CI: 0.212, 0.300; $p < 0.001$)
- Among patients who received sotorasib, median OS was 10.18 months (95% CI: 9.1, 12.02) and median TTNTD was 8.51 months (95% CI: 7.33, 9.43). Among patients who received docetaxel, median OS was 6.87 months (95% CI: 6.01, 7.82) and median TTNTD was 5.62 months (95% CI: 5.06, 6.18)
 - Sotorasib prolonged median OS by approximately 3.25 months, median TTNTD by approximately 3 months, and median TTDD by 2.75 months.

Conclusion

- Taken together, the CodeBreak 200 trial, CodeBreak 100 trial, and CAS RWE study provide sufficient evidence of the clinical effectiveness of sotorasib relative to previous standard of care, docetaxel. Sotorasib is an important treatment for patients with *KRAS G12C*-mutated NSCLC, for whom alternative treatment with non-targeted agents is associated with very poor outcomes
- While CodeBreak 200 provides important data with respect to PFS, AEs, and QoL, due to sample size reductions, the crossover design, and open-label nature of CodeBreak 200, this study was no longer adequately powered to detect an OS benefit. As a result of these limitations, the CAS RWE study is presented as the pivotal evidence to robustly estimate OS outcomes in a UK population
- The results from the CAS RWE study are broadly consistent with other published studies, and are closely aligned to those of a real-world study of US electronic health record data from the Flatiron database, which reported an adjusted median OS of 10.2 months (95% CI: 8.0, 14.6) for patients treated with sotorasib and 7.2 months (95% CI: 5.1, 10.6) for those treated with docetaxel monotherapy or combination therapy in 2L+, resulting in a 35% lower risk of death (HR: 0.65; 95% CI: 0.49, 0.87) with sotorasib (71)
- The consistency strengthens the robustness of the findings across different healthcare settings and supports the credibility of the underlying study methodology in evaluating sotorasib versus docetaxel

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical data assessing the clinical effectiveness and safety of treatments, including sotorasib and relevant comparators, for patients with previously treated *KRAS G12C*-mutated NSCLC.

An overview of the methodology, including search strategy, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, list of included studies and list of excluded studies at full paper review is provided in Appendix B.

2.2 List of relevant clinical effectiveness evidence

The SLR identified two clinical trials of sotorasib monotherapy in patients with *KRAS G12C*-mutated NSCLC:

- CodeBreak 200: Phase 3, multicentre, randomised, open-label, active-controlled study comparing sotorasib with docetaxel in patients with locally advanced/ unresectable or metastatic *KRAS G12C*-mutated NSCLC
- CodeBreak 100: Single-arm open-label Phase 1/2 trial of sotorasib in patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC after progression on prior therapies

Sotorasib entered the CDF in 2022 on the basis of data from the CodeBreak 100 trial. In this submission, longer-term data from CodeBreak 100 are provided, as well as comparative data versus docetaxel from CodeBreak 200. Additional comparative RWE for sotorasib versus docetaxel in a UK population is also available from CAS, given use of sotorasib through the CDF.

An overview of the studies discussed in this submission is provided in Table 6 and Table 7.

Table 6: Clinical effectiveness evidence: clinical trials

Study	CodeBreak 200	CodeBreak 100
Study design	Randomised, open-label, active-controlled Phase 3 trial	Single-arm, multicentre Phase 2 trial
Population	Locally advanced/ unresectable or metastatic <i>KRAS G12C</i> -mutated NSCLC; ≥1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor	Confirmed <i>KRAS G12C</i> -mutated NSCLC who had progressed after receiving 1-3 prior lines of anticancer therapy
Intervention(s)	Sotorasib	Sotorasib
Comparator(s)	Docetaxel	None
Indicate if study supports application for marketing authorisation	At the time of the conditional marketing authorisation, CodeBreak 200 was ongoing and results from this study were intended to provide a comprehensive data package and potentially convert the conditional marketing authorisation into a full marketing authorisation. However, the conditional marketing authorisation was not converted to full marketing authorisation following data readout of CodeBreak 200	Yes
Indicate if study used in the economic model	Yes	No
Rationale if study not used in model	N/A	More relevant data are available from CodeBreak 200 and the CAS RWE study
Reported outcomes specified in the decision problem	PFS, OS , response rates, AEs , HRQoL	PFS, OS, response rates, AEs, HRQoL
All other reported outcomes	DCR, PK	DCR, PK

Abbreviations: AE, adverse event; DCR, disease control rate; HRQoL, health-related quality of life; KRAS, Kirsten rat sarcoma; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics.

Bold indicates outcomes used in the economic model

Table 7: Clinical effectiveness evidence: CAS RWE study

Study	CAS RWE study
Study design	Comparative, retrospective, new-user cohort study using secondary real-world data
Population	Locally advanced or metastatic NSCLC
Intervention(s)	Sotorasib

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Study	CAS RWE study
Comparator(s)	Docetaxel
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	OS, TTD(D)
All other reported outcomes	TTNTD (as a proxy for PFS in the economic model)

Abbreviations: CAS, Cancer Analysis System; NSCLC, non-small cell lung cancer; OS, overall survival; RWE, real word evidence; TTD(D), time to treatment discontinuation (or death); TTNTD, time to next treatment or death.

Bold indicates outcomes used in the economic model

2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

2.3.1 **CodeBreak 200**

The methodology for, and data from, CodeBreak 200 are drawn from multiple sources. These include:

- CodeBreak 200 protocol (72)
- CodeBreak 200 clinical study report (CSR) (68)
- De Langen et al. Lancet 2023; 401: 733–46 (34)
- Waterhouse et al. Lung Cancer. 2024 Oct;196:107921 (69)

2.3.1.1 *Summary of trial methodology*

CodeBreak 200 (NCT04303780) is an ongoing Phase 3, multicentre, randomised, open-label, active-controlled study to evaluate the efficacy, safety, and tolerability of sotorasib versus docetaxel in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with centrally confirmed *KRAS G12C* mutation.

2.3.1.1.1 **Data cut-off**

CodeBreak 200 was initiated on 4th June 2020 and is currently ongoing; the data presented in this submission are based on the primary analysis of PFS, with a database cut-off date of 2nd August 2022 and a database snapshot date of 23rd August 2022.

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2.3.1.2 Study objectives

The aim of CodeBreakK 200 is to evaluate the efficacy, safety, and tolerability of sotorasib compared with docetaxel in subjects with previously treated, locally advanced, and unresectable or metastatic NSCLC with *KRAS G12C* mutation. CodeBreakK 200 is to confirm the benefit from the Phase 1/2 CodeBreakK 100 trial.

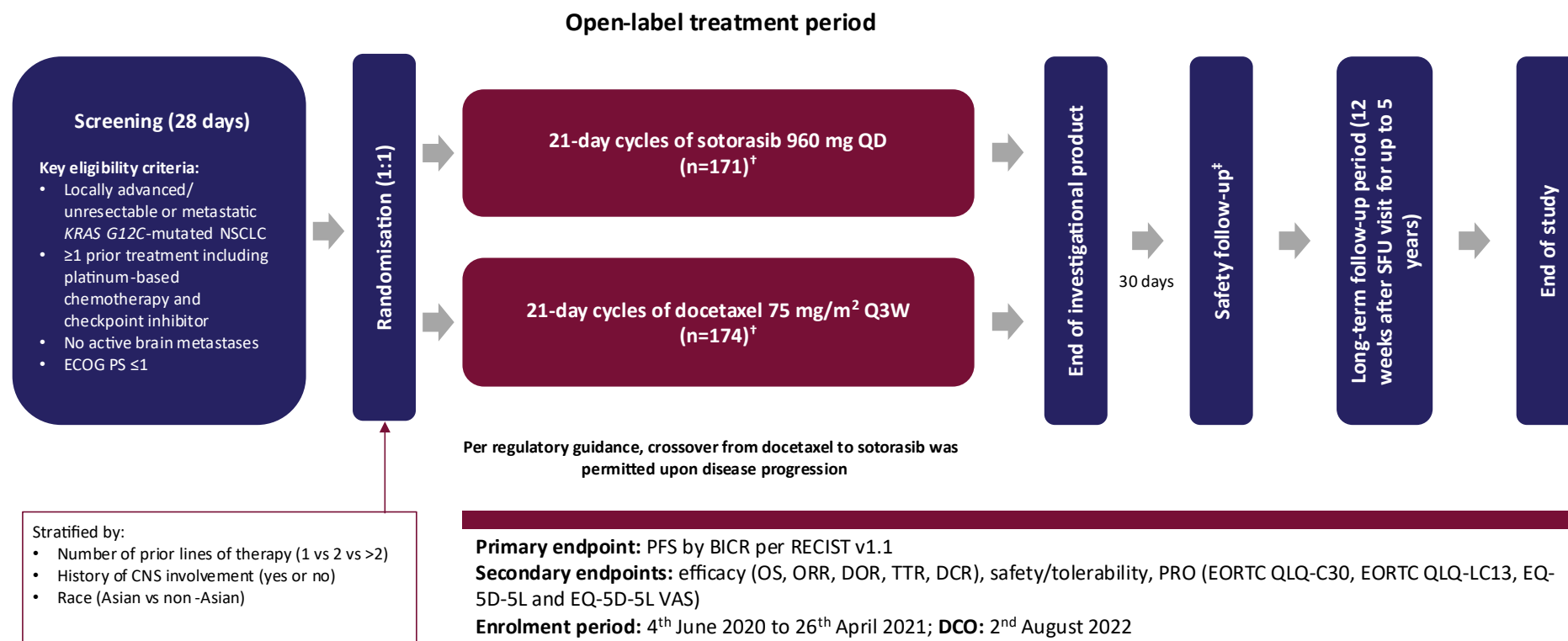
2.3.1.3 Study locations

The study is being conducted at 149 centres in Europe (including UK), North America, Asia, Australia, and South America.

2.3.1.4 Trial design

Patients meeting the eligibility criteria were randomised 1:1 to receive sotorasib or docetaxel. An overview of the CodeBreakK 200 trial design is shown in Figure 2.

Figure 2: Overview of CodeBreak 200 trial design



Abbreviations: BICR, blinded independent central review; CNS, central nervous system; DCO, data cut-off; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QD, once daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; SFU, safety follow-up; TTR, time to response.

† Treatment with investigational product continues until independent central confirmation of progression, intolerance of treatment, initiation of another anticancer therapy, withdrawal of consent, or death. Subjects that consent to treatment beyond progression or consent to crossover, from docetaxel to sotorasib, will continue to receive investigational product after independent central confirmation of progression at the time of first progressive disease. ‡ Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed 30 days (±7 days) after the end of the last dosing interval of investigational product.

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2.3.1.4.1 Method of randomisation and blinding

After meeting all enrolment requirements, subjects were randomised in a 1:1 allocation ratio to either sotorasib or docetaxel. The randomisation was performed by interactive response technology, and the randomisation number was provided to the study centre by the interactive response technology system.

Randomisation was stratified by number of prior lines of therapy in advanced disease (1 versus 2 versus >2), race (Asian versus non-Asian), and history of central nervous system (CNS) involvement (present or absent). The randomisation date was documented in the subject's medical record and on the enrolment case report form (CRF).

The study is open-label. Aggregated safety and efficacy data were only disclosed to the study team at protocol prespecified analyses. Study team members authorised with access to ongoing clinical study data exercised precautions to maintain data confidentiality during study team interactions so as to not let the data influence their input into any changes to the study design or conduct.

2.3.1.4.2 Eligibility criteria

Eligible subjects:

- Were ≥18 years of age
- Had histologically or pathologically documented locally advanced and unresectable or metastatic NSCLC with *KRAS G12C* mutation and no other known oncogenic driver mutation (e.g. *EGFR* or *ALK*) for which there is an approved targeted therapy according to local standard of care or guidelines
- Must have received and progressed or experienced disease recurrence on or after receiving at least one prior systemic therapy for advanced disease, including a platinum-based doublet chemotherapy and a checkpoint inhibitor, either as one line or individual lines of therapy, unless there was a contraindication to those therapies
- Must have had measurable disease per RECIST v1.1 criteria, an ECOG PS of ≤1, and no active brain metastases

A full list of eligibility criteria is provided in Appendix J.

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2.3.1.4.3 Trial drugs

An overview of the investigational products used in the study is provided in Table 8.

Table 8: Overview of trial drugs in CodeBreak 200

Treatment	Sotorasib	Docetaxel
Dosage formulation	Solid dosage form in strengths of 120 mg coated tablets	20 mg/1 mL single dose vial
Unit dose strengths/dosage levels and dosage frequency	960 mg/QD (8 tablets)	75 mg/m ² every 3 weeks
Route of administration	Oral	IV

Abbreviations: IV, intravenous; QD, once daily.

Crossover

Once subjects in the docetaxel group were determined to have radiological progression according to RECIST v1.1 by the investigator and progressive disease confirmed by independent central imaging review, they had the opportunity to crossover and receive sotorasib.

2.3.1.4.4 Concomitant medications

Prior anticancer therapies (including radiotherapy or surgeries for current malignancy) from the time of the original diagnosis through enrolment, as well as all other prior therapies taken 28 days before enrolment through enrolment, were recorded in the subject's appropriate CRF(s). Throughout the study, investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the protocol. Concomitant therapies (including supplemental oxygen) from enrolment through the end of safety follow-up (SFU; 30 days after the last dose of all investigational products) were recorded on the appropriate CRF. Subsequent treatment for NSCLC was recorded after the SFU period during the long-term follow up. Coadministration of sotorasib with proton pump inhibitors and H₂ receptor antagonists was to be avoided; when this was not possible, sotorasib was to be administered 4 hours before or 10 hours after a local antacid. Breast cancer resistance protein substrates were to be used with caution when co-administered with sotorasib, which may increase the circulating concentrations of the substrates.

2.3.1.4.5 Assessment of treatment compliance

During clinic visits, sotorasib was administered at the study centre, and on days outside the clinic, subjects self-administered sotorasib daily. Treatment compliance was documented in the medical records and collected in the CRF and through an electronic dosing diary provided to subjects. Subjects were instructed to complete the electronic diary daily with the response yes (if investigational product was taken) or no (in the event of dose interruption due to AE, etc). Subjects were also required to bring bottle(s) of sotorasib to the clinic (as per guidance in the Investigational Product Instruction Manual) and return remaining tablets when they came off treatment. Tablet counts were collected by study staff, and at treatment discontinuation, or SFU.

2.3.1.4.6 Withdrawals and discontinuations

Subjects had the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution. The investigator and/or sponsor could decide to withdraw a subject from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time before study completion.

The investigator discussed with the subject the appropriate processes for discontinuation of investigational product or other protocol-required therapies and the possibilities for continuation of the schedule of activities, including options for follow-up and collection of data (e.g. endpoints, AEs).

Reasons for discontinuation of study treatment or discontinuation from study were documented.

2.3.1.5 Outcomes

2.3.1.5.1 Primary outcome

The primary outcome was PFS, defined as time from randomisation until disease progression or death from any cause, whichever occurred first for all subjects. Progression was based on blinded independent central review (BICR) of disease response per RECIST v1.1.

2.3.1.5.2 Secondary outcomes

Secondary outcomes are outlined in Table 9.

Table 9: CodeBreakK 200 secondary outcome measures

Outcome	Definition
OS	Defined as time from randomisation until death from any cause
ORR	CR + PR, assessed per RECIST v1.1 by BICR. CR and PR required confirmatory repeat radiologic assessment at no less than 4 weeks after the original response. The normal subsequent assessment was acceptable to confirm response
PRO	Change from baseline (cycle 1 day 1) over time to week 12 in disease-related symptoms of: - Dyspnoea as measured by a 4-item dyspnoea domain from EORTC QLQ-C30 and QLQ-LC13 - Cough as measured by QLQ-LC13 - Chest pain as measured by QLQ-LC13 Change from baseline over time to week 12 in - Physical functioning as measured by QLQ-C30 - Global health status as measured by QLQ-C30
DOR	Defined as time from first evidence of PR or CR to disease progression or death due to any cause, whichever occurred first. Progression was based on a BICR assessment of disease response per RECIST v1.1
TTR	Defined as time from randomisation to first evidence of PR or CR
DCR	Defined as rate of confirmed objective response (CR or PR) + stable disease per RECIST v1.1 of at least 6 weeks measured
Safety and tolerability	Subject incidence of TEAEs, treatment-related AEs, changes in vital signs, and clinical laboratory tests
HRQoL	- Change from baseline over time to week 12 for the remaining subscales for EORTC QLQ-LC13 and QLQ-C30 - Time to deterioration for the subscales for QLQ-LC13 and QLQ-C30 - Summary scores at each assessment and changes from baseline of VAS scores as measured by EQ-5D-5L
PK	PK parameters of sotorasib including, but not limited to, maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) on days 1 and 8, and predose (trough) concentrations through cycle 4

Abbreviations: AE, adverse event; BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PK, pharmacokinetics; PR, partial response; PRO, patient reported outcome; QLQ-C30, Quality-of-life Questionnaire Core 30; QLQ-LC13, Cancer Quality-of-life Questionnaire Lung Cancer 13; RECIST, Response Evaluation Criteria in Solid Tumours; TEAE, treatment-emergent adverse event; TTR, time to response; VAS, visual analogue scale.

2.3.1.6 Pre-planned subgroups

Pre-planned subgroup analyses were conducted, as outlined in Section 2.8.1.

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2.3.1.7 Protocol amendments

The protocol for this study (originally dated 19th November 2019) was amended four times. Each protocol amendment included a number of changes. Key changes which had a substantial impact on the study conduct are described below.

The study began in November 2019 and is ongoing as of the data cut-off date for this analysis; this timeframe included the period during which the COVID-19 pandemic was occurring globally. The study was at the stage of recruitment when the pandemic occurred. Contingency measures were implemented to manage study conduct during the COVID-19 pandemic.

Following regulatory feedback from the US Food and Drug Administration (FDA), a substantial change in study conduct was the reduction of the sample size in amendment 3 from 650 subjects (powered for the secondary endpoint of OS) to 330 subjects (powered for the primary endpoint of PFS). This change was brought forth following data that became available at the time from the primary analysis of CodeBreakK 100, which demonstrated a rapid and durable response and a high DCR, providing evidence that sotorasib offers a benefit over docetaxel. Sotorasib became the first KRAS^{G12C} inhibitor to show PFS (median of 6.8 months) in a Phase 2 study. As a result of this change, the study was no longer powered to detect an OS benefit.

Another noteworthy change in study conduct following FDA feedback was to allow subjects randomised to the docetaxel group to crossover to the sotorasib group, to maximise the number of patients who received sotorasib due to the positive data from CodeBreakK 100. With the option for crossover, investigators could consider if allowing their subjects in the docetaxel group to crossover to sotorasib would be beneficial with regard to disease-related symptoms and QoL relative to docetaxel. Additionally, crossover would have been considered if, at the time of PFS interim analysis, efficacy (statistically significant and clinically meaningful) was noted by the independent Data Monitoring Committee (DMC) regardless of the progression status.

2.3.1.8 Baseline characteristics and demographics

The majority of subjects in the study were men (204 subjects [59.1%]), white (286 subjects [82.9%]) or Asian (43 subjects [12.5%]), and not Hispanic/Latino (328 Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

subjects [95.1%]. The median age was 64.0 (range: 32 to 88) years, and approximately half of subjects were <65 years (186 subjects [53.9%]). The majority of subjects were from Europe (252 subjects [73.0%]), followed by rest of world (51 subjects [14.8%] in Asia, Australia, and South America), and North America (42 subjects [12.2%]).

Most subjects had non-squamous (334 subjects [96.8%]), metastatic disease (328 subjects [95.1%]). All 345 subjects had a first prior line of therapy, 197 subjects (57.1%) had a second line of therapy, 56 subjects (16.2%) had a third line of therapy, and 118 subjects (34.2%) were on maintenance therapy. The majority of subjects had no history of CNS involvement (227 subjects [65.8%]) and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 at screening (227 subjects [65.8%]). PD-L1 protein expression was <1% for 112 subjects (32.5%), ≥1% to <50% for 116 subjects (33.6%), and ≥50% for 100 subjects (29.0%). Other co-mutations at baseline included *TP53* (10 subjects [2.9%]), *STK11* (8 subjects [2.3%]), *MET* and *KEAP1* (3 subjects [0.9%] each), *BRAF* (2 subjects [0.6%]), and *EGFR*, *ALK*, and *ROS1* (1 subject [0.3%] each).

Overall, no noteworthy differences in baseline demographics or characteristics were observed between the treatment groups. An overview of key baseline characteristics and demographics is provided in Table 10.

Table 10: Key baseline characteristics of participants in CodeBreakK 200

	Docetaxel (N=174)	Sotorasib (N=171)
Age at randomisation, years		
N	174	171
Mean	63.6	63.4
Median	64.0	64.0
Min, max	35, 87	32, 88
<65 years, n (%)	95 (54.6)	91 (53.2)
≥65 years, n (%)	79 (45.4)	80 (46.8)
Sex, n (%)		
Male	95 (54.6)	109 (63.7)
Female	79 (45.4)	62 (36.3)
Ethnicity, n (%)		
Hispanic/Latino	9 (5.2)	5 (2.9)

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	Docetaxel (N=174)	Sotorasib (N=171)
Not Hispanic/Latino	163 (93.7)	165 (96.5)
Unknown	2 (1.1)	1 (0.6)
Race, n (%)		
American Indian or Alaska Native	0 (0.0)	0 (0.0)
Asian	22 (12.6)	21 (12.3)
Black or African American	0 (0.0)	2 (1.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
White	144 (82.8)	142 (83.0)
Multiple	0 (0.0)	1 (0.6)
Other	7 (4.0)	4 (2.3)
Unknown	1 (0.6)	1 (0.6)
ECOG PS at screening, n (%)		
0	59 (33.9)	59 (34.5)
1	115 (66.1)	112 (65.5)
ECOG PS at Cycle 1 Day 1, n (%)		
0	46 (26.4)	66 (38.6)
1	105 (60.3)	100 (58.5)
2	1 (0.6)	1 (0.6)
3	1 (0.6)	0 (0.0)
Missing	21 (12.1)	4 (2.3)
Prior line of therapy, n (%)†		
First	174 (100.0)	171 (100.0)
Second	100 (57.5)	97 (56.7)
Third	27 (15.5)	29 (17.0)
Fourth	6 (3.4)	6 (3.5)
Fifth	2 (1.1)	2 (1.2)
Sixth	1 (0.6)	0 (0.0)
Seventh	0 (0.0)	0 (0.0)
Maintenance	56 (32.2)	62 (36.3)
Other	2 (1.1)	2 (1.2)
History of CNS involvement, n (%)		
Yes	60 (34.5)	58 (33.9)
No	114 (65.5)	113 (66.1)
Liver metastasis, n (%)		
Yes	35 (20.1)	30 (17.5)
No	139 (79.9)	141 (82.5)

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	Docetaxel (N=174)	Sotorasib (N=171)
Smoking history – tobacco, n (%)		
Never	8 (4.6)	5 (2.9)
Current	35 (20.1)	32 (18.7)
Former	131 (75.3)	134 (78.4)
Histology, n (%)		
Squamous	7 (4.0)	1 (0.6)
Non-squamous	165 (94.8)	169 (98.8)
Other	2 (1.1)	1 (0.6)
Disease stage, n (%)		
Locally advanced and unresectable	8 (4.6)	9 (5.3)
Metastatic	166 (95.4)	162 (94.7)
Other	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Best response on prior therapy, n (%)		
Primary refractory (progression on first scan)	57 (32.8)	67 (39.2)
Suboptimal response (stable disease)	53 (30.5)	50 (29.2)
Recurrent (initial response with subsequent growth)	47 (27.0)	35 (20.5)
Not evaluable	11 (6.3)	10 (5.8)
Non-PD/non-CR	6 (3.4)	9 (5.3)
Time from initial diagnosis to randomisation, months		
N	161	162
Mean	24.47	23.33
Median	16.92	16.21
Min, max	1.5, 227.3	2.3, 132.3
PD-L1 protein expression, n (%)		
<1%	55 (31.6)	57 (33.3)
≥1 to <50%	70 (40.2)	46 (26.9)
≥50%	40 (23.0)	60 (35.1)

Abbreviations: CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PS, performance status.

The subject with "Multiple" race has listed "White" as primary race in case report form, thus is considered under "White" in the by race subgroup analysis.

History of CNS involvement is the presence of brain metastasis at baseline.

† Same subject can be counted under multiple categories.

2.3.2 CodeBreak 100

The methodology for, and data from, CodeBreak 100 (NCT03600883) are drawn from multiple sources. These include:

- Hong et al. N Engl J Med 2020;383:1207-1217 (73)
- Dy et al. J Clin Oncol. 2023 Jun 20;41(18):3311-3317 (70)
- CodeBreak 100 protocol (74)
- CodeBreak 100 CSR (75)

2.3.2.1 Summary of study methodology

CodeBreak 100 is an ongoing, single-arm open-label Phase 1/2 trial of sotorasib in patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC after progression on prior therapies. An overview of the study methodology is provided in Table 11 and Figure 3.

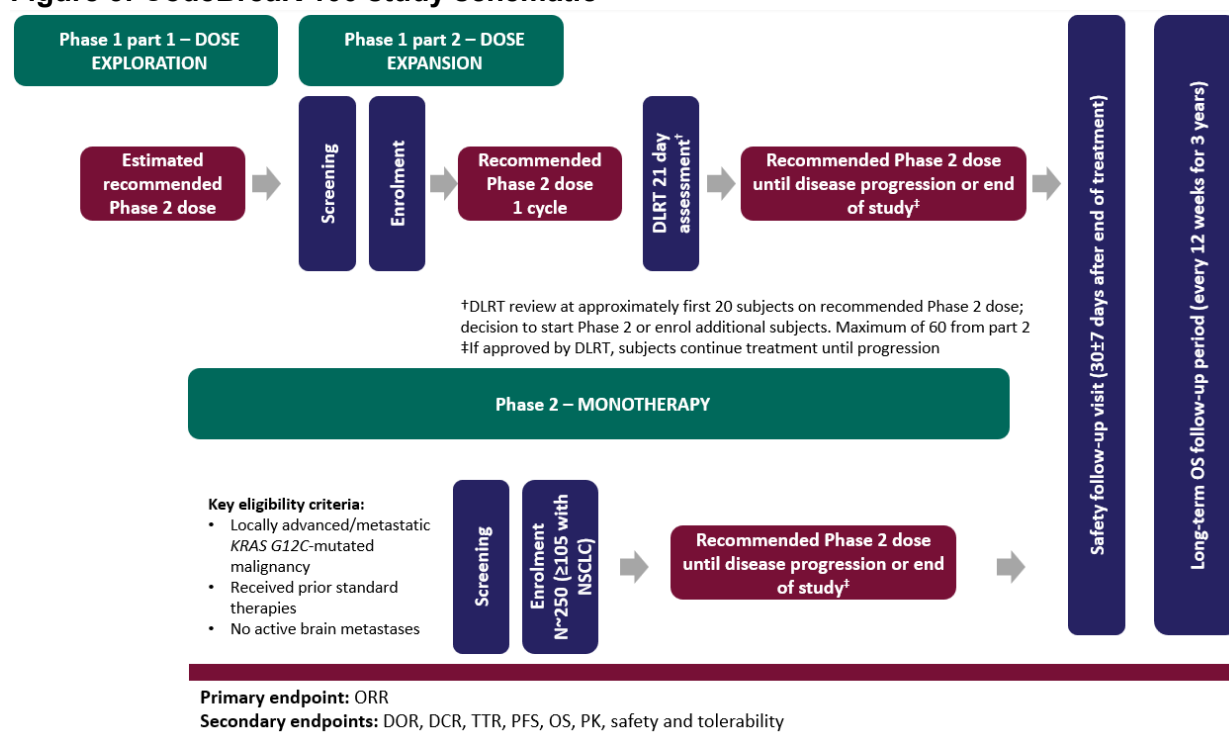
Table 11: Summary of CodeBreak 100 methodology

Study	CodeBreak 100
Study design	Single-arm open-label Phase 1/2 trial
Study locations	Australia, Austria, Brazil, Canada, France, Germany, Greece, Hungary, Japan, Korea, Portugal, Romania, Spain, Switzerland, United States
Trial drugs	Sotorasib
Key endpoints	Phase 1 Primary: safety and tolerability <i>Key secondary</i> : DOR, PFS Phase 2 <i>Primary</i> : ORR by BICR <i>Key secondary</i> : DOR, PFS, OS, safety
Key eligibility criteria	• Adult subjects (≥18 years of age) with advanced <i>KRAS G12C</i>-mutated solid tumours as assessed by molecular testing and confirmed by central testing • Subjects must have had: – ≥1 prior line of systemic anticancer therapy – Progression on prior line of therapy – Measurable disease per RECIST 1.1 criteria – ECOG PS of ≤1 – No active brain metastases (but patients with treated and stable brain metastases could enrol) – QTc ≤470 msec (based on average of screening triplicates) – Ability to take oral medications – Adequate haematological, renal, hepatic, and coagulation laboratory assessments

Abbreviations: BICR, blinded independent central review; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; PS, performance status; QTc, corrected QT (interval).

Company evidence submission template for sotorasib for previously treated *KRAS G12C* mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

Figure 3: CodeBreak 100 study schematic



Abbreviations: DCR, disease control rate; DLRT, dose level review team; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; TTR, time to response.

2.3.2.2 Baseline characteristics and demographics

As of 22nd February, 2022, 174 patients (Phase 1, N=48; Phase 2, N=126) received sotorasib. Median treatment duration was 5.6 months (range, 0.2–35.9); 13 patients remained on treatment at cut-off. Median prior lines of therapy was 2.0 (range, 0–4+). Prior therapies included anti-PD-(L)1 (157 [90%]) and platinum-based chemotherapy plus anti-PD-(L)1 (144 [83%]). An overview of patient demographics and baseline characteristics is provided in Table 12.

Table 12: Patient demographics and baseline characteristics in CodeBreak 100

	Phase 1 (N=48)	Phase 2 (N=126)	Total (N=174)
Age, years, median (range)	68.5 (49-86)	63.5 (37-80)	65.0 (37-86)
Female, n (%)	28 (58)	63 (50)	91 (52)

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	Phase 1 (N=48)	Phase 2 (N=126)	Total (N=174)
Race, n (%)			
White	38 (79)	103 (82)	141 (81)
Asian	6 (13)	19 (15)	25 (14)
Black	2 (4)	2 (2)	4 (2)
Other	2 (4)	2 (2)	4 (2)
ECOG PS at baseline, n (%)			
0	11 (23)	38 (30)	49 (28)
1	37 (77)	88 (70)	125 (72)
Metastatic sites, n (%)			
Bone	20 (42)	61 (48)	81 (47)
Brain	14 (29)	26 (21)	40 (23)
Liver	12 (25)	26 (21)	38 (22)
Disease stage at screening, n (%)			
III	1 (2)	5 (4)	6 (3)
IV	47 (98)	121 (96)	168 (97)
PD-L1 protein expression, n (%)[†]			
<1%	13 (27)	33 (26)	46 (26)
≥1 to 49%	12 (25)	30 (24)	42 (24)
≥50%	9 (19)	35 (28)	44 (25)
Unknown	14 (29)	28 (22)	42 (24)
Prior lines of therapy, n (%)			
0	2 (4)	0	2 (1)
1	17 (35)	54 (43)	71 (41)
2	14 (29)	44 (35)	58 (33)
≥3	15 (31)	28 (22)	43 (25)
Type of prior therapy, n (%)[‡]			
Platinum-based chemotherapy	48 (100)	113 (90)	161 (93)
Anti-PD-(L)1	41 (85)	116 (92)	157 (90)
Platinum-based chemotherapy and anti-PD-(L)1	41 (85)	103 (82)	144 (83)
Anti-VEGF biological therapy	10 (21)	26 (21)	36 (21)
Targeted small molecules	10 (21)	9 (7)	19 (11)

	Phase 1 (N=48)	Phase 2 (N=126)	Total (N=174)
Best response to last prior line of therapy, n (%)			
Complete response	0	1 (1)	1 (1)
Partial response	2 (4)	12 (10)	14 (8)
Stable disease	11 (23)	33 (26)	44 (25)
Progressive disease	24 (50)	48 (38)	72 (41)
Unevaluable/unknown/missing	9 (19)	32 (25)	41 (24)
Duration of sotorasib treatment, months, median (range)	6.0 (0.2-35.9)	5.5 (0.2-26.9)	5.6 (0.2-35.9)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; VEGF, vascular endothelial growth factor.

† Determined locally.

‡ Each patient may have had more than one prior therapy.

2.3.3 CAS RWE study

The methodology for, and data from, the CAS RWE study are drawn from multiple sources. These include:

- CAS RWE study protocol (76)
- CAS RWE study report (77)

2.3.3.1 Summary of study methodology

The CAS RWE study is a comparative, retrospective cohort study using real-world data from the CAS database in England to generate evidence on the comparative effectiveness of sotorasib versus docetaxel monotherapy in second-line and beyond (2L+) locally advanced or metastatic NSCLC who have previously been treated with platinum-doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy. The CAS database captures patients in receipt of sotorasib through the CDF. The study was designed taking into account input from NICE and NHS England, to support a robust evidence package and validation of real-world outcomes with sotorasib.

2.3.3.2 Study objectives

2.3.3.2.1 Primary objective

The primary objective of the study was to compare OS in patients with locally advanced or metastatic NSCLC who initiated treatment with sotorasib monotherapy versus docetaxel monotherapy in 2L+.

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2.3.3.2.2 Secondary objective

The secondary objective of the study was to compare TTNTD in patients with locally advanced or metastatic NSCLC who initiated treatment with sotorasib monotherapy versus docetaxel monotherapy in 2L+.

2.3.3.2.3 Exploratory objective

The exploratory objective of the study was to compare TTDD in patients with locally advanced or metastatic NSCLC who initiated treatment with sotorasib monotherapy versus docetaxel monotherapy in 2L+.

2.3.3.3 Study design

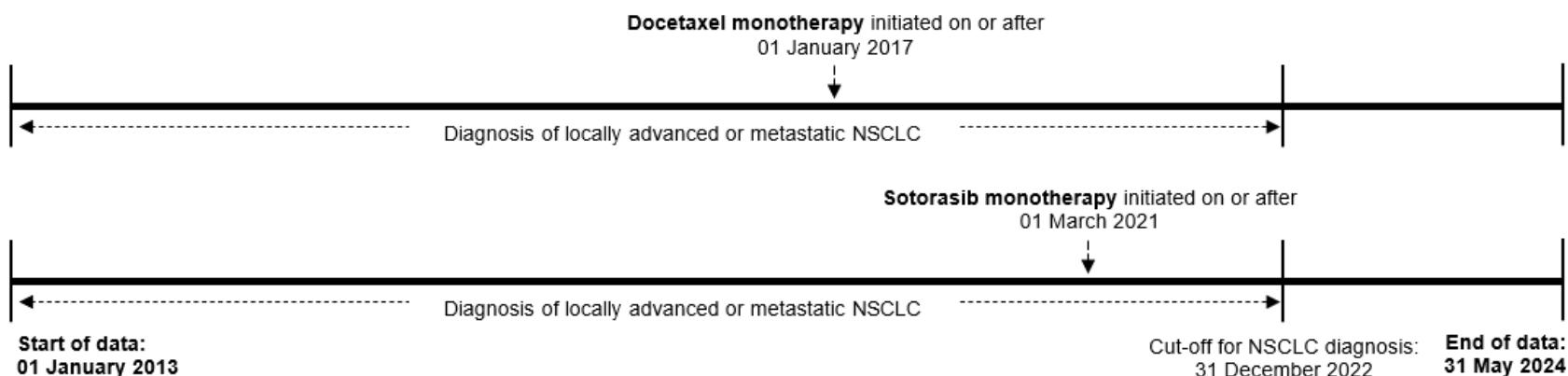
This was a comparative, retrospective, new-user cohort study using the CAS database in England to generate evidence on the comparative effectiveness of sotorasib monotherapy in 2L+ in patients with locally advanced or metastatic NSCLC who have previously been treated with platinum-doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy. Eligible patients with *KRAS* G12C-mutated NSCLC who initiated sotorasib monotherapy were compared against patients with NSCLC who initiated docetaxel monotherapy. Patients who initiated docetaxel monotherapy were included irrespective of *KRAS* mutation status (i.e. with mutated, wild type, or unknown *KRAS* status), as an initial pilot study in the CAS database found that there were few eligible patients with any *KRAS* mutation or specific G12C mutation due to limited testing for *KRAS* mutations prior to the introduction of *KRAS* inhibitors.

The study design and analytical approaches were informed by the target trial emulation framework, which provides a formal methodology for designing studies aimed to estimate causal effects using real-world data and is the preferred approach of NICE, as specified in the NICE RWE Framework (78).

An overview of the study design is provided in Figure 4.

Figure 4: Overview of CAS RWE study design

- Baseline period to assess demographics, clinical characteristics, tumour characteristics, and prior therapies for advanced NSCLC from 01 January 2013 until initiation of either sotorasib or docetaxel monotherapy (index date). Molecular characteristics to be assessed from any point in patient records.
- Follow-up period to assess clinical study outcomes from start of either sotorasib or docetaxel monotherapy (index date) to the earliest date of death, loss to follow-up, 31 May 2024, or 39 months post-index date.



Data source: Study data were collected from the Cancer Analysis System (CAS) database, which contains data on nearly all cancer patients treated in National Health Service hospitals in England. Patients were included if they are aged ≥ 18 years and had a diagnosis of advanced NSCLC between 1 January 2013 and up to 31 December 2022. Patients who initiated docetaxel monotherapy in 2L+ between 01 January 2017 and 31 May 2024 were part of the docetaxel cohort, while patients who initiated sotorasib monotherapy in 2L+ between 01 March 2021 and 31 May 2024 were part of the sotorasib cohort. Index date for assessing clinical study outcomes was the date of treatment initiation of sotorasib or docetaxel monotherapy.

Patient-level characteristics collected:

- Demographics (e.g., age, ethnicity, gender)
- Clinical and tumour characteristics (e.g., staging, histology, performance status, comorbidities)
- Treatments received in the advanced setting
- Molecular profile (e.g., *KRAS*, *EGFR*, *ALK*, PD-L1, *ROS1*, *BRAF*, *RET*, *NTRK*, *MET*, *STK11*, *TP53*)

Clinical study outcomes:

- Overall survival (OS)
- Time to next treatment or death (TTNTD)
- Time to treatment discontinuation or death (TTDD)

Abbreviations: CAS, Cancer Analysis System; NSCLC, non-small cell lung cancer; RWE, real-world evidence.

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2.3.3.4 *Setting and study population*

Patients with locally advanced or metastatic NSCLC were identified in the CAS database, which includes diagnosis, treatment, tumour, molecular, and survival data relating to nearly all patients diagnosed with cancer in England. Diagnoses of NSCLC were identified according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes and International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) codes.

2.3.3.5 *Study period*

The overall study period ran from 1st January 2013 to 31st May 2024, based on most recent data availability in the CAS database at the time of analysis.

2.3.3.5.1 *Index date*

Patients were indexed at the earliest date of initiation of sotorasib monotherapy or docetaxel monotherapy in 2L+ which occurs within the indexing period. Due to differing approval dates and dates of availability of the two treatments of interest, the indexing period varied according to treatment cohort:

- Sotorasib was approved by the MHRA in September 2021, however, it was made available to eligible patients with locally advanced or metastatic NSCLC in England through the Early Access to Medicines Scheme in March 2021 and through the CDF in March 2022. The indexing period for sotorasib monotherapy therefore ran from 1st March 2021 to 31st May 2024. The end of the indexing period was based on the most recent data available in CAS at the time of analysis
- To ensure that patients in the docetaxel cohort had an opportunity to receive prior PD-1/PD-L1 targeted immunotherapy and to provide a contemporary cohort, the indexing period for the docetaxel cohort ran from 1st January 2017 to 31st May 2024. The end of the indexing period was based on the most recent data available in CAS at the time of analysis

Note that the end of the indexing period for both cohorts was equal to the end of the study period, such that there is no imposed minimum opportunity for follow-up. This decision was taken due to sample size considerations.

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2.3.3.5.2 Baseline period and study follow-up

Patients were followed from their index date to the earliest date of death, loss to follow-up, or end of study period (see Section 2.3.3.5). As the indexing period for the sotorasib cohort was shorter due to sotorasib being more recently approved, the maximum potential duration of follow-up in the sotorasib cohort is shorter than in the docetaxel cohort. Therefore, to ensure that the opportunity for follow-up is the same for both treatment cohorts, the maximum period of follow-up was defined as 39 months post-index date, which is based on the maximum potential duration of follow-up for a patient in the sotorasib cohort. Consequently, patients in the docetaxel cohort with available follow-up exceeding 39 months were censored at 39 months.

For all main analyses, patients who switched from docetaxel monotherapy to sotorasib monotherapy (or vice versa) were not censored at the time of treatment switching. Two sensitivity analyses for the primary objective were performed in which patients were censored at switching.

2.3.3.6 Eligibility criteria

Staging in CAS is only recorded at initial diagnosis, and treatment intent (i.e. curative versus palliative) is not reliably captured. Consequently, the study population for all main analyses was restricted to patients with *de novo* stage III or stage IV NSCLC. As LoTs are not directly recorded in the CAS database, LoTs were derived according to an algorithm to determine study eligibility (see Appendix K). The algorithm is applicable to patients with *de novo* stage III or stage IV NSCLC and has previously been internally validated in this population. Sensitivity analyses were conducted in an expanded study population which includes patients who received sotorasib but were initially diagnosed with stage I or stage II NSCLC.

To ensure comparability of the two cohorts, study eligibility criteria were based on the key eligibility criteria for the use of sotorasib in the CDF, as outlined in Table 13. Due to restrictions on the use of sotorasib, it can be reasonably assumed that patients who initiated sotorasib within the indexing period will have received treatment according to the conditions specified in the Managed Access Agreement.

Therefore, to preserve sample size, most key criteria were assumed to apply to the sotorasib cohort and only explicitly applied to the docetaxel cohort.

Table 13: Summary of key eligibility criteria for sotorasib treatment through the CDF and applicability to CAS RWE study cohorts

Eligibility criterion in Managed Access Agreement for sotorasib [†]	Applicability to sotorasib cohort	Applicability to docetaxel cohort
Patient has locally advanced or metastatic NSCLC	Assumed to apply, but main study population restricted to <i>de novo</i> stage III and stage IV NSCLC due to limitations of CAS database and use of algorithm for classifying LoTs	Main study population restricted to <i>de novo</i> stage III and stage IV NSCLC due to limitations of CAS database and use of algorithm for classifying LoTs
Patient has a histologically confirmed diagnosis of NSCLC that has been shown to exhibit a <i>KRAS G12C</i> mutation at any point prior to index date	Assumed to apply	Not applied to main study population due to sample size limitations but applied in descriptive sensitivity analyses; measurements at any point in patient records allowed to preserve sample size
Patient has been treated with platinum doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy at any point prior to index date	Assumed to apply	Applied directly as inclusion criterion
Patient has an ECOG performance status score of 0 or 1 at index date	Assumed to apply; confirmed during data extraction that all patients have an ECOG score of 0, 1, or 2 [‡] (or missing) within ±7 days of index date [§]	Applied directly as exclusion criterion (i.e. ECOG score >2 [‡]); measurements within ±7 days of index date allowed to preserve sample size [§]
Patient either has no known brain metastases or is symptomatically stable if he/she does have brain metastases at index date	Assumed to apply	Unable to apply due to limitations of metastasis and symptom recording in CAS

Abbreviations: CAS, Cancer Analysis System; CDF, Cancer Drugs Fund; ECOG, Eastern Cooperative Oncology Group; LoT, line of therapy; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PS, performance status; RWE, real-world evidence.

[†] There are not expected to be major differences in eligibility for patients who received sotorasib via the Early Access to Medicines Scheme versus the CDF, and the proportion of patients who received sotorasib via the Early Access to Medicines Scheme is expected to be low.

[‡] Although the eligibility criterion for the Managed Access Agreement specified sotorasib patients should have an ECOG PS ≤1, patients with ECOG 2 were identified in the CAS database. Accordingly, to ensure comparability an exclusion criteria of ECOG >2 was applied to the docetaxel cohort.

[§] To allow for variations in the measurement timings in real-world data, values of ECOG score within ±7 days of index date were allowed to preserve sample size. To quantify the potential magnitude of any immortal time bias due post-index date selection criteria, the timing of ECOG measurement at index date was reported descriptively as part of study outputs.

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Other eligibility criteria were applied to both cohorts to facilitate an unbiased comparison of sotorasib monotherapy versus docetaxel monotherapy in 2L+. Patients previously treated with sotorasib monotherapy or docetaxel monotherapy in the advanced setting were excluded from both cohorts, to ensure that the treatment received at index date represents a patient's first receipt of either treatment of interest. Patients with any record of prior malignancy or systemic anti-cancer therapy were also excluded, to ensure that baseline prognosis and classification of LoTs was not affected by treatments received for other tumours. Finally, applying an algorithm to determine LoTs and identify eligible patients from the CAS database first requires that a patient has valid treatment records and is not missing key information required to run the algorithm. Although removing patients with missing data was more appropriately considered a data cleaning step rather than a true exclusion criterion, it was included as an explicit criterion as it contributed to patient attrition from the CAS database.

Inclusion and exclusion criteria for the sotorasib and docetaxel groups are outlined in Table 14.

Table 14: CAS RWE study inclusion and exclusion criteria

	Docetaxel group	Sotorasib group
Inclusion criteria	Patients must satisfy all of the following criteria: • Diagnosis of NSCLC between 1st January 2013 and 31st December 2022, defined according to ICD-10 codes indicating lung cancer and excluding ICD-O-3 morphology codes indicating SCLC • Aged ≥18 years at NSCLC diagnosis date • Eligible to have LoTs derived algorithmically[†] • Stage III or stage IV tumour at NSCLC diagnosis • Documented initiation of docetaxel or sotorasib monotherapy in 2L+ for locally advanced or metastatic NSCLC within the indexing period, as identified using the LoT algorithm	
	Any record of treatment with platinum-doublet chemotherapy (i.e. cisplatin or carboplatin in combination with one of: docetaxel, paclitaxel, vinorelbine, gemcitabine, irinotecan, pemetrexed, or tegafur gimeracil oteracil) and/or PD-1/PD-L1 targeted immunotherapy (atezolizumab, durvalumab, ipilimumab, nivolumab, or pembrolizumab) at any point prior to index date	To maximise available sample size, no additional inclusion criteria were applied to the sotorasib cohort, since it can be reasonably assumed that all patients who initiated sotorasib within the indexing period will have received treatment according to the conditions specified in the Managed Access Agreement, as summarised in Table 13.

Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

	Docetaxel group	Sotorasib group
Exclusion criteria	• Diagnosis of any other primary malignancy (excluding non-melanoma skin cancer, defined according to ICD-10 codes) at any point prior to index date • Record of any systemic anti-cancer therapy more than 30 days prior to diagnosis date[†] • Treated with sotorasib monotherapy or docetaxel monotherapy in the advanced setting at any point prior to index date	
	• Any record of treatment with atezolizumab with carboplatin and etoposide (used exclusively for patients with SCLC) at any point prior to index date, as identified using the LoT algorithm • ECOG performance score of >1 within 7 days $\pm$ index date[§]	-

Abbreviations: CAS, Cancer Analysis System; COSD, Cancer Outcomes and Services Dataset; ECOG, Eastern Cooperative Oncology Group; ICD, International Classification of Diseases; LoT, line of therapy; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; RWE, real-world evidence; SACT, systemic anti-cancer therapy; SCLC, small cell lung cancer.

[†] To be eligible to have LoTs derived algorithmically, patients must have a record of receiving at least one eligible NSCLC treatment, and at least one recorded regimen must have non-missing cycle information.

[‡] Diagnoses and SACT are recorded in different components of the CAS database (i.e. the COSD and the SACT dataset, respectively). Consequently, we allow for SACT to begin within 30 days prior to diagnosis to account for possible delays in the administrative recording of diagnoses. SACT which is recorded >30 prior to diagnosis of NSCLC is assumed to relate to a different tumour.

[§] Although the eligibility criterion for the Managed Access Agreement specified sotorasib patients should have an ECOG PS $\leq$ 1, patients with ECOG 2 were identified in the CAS database. Accordingly, to ensure comparability an exclusion criteria of ECOG >2 was applied to the docetaxel cohort – see Table 13.

2.3.3.7 Data sources

NHS Digital collects, stores, and analyses data through the National Disease Registration Service (NDRS). An important component of NDRS is the National Cancer Registration and Analysis Service (NCRAS), which maintains the datasets that comprises CAS (79).

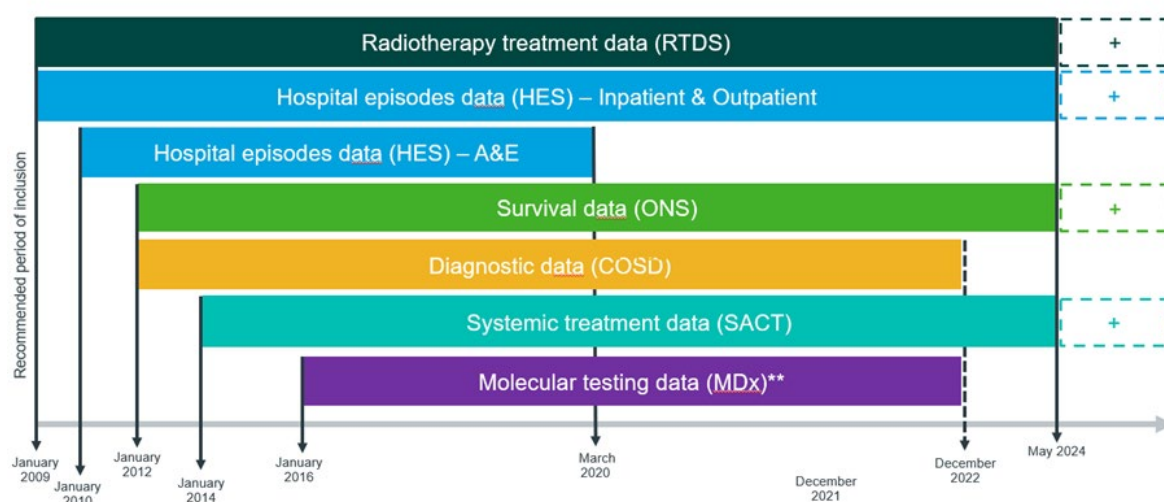
The CAS database is one of the most granular cancer registries in the world, containing data on nearly all cancer patients treated in NHS hospitals in England. It provides timely data, with detailed clinical information, on all 500,000 patients diagnosed with cancer in England each year. CAS data are captured in a range of formats from multiple healthcare sources, including hospitals and histopathology laboratories.

The CAS database comprises several distinct datasets. For the purposes of this study, the Cancer Outcomes and Services Dataset (COSD), Systemic Anti-Cancer Therapy (SACT), and Molecular Diagnostics (MDx) datasets were used, containing

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detailed patient-level information about tumours, therapies, somatic mutations, and mortality, as well as other linked datasets. Due to data quality assurance processes, there is a time lag from data collection to data being available for research on each of the datasets that form CAS. Figure 5 displays data availability for each dataset in CAS at the time of analysis. The study population came from the overlap between the COSD and SACT datasets.

Figure 5: Data availability in CAS



Abbreviations: A&E, accident and emergency; COSD, Cancer Outcomes and Services Dataset; HES; Hospital Episode Statistics; MDx, Molecular Diagnostics; NHS, National Health Service; ONS, Office for National Statistics; RTDS; Radiotherapy Data Set; SACT, systemic anti-cancer therapy.

**PD-L1/MMR biomarker data availability: January 2019 to December 2022.

2.3.3.8 Variables

Demographic and clinical characteristics, tumour characteristics, and prior therapies for advanced NSCLC were assessed from the start of available data (i.e. 1st January 2013) until index date. Molecular characteristics were assessed from any point in patient records.

2.3.3.8.1 Exposure assessment

The primary exposure of interest was sotorasib monotherapy, and the comparator exposure of interest was docetaxel monotherapy. Both exposures must be delivered after at least one prior LoT in the advanced setting (i.e. in 2L+). No restrictions on dose or duration of therapy were applied. Exposures were identified according to information recorded in the SACT database (a component of CAS, see Section

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2.3.3.7). LoTs were derived from systemic treatments which are recorded in patient records, according to the algorithm outlined in Appendix K.

2.3.3.8.2 Outcome assessment

The following outcomes were evaluated:

- OS: defined as the time from index date to the date of death due to any cause; patients who did not experience death were censored at the earliest date of loss to follow-up, end of study period, or 39 months post-index date
- TTNTD: defined as the time from index date to the earliest date of start of next LoT or date of death due to any cause; patients who did not experience a next LoT or death were censored at the earliest date of loss to follow-up, end of study period, or 39 months post-index date
- TTDD: defined as the time from index date to the earliest date of discontinuation of the current LoT or date of death due to any cause; patients who did not experience treatment discontinuation or death were censored at the earliest date of loss to follow-up, end of study period, or 39 months post-index date

Date of death was obtained from the COSD (a component of CAS; see Section 2.3.3.7). Mortality data in COSD is updated regularly using data from the Office for National Statistics (ONS).

LoTs were derived from systemic treatments which are recorded in the SACT database, according to the algorithm described in Appendix K. The end date of the current LoT and the start date of next LoT were derived from treatment data which are recorded in the SACT database. As treatment end dates are not recorded in the SACT database, the end date of the current LoT was derived using the recorded start date and number of cycles, according to the rules described within the LoT algorithm.

The following variables relating to study follow-up were also described for all patients:

- Time (in months) from index date to end of follow-up

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- Treatment switching after index date (i.e. from sotorasib to docetaxel, and vice versa)
- Subsequent LoT initiated after index date

2.3.3.8.3 Covariate assessment

A summary of key covariates of interest is provided in Table 15, including parameterisation and data source(s).

Table 15: Key covariates describing baseline characteristics

Variable	Parameterisation	Data Source(s)
Year of diagnosis	Categorical (2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021)*	COSD
Age at diagnosis	Continuous; and Categorical (<65, 65-74, 75-84, ≥85)	COSD
Sex	Categorical (Male, Female, Missing/Unknown)	COSD
Ethnicity	Categorical (White, Black, Asian, Chinese, Mixed, Other, Missing/Unknown)	COSD
Stage at diagnosis	Categorical (Stage Ia, Stage Ib, Stage IIa, Stage IIb, Stage IIIa, Stage IIIb, Stage IIIc, Stage IV)	COSD
Histologic type at diagnosis	Categorical (Squamous cell carcinoma, Non-squamous cell carcinoma, Missing/Unknown)	COSD
Tumour size at diagnosis	Continuous	COSD
ECOG score at diagnosis	Categorical (0, 1, 2, 3, 4, Missing/Unknown)	SACT
Year of index date	Categorical (2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024)	SACT
Age at index date	Continuous; and Categorical (<65, 65-74, 75-84, ≥85)	COSD
ECOG score at index date	Categorical (0, 1, Missing/Unknown)	SACT
LoT number at index date	Categorical (2, 3, 4, ≥5)*	SACT
Diagnosis of brain metastasis prior to index date	Categorical (Yes, No Record)	HES
Record of brain metastasis prior to index date	Categorical (Yes, No Record)	HES
Diagnosis of liver metastasis prior to index date	Categorical (Yes, No Record)	HES
Record of any metastasis prior to index date	Categorical (Yes, No Record)	HES
Prior treatment with PD-1/PD-L1 targeted immunotherapy	Categorical (Yes, No)	SACT

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Variable	Parameterisation	Data Source(s)
<i>KRAS</i> mutation status	Categorical (Mutated, Borderline, Normal, Missing/Unknown, No Record of Test)	MDx
<i>KRAS</i> G12C mutation status	Categorical (Mutated, Missing/Unknown, No Record of Test)	MDx
Presence of any actionable non- <i>KRAS</i> gene alteration or rearrangement (i.e. <i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>BRAF</i> , <i>RET</i> , <i>NTRK</i> , <i>MET</i> , <i>STK11</i> , <i>TP53</i>)	Categorical (Yes, No, No Record of Any Test)	MDx
PD-L1 expression	Categorical (<1%, 1-49%, ≥50%, Missing/Unknown, No Record of Test)	MDx
Treatment switching after index date	Categorical (Yes, No)	SACT
Time (in months) from diagnosis to index date	Continuous	COSD, SACT
Time (in months) from 1L initiation to index date	Continuous	SACT
Time (in months) from end of previous LoT to index date	Continuous	SACT
Time (in months) from index date to end of follow-up	Continuous	SACT, ONS

Abbreviations: 1L, first-line; COSD, Cancer Outcomes and Services Dataset; ECOG, Eastern Cooperative Oncology Group; HES, Hospital Episode Statistics; LoT, line of therapy; MDx, Molecular Diagnostics; ONS, Office for National Statistics; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SACT, systemic anti-cancer therapy.

2.3.3.9 Baseline characteristics and demographics

Key patient characteristics at baseline are outlined in Table 16.

In the sotorasib cohort (N=394), █ patients (█%) were female and █ (█%) were of white ethnicity. The median age at diagnosis was █ years (Q1-Q3: █), and █ (█%) patients were diagnosed with stage IV NSCLC, whilst █ (█%) tumours were non-squamous cell carcinomas. There was no record of any *KRAS* test in █ patients (█%). Though not all patients had record of any *KRAS* test, █ (█%) had a record of *KRAS* G12C mutation.

In the docetaxel cohort (N=1,271), █ patients (█%) were female and █ (█%) were of white ethnicity. The median age at diagnosis was █ years (Q1-Q3: █), and █ (█%) patients were diagnosed with stage IV NSCLC, whilst █ (█%) were non-squamous cell carcinomas. There was no record of any *KRAS*

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test in [REDACTED] patients ([REDACTED] %); record of *KRAS* G12C mutation was reported in [REDACTED] patients ([REDACTED] %).

Table 16: Characteristics of participants in CAS RWE

	Docetaxel (N=1,271)	Sotorasib (N=394)
Age at diagnosis, years		
N	1,271	394
Mean (SD)	[REDACTED]	[REDACTED]
Median (Q1, Q3)	[REDACTED]	[REDACTED]
Sex, n (%)		
Male	[REDACTED]	[REDACTED]
Female	[REDACTED]	[REDACTED]
Ethnicity, n (%)		
White	[REDACTED]	[REDACTED]
Asian	[REDACTED]	[REDACTED]
Black	[REDACTED]	[REDACTED]
Chinese/Other	[REDACTED]	[REDACTED]
Mixed	[REDACTED]	[REDACTED]
Missing	[REDACTED]	[REDACTED]
Stage at diagnosis, n (%)		
I	[REDACTED]	[REDACTED]
II	[REDACTED]	[REDACTED]
III	[REDACTED]	[REDACTED]
IV	[REDACTED]	[REDACTED]
Histology, n (%)		
Squamous	[REDACTED]	[REDACTED]
Non-squamous	[REDACTED]	[REDACTED]
Unspecified carcinoma	[REDACTED]	[REDACTED]
Other and unspecified types of cancer	[REDACTED]	[REDACTED]
Age at index, years		
N	[REDACTED]	[REDACTED]
Mean (SD)	[REDACTED]	[REDACTED]
Median (Q1, Q3)	[REDACTED]	[REDACTED]
ECOG PS at index, n (%)		
0	[REDACTED]	[REDACTED]
1	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]

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	Docetaxel (N=1,271)	Sotorasib (N=394)
3	████	████
4	████	████
Missing	████	████
Line of therapy number at index, n (%)		
2	████	████
3	████	████
4	████	████
≥5	████	████
Diagnosis of brain metastasis prior to index date, n (%)		
Yes	████	████
No record	████	████
Record of any metastasis prior to index date, n (%)		
Yes	████	████
No record	████	████
Prior treatment with PD-1/PD-L1 targeted immunotherapy, n (%)		
Yes	████	████
No	████	████
KRAS mutation status, n (%)		
Mutated	████	████
Borderline	████	████
Normal	████	████
No record of test	████	████
Missing/unknown	████	████
KRAS G12C mutation status, n (%)		
Mutated	████	████
Not mutated	████	████
No record of test	████	████
Time from initial diagnosis to index date, months		
N	██	█
Mean (SD)	████	████
Median (Q1, Q3)	████	████

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PS, performance status; SD, standard deviation.

* Numbers from 1-5 may be masked, in accordance with NHS England policy to minimise the risk of patient identification.

** Numbers are masked to prevent back-calculation of masked values.

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2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 CodeBreak 200

2.4.1.1 Population analysis sets

The key analysis sets used in this study are outlined in Table 17.

Table 17: Population analysis sets

Analysis set	Definition
FAS (ITT population)	Includes all randomised subjects. All subjects were analysed according to treatment to which they were randomised. The FAS was used for the primary and key secondary efficacy endpoints
SAS	Includes subjects in the FAS who received at least one dose of investigational product. For analyses using SAS, subjects were analysed based on actual treatment received
PPS	Subset of the FAS that includes subjects who did not have select important protocol deviations. The list of important protocol deviations was maintained on an ongoing basis and was finalised before the primary analysis of the study
EORTC QLQ-C30 Analysis Set	Consists of all randomised subjects with a non-missing baseline and at least one non-missing postbaseline results of any EORTC QLQ-C30 sub-scales. Subjects will be included in the analysis of each EORTC QLQ-C30 subscale for which they have non-missing data
EORTC QLQ-LC13 Analysis Set	Consists of all randomised subjects with a non-missing baseline and at least one non-missing postbaseline results of any EORTC QLQ-LC13 subscales. Subjects will be included in the analysis of each EORTC QLQ-LC13 subscale for which they have non-missing data

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; FAS, full analysis set; ITT, intent-to-treat; PPS, per protocol set; QLQ-C30, Quality of Life Questionnaire 30-Item Core Module; QLQ-C13, Quality of Life Questionnaire Lung Cancer Module; SAS, safety analysis set.

2.4.1.2 Statistical analysis

2.4.1.2.1 PFS

The PFS analyses were conducted using the FAS, unless otherwise specified, with the primary analysis based on outcomes assessed by BICR per RECIST v1.1. The distribution of PFS time was summarised descriptively using the KM method. The corresponding 95% CIs for the median and quartiles were constructed using the method of Klein and Moeschberger, 1997 (80) with log-log transformation. PFS rates at selected landmark time points were provided, and the corresponding 95% CIs were calculated using the method of Kalbfleisch and Prentice, 1980 (81). The duration of the follow-up for PFS was estimated by reverse KM method (82).

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The inferential comparison between treatment groups used the log-rank test stratified by the randomisation stratification factors at level of 0.025 (1-sided). The HR and its 95% CI were estimated using a Cox proportional hazards (PH) model stratified by the same randomisation stratification factors.

The primary endpoint of PFS was analysed within each of the subgroups listed in Section 2.8.1.1. Specifically, to determine whether the treatment effect was consistent across subgroups, the estimate of the HRs (with 95% CI) for PFS between the treatment groups was provided.

Piecewise Cox models were explored given evidence of non-PH (83). This model allowed estimation of an overall weighted HR (weights equal to fraction of total events in each interval (84) as well as within interval treatment HR.

2.4.1.2.2 Key secondary endpoints

The efficacy analyses of key secondary endpoints were conducted using the FAS, unless otherwise specified.

The inferential comparison between treatment groups for ORR was made using the Cochran Mantel Haenszel chi-square test controlling for the randomisation stratification factors. The ORR was calculated by treatment group and the associated 95% CI were estimated using the Clopper-Pearson method (85). An estimate of the common odds ratio (OR) (95% CI) was provided as a measure of the relative treatment effect. The OR (and 95% CI) was estimated using the Mantel-Haenszel method. The docetaxel group served as the reference treatment group in the calculation of the OR. The primary analysis of ORR was based on outcomes assessed by BICR per RECIST v1.1. The analyses based on investigator-assessed served as supportive analyses. For subgroups listed in Section 2.8.1.1, the inferential comparisons between treatment groups for ORR and estimates of ORR with 95% CI were performed using the same aforementioned methods.

OS was analysed using the same method as described for the PFS endpoints. Subgroup analysis for OS was performed using the same method described for PFS as appropriate. If there was evidence to support non-PH, a piecewise PH model may

be explored as described for PFS. OS at selected landmark time points was provided and the corresponding 95% CIs were calculated.

Crossover adjustment

To account for the potential confounding effect of subjects randomised to docetaxel who subsequently received sotorasib, additional analyses of OS that adjust for the effect of crossover were conducted. Three crossover methods were pre-specified: two-stage estimation (TSE), inverse probability of censoring weighting (IPCW), and rank preserving structural failure time (RPSFT). Among these, only the TSE is considered appropriate due to the trial design and the covariates considered for adjustment.

TSE

The TSE (86) adjusted for crossover effect by estimating the relative treatment effect of OS that would have been observed in the docetaxel group in the absence of crossover, based on the adjusted survival time fitted, by means of an accelerated failure time model on post-progression subjects in the docetaxel group. Similarly to the IPCW method, it assumed no unmeasured confounders. An additional post-hoc TSE crossover adjustment was conducted, including off-protocol crossover to commercial sotorasib, as well as per-protocol crossover.

The TSE has been developed for trials designed exactly as CodeBreak 200 was designed. The TSE assumes there is a “secondary baseline” before which crossover is not allowed. Furthermore, crossover should occur close to this secondary baseline. In the context of CodeBreak 200, this secondary baseline is disease progression (i.e. the date of the first scan determined to exhibit progressive disease by investigator which underwent independent central confirmation). Once subjects of the docetaxel arm progressed, their decision to crossover is analysed as in the context of an observational study. The post-progression crossover effect, adjusted for confounders, is used to re-adjust the observation times. For the TSE, the key limitation is the assumption of “no unmeasured confounders”. Based on a structured interview of experienced NSCLC physicians, multiple confounders in CodeBreak 200 were identified and pre-specified for adjustment. The remaining bias should therefore be small.

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IPCW

The IPCW (87) method censors subjects who crossover at the time of crossover (i.e. weight = 0 during the intervals after crossover and, therefore, dropped from the model), and then up-weights similar subjects who do not crossover, therefore adjusts for bias of informative censoring due to crossover associated with potential time-dependent confounders. Weights for subjects who did not crossover were estimated by fitting log-logistic regression models with crossover as a dependent variable and with baseline and time-dependent covariates, which have a confounding effect on both the likelihood of switching and on the OS, as independent variables. Then the variables weights were used in the weighted Cox PH regression model to calculate the HR and corresponding CI of the relative OS effect of sotorasib versus docetaxel. This method relies on the assumption that there are no unmeasured confounders.

For the IPCW method, no secondary baseline needs to be defined. Once a subject crosses over, the subject is censored. However, the prior weight of this subject is reassigned to similar subjects who did not crossover. As in the TSE, the assumption is made that all relevant confounders are included and that there are no unmeasured confounders. The data requirement is higher as confounders may be time varying, and therefore would need to be measured continuously. In contrast, the confounders only need to be available at the secondary baseline for the TSE.

Per pre-specification, the same confounders were defined for the IPCW method as for the TSE. However, for IPCW, time-dependent covariates need to be measured continuously, which in the context of CodeBreak 200, has high levels of missing data, particularly for later intervals. In such cases, the weights were imputed, introducing potentially substantial bias. Furthermore, the progression status was not accounted for in time varying covariates. Not capturing this key confounder is a major miss. 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 disfavour of sotorasib. Conducting an IPCW ad hoc analysis addressing this issue is challenging for the following reasons:

- If certain patient characteristics are very strong predictors of switching, extreme weights can be obtained. In these circumstances the IPCW becomes prone to error (88).

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- Per European Medicines Agency (EMA) Guidance (89): “Furthermore, sufficient heterogeneity in the crossover pattern should be present in the sense that baseline and time-dependent covariates should not be (close to) perfectly predicting crossover; for if they do, the weights used in IPCW would be (close to) infinity, and the method would break down.”
- Finally, even if the progression status would have been included as a time varying covariate, and the instability and bias issue above would have overcome, the issue would remain that also the time since progression could be a relevant predictor. As the timing of disease progression between crossover and non-crossover subjects differs, it would be about impossible to find similar subjects for appropriate weight assignment.

In conclusion, the IPCW method is not appropriate for CodeBreak 200.

RPSFT

Analysis of OS based on the RPSFT model (90) was conducted to correct the treatment effect estimate for bias introduced by crossover from docetaxel to sotorasib. The RPSFT model provides a randomisation-based estimate of treatment effect assuming a multiplicative effect of treatment on time to event. The approach also allows reconstruction of the hypothetical docetaxel time to event curve assuming all subjects initially randomised to docetaxel would not crossover to sotorasib. The RPSFT adjusted HR (95% CI), as well as the treatment effect measured by the acceleration factor (95% CI) are presented. Additionally, KM curves were used to display the OS between the sotorasib and the RPSFT model-adjusted docetaxel groups. One of the key assumptions of the RPSFT “common treatment effect,” i.e. the treatment effect of sotorasib is the same regardless of when the subject started taking sotorasib, was verified.

The RPSFT model is incompatible with the CodeBreak 200 trial design. The key limitation of the RPSFT model is the assumption of a ‘common treatment effect’. More specifically, the treatment effect is assumed to be the same in the intervention arm and for subjects after crossover. This simple assumption in the context of the CodeBreak 200 trial, however, is heavily breached for three reasons:

- First, treatment switching is only permitted after disease progression; therefore, crossover subjects have more advanced disease.
- Second, the comparator in CodeBreakK 200 is not placebo; rather, it is an active treatment that prolongs survival. This situation was identified by Latimer & Abrams, 2014 as an important biasing factor. This is because the RPSFT counterfactual survival model requires that patients are either 'on' or 'off' at any one time. If patients in the control group receive an active treatment followed by supportive care upon treatment failure, the 'off' treatment category represents more than one type of treatment, and the counterfactual survival model is not appropriate.
- Third, in CodeBreakK 200, the RPFST model does not consider whether a subject is still actively taking the drug or has already discontinued the drug. Subjects in the sotorasib treatment arm are always considered to be on treatment. Correspondingly, crossover subjects are considered to be on treatment after crossover. This assumption does not reflect reality as the proportion of those "on" vs "off" active treatment may substantially differ between the intervention arm and the crossover subjects.

2.4.1.2.3 Other secondary endpoints

DOR was calculated only for subjects who achieved a confirmed best overall response of PR or CR. For those who were alive and did not have disease progression at the time of data cut-off for analysis, DOR was right-censored based on the censoring conventions defined previously for PFS. Progression was based on outcomes assessed by BICR per RECIST v1.1. The distribution of DOR, including the median and quartiles and their corresponding 95% CIs, were characterised using the KM method based on the subjects who achieved a best response of PR or better. No inferential comparison between treatment groups was made for DOR.

TTR was calculated only for subjects who achieved a confirmed best overall response of PR or CR. TTR was summarised by the non-missing sample size (n), mean, standard deviation (SD), median, minimum, and maximum for responders by study and regimen (side-by-side) based on the FAS.

DCR was analysed using the same method as described for the ORR endpoints.

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The analyses of DOR, TTR, and DCR were mainly performed based on outcomes assessed by BICR. The sensitivity analyses were performed based on the investigator assessments.

2.4.1.2.4 Safety analyses

The Medical Dictionary for Regulatory Activities (MedDRA) was used to code AEs to a system organ class and a preferred term. The National Cancer Institute grading scale, Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, was used to grade the severity of AEs. Treatment emergent adverse events (TEAEs) included all AEs with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days of the last dose of any study treatment, or before the first dose of sotorasib if subjects crossed over from docetaxel to sotorasib, whichever occurred earlier.

Safety analyses, using the safety analysis set (SAS), were descriptive in nature and included investigational product administration and exposure, AEs, laboratory measurements, vital signs, and concomitant medications.

2.4.1.3 Sample size and power calculation

While the study was initially powered for both PFS and OS, protocol amendments based on regulatory feedback (see Section 2.3.1.7) resulted in the study only being powered for PFS. The final calculation of sample size and power based on the latest protocol is outlined below.

The primary analysis of PFS was to occur when approximately 230 PFS events were observed. With 230 PFS events, the study would have approximately 90% power to show a statistically significant PFS at the 2.5% 1-sided significance level, if the true treatment effect HR is assumed 0.65 for the sotorasib group versus the control group. The sample size was chosen to have 70% maturity realising PFS events, which is approximately 330 subjects with 1:1 randomisation ratio into the sotorasib group and the docetaxel group. The PFS primary analysis could be delayed to ensure that the enrolment was finished, and the delayed primary analysis would have been triggered when the last randomised subject had had the opportunity for at least 6 weeks of follow-up.

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An interim analysis was planned to occur when approximately 70% (160) of the target PFS events were observed from both groups, or when the enrolment was finished and the last randomised subject had the opportunity to have 6 weeks of follow-up, whichever occurred later. The monitoring boundary for early stopping for efficacy was based on an O'Brien-Fleming type alpha spending function for multiplicity adjustment. The actual information fraction was calculated based on the number of observed events at the time of the analysis. Under exponential distribution, the minimum detectable difference for success in this design is an HR of 0.68 between the sotorasib group and the docetaxel group with 160 PFS events, 70% of the target PFS events, and an HR of 0.769 at the primary analysis with 230 PFS events. Assuming an enrolment rate of 40 subjects per month after a 3-month ramp-up period, with a total sample size of 330, it was estimated that approximately 19 months would be required to reach 230 PFS events, and 13 months would be required to reach 70% (160) of the target PFS events. This estimation was based on a median PFS of 5 months for the control group (91) and 7.7 months for the sotorasib group, and a 10% dropout rate.

If the primary endpoint of PFS achieved statistical significance, all subjects remaining on study would still be followed for their survival data until the OS primary analysis, to enable OS analyses and a robust description of the totality of the data.

An administrative interim summary for OS was performed at the PFS interim analysis with approximately 107 OS events (approximately 32% maturity) observed, if PFS had achieved statistical significance at the interim analysis. A nominal alpha of 0.01% (negligible impact on overall type I error rate) would be spent on this OS interim summary.

There were 2 planned OS analyses with testing for superiority of sotorasib over docetaxel, an OS interim analysis and an OS primary analysis. The OS interim analysis was to be performed either at the time when PFS achieves statistical significance or after 175 OS events (approximately 53% maturity) were observed, whichever was later. Assuming the actual crossover rate of approximately 30% at the time of PFS primary analysis for subjects in the control group who have disease progression, then with 175 OS events, the study has approximately 96% probability

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to observe a HR <1 when the true OS HR is 0.75. The OS primary analysis was to occur when at least 198 OS events (approximately 60% maturity) had been observed, which was expected to be at approximately 3 months after PFS primary analysis. The estimation was based on a median OS of 9 months for the control group and 12 months for the sotorasib group (OS HR = 0.75). The multiplicity was to be adjusted as necessary based on O'Brien-Fleming type alpha spending function.

As designed, the study was not terminated at the time of PFS analyses, and subjects will continue to be followed for OS data until the targeted number of events is reached, regardless of the OS analysis result at the PFS primary analysis, to enable OS analyses and a robust description of the totality of the data.

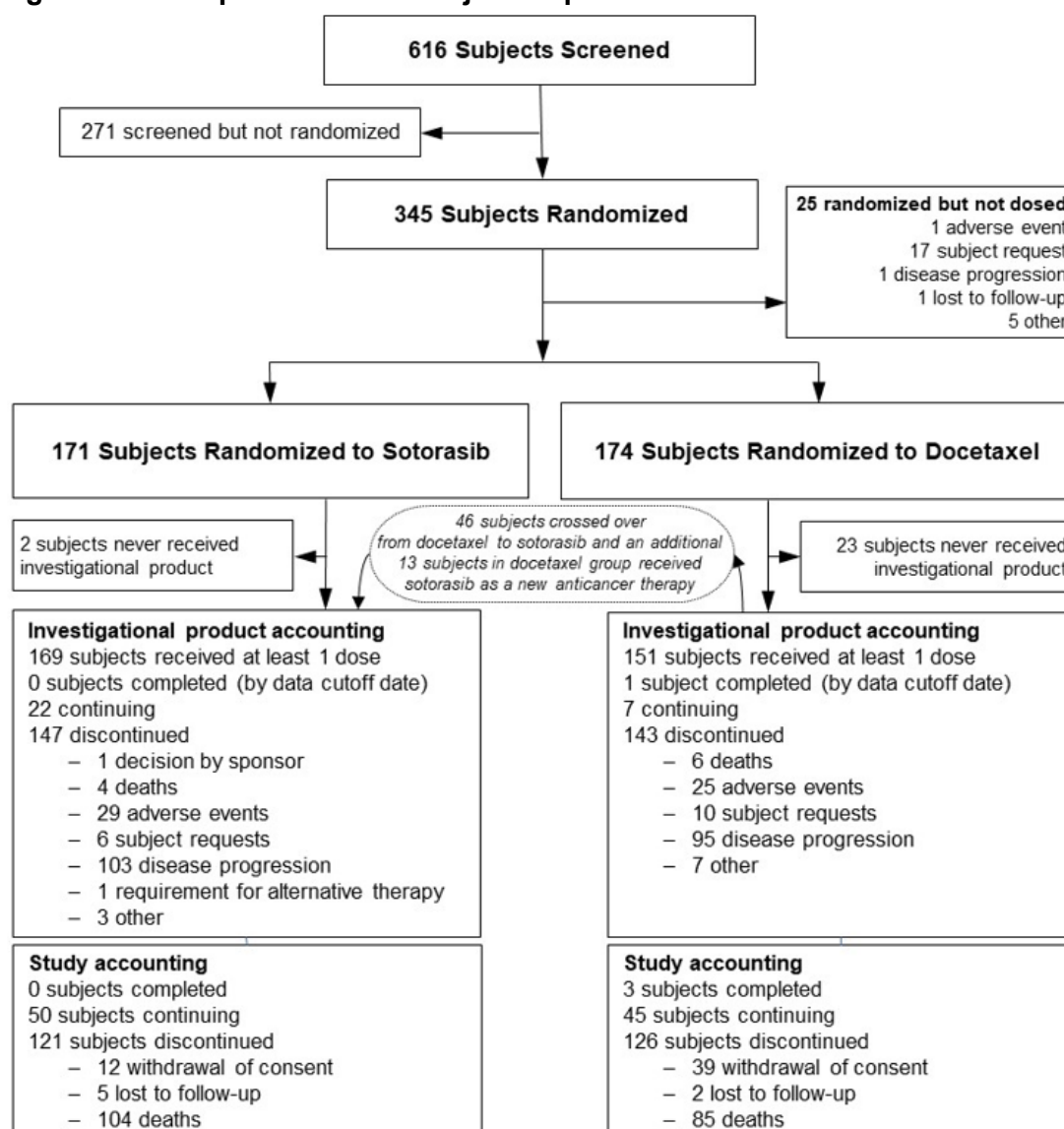
2.4.1.4 Data management and patient withdrawals

Incomplete AE start dates, concomitant medications start or stop dates, and death date were imputed based on rules specified in the statistical analysis plan (SAP). No imputation was done for the primary analysis of the primary and key secondary endpoints. The frequency of missing disease assessments and deviation of the actual disease assessment times from the scheduled assessment times was summarised by treatment arm. Sensitivity analyses were performed to assess the impact on the analysis of PFS due to any missing data/assessment, and any lost to follow-up or discontinuation of assessment of PFS not due to an event. Similar analyses were performed for clinical outcome assessments endpoints.

2.4.2 Participant flow in CodeBreak 200

CodeBreak 200 is ongoing; the present results are from the date the first subject was randomised (4th June 2020) to the data cut-off date for the primary analysis of PFS (2nd August 2022). In total, 616 subjects were screened, of which 345 were enrolled and randomised to sotorasib (N=171) or docetaxel (N=174). Two (1.2%) subjects in the sotorasib group and 23 (13.2%) subjects in the docetaxel group never received investigational product. At the data cut-off date, a total of 290 subjects discontinued investigational product (147 [86.0%] sotorasib, 143 [82.2%] docetaxel), with the main reasons in both treatment groups being disease progression and AE. Participant flow is summarised in Figure 6.

Figure 6: Participant flow and subject disposition in CodeBreak 200



2.4.3 CodeBreak 100

Details of the primary analysis of CodeBreak 100 were provided in the original submission for TA781. Here we present a pooled analysis of patients in the Phase 1 and Phase 2 cohorts, with a data cut-off date of 22nd February 2022.

2.4.4 Participant flow in CodeBreak 100

As of 22nd February 2022, 174 patients received sotorasib 960 mg once daily. An overview of subject disposition and reasons for discontinuation is shown in Table 18.

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Table 18: Subject disposition in CodeBreak 100

	Phase 1 NSCLC (N=48) n (%)	Phase 2 NSCLC (N=126) n (%)	Phase 1/2 NSCLC (N=174) n (%)
Investigational product accounting			
Subjects who never received sotorasib	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who received sotorasib	48 (100.0)	126 (100.0)	174 (100.0)
Subjects who discontinued sotorasib	43 (89.6)	118 (93.7)	161 (92.5)
AE	6 (12.5)	11 (8.7)	17 (9.8)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	3 (2.4)	3 (1.7)
Subject request	3 (6.3)	6 (4.8)	9 (5.2)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance	0 (0.0)	1 (0.8)	1 (0.6)
Disease progression	33 (68.8)	95 (75.4)	128 (73.6)
Requirement for alternative therapy	1 (2.1)	2 (1.6)	3 (1.7)
Protocol specified criteria	0 (0.0)	0 (0.0)	0 (0.0)
Study completion accounting			
Subjects continuing study	11 (22.9)	28 (22.2)	39 (22.4)
Subjects who discontinued study	37 (77.1)	98 (77.8)	135 (77.6)
Decision by sponsor	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	3 (2.4)	3 (1.7)
Death	27 (56.3)	82 (65.1)	109 (62.6)
Withdrawal of consent from study	10 (20.8)	13 (10.3)	23 (13.2)

Abbreviations: AE, adverse event; NSCLC, non-small cell lung cancer.

2.4.5 CAS RWE study

2.4.5.1 Population analysis sets

A description of key analysis sets is provided in Table 19. In each analysis set, patients could belong to only one treatment group (i.e. sotorasib or docetaxel) for all analyses. Consequently, any patients who received both sotorasib monotherapy and docetaxel monotherapy during follow-up were classified according to whichever was received first.

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The main analytical cohort for the study was the 2L+ analysis set, which included all eligible patients who received either sotorasib or docetaxel. This cohort was used to address all primary, secondary, and exploratory study objectives.

Table 19: Population analysis sets

Analysis set	Definition	Applicable analyses and rationale
2L+	The 2L+ analysis set consists of: - All patients in the sotorasib cohort[†]; <i>and</i> - All patients in the docetaxel cohort	Main analysis set and utilised for sensitivity analyses to assess the impact of different censoring criteria and estimands
2L+ any <i>KRAS</i>	The 2L+ any <i>KRAS</i> analysis set consists of: - All patients in the sotorasib cohort[†]; <i>and</i> - All patients in the docetaxel cohort who have a positive test result for any <i>KRAS</i> mutation at any point in patient records	Sensitivity analysis set to assess the impact of including patients with negative or unknown <i>KRAS</i> mutation status in the docetaxel cohort
2L+ <i>KRAS</i> G12C	The 2L+ <i>KRAS</i> G12C analysis set consists of: - All patients in the sotorasib cohort[†]; <i>and</i> - All patients in the docetaxel cohort who have a positive test result for <i>KRAS</i> G12C mutation at any point in patient records	Sensitivity analysis set to assess the impact of including patients with negative or unknown <i>KRAS</i> G12C mutation status in the docetaxel cohort
2L+ expanded stage	The 2L+ expanded stage analysis set consists of: - All patients in the sotorasib cohort[†] inclusive of patients with stage I or stage II tumours at NSCLC diagnosis who progress to treatment with sotorasib, <i>and</i> - All patients in the docetaxel cohort	Sensitivity analysis set to assess the impact of including only patients who were stage III or stage IV at initial diagnosis of NSCLC
2L+ 6-month minimum potential follow-up	The 2L+ 6-month minimum potential follow-up analysis set consists of: - All patients in the sotorasib cohort[†] who initiated sotorasib monotherapy in 2L+ between 1st March 2021 and 30th November 2023 (i.e. at least 6 months prior to the end of data availability); <i>and</i> - All patients the docetaxel cohort who initiated docetaxel monotherapy in 2L+ between 1st January 2017 and 30th November 2023 (i.e. at least 6 months prior to the end of data availability)	Sensitivity analysis set to assess the impact of administrative censoring due to not imposing any minimum opportunity for follow-up

Abbreviations: 2L, second-line; NSCLC, non-small cell lung cancer.

[†] All patients in the sotorasib cohort must have *KRAS* G12C-mutated NSCLC in line with the criteria for conditional reimbursement set out in the Managed Access Agreement.

2.4.5.2 Statistical analysis

2.4.5.2.1 General considerations

Continuous variables are described by the mean, SD, median, interquartile range (IQR), and 5th and 95th percentile values, where appropriate. Categorical variables are summarised using the number and percentage of patients in each category (N, %). For all variables, the number and percentage of patients with missing data were reported (N, %).

The relative effect of sotorasib monotherapy versus docetaxel monotherapy in 2L+ was expressed as a HR, with associated 95% CI. Survival curves and median time-to-event and two-sided 95% CI were reported for each outcome, along with the first and third quartiles (Q1 and Q3).

Comparative analyses aim to estimate the relative effect of sotorasib monotherapy versus docetaxel monotherapy in 2L+. Two-tail tests were conducted to draw statistical inferences at a significance level of $\alpha = 0.05$. To maximise the sample size available for analysis, no matching procedures were implemented. Instead, PS-based weighting methods were applied to balance treatment cohorts with respect to important baseline confounders and prognostic factors.

2.4.5.2.2 Missing or incomplete data

Missing baseline data for all variables were reported descriptively (N, %), with no imputation performed. To preserve sample size in PS modelling, key covariates like ECOG and body mass index (BMI) included a “missing” category. Endpoint missingness was expected to be minimal.

2.4.5.2.3 Analysis of primary, secondary and exploratory endpoints

Analyses compared sotorasib monotherapy versus docetaxel monotherapy in 2L+ for the outcomes OS (primary objective), TTNTD (secondary objective), and TTDD (exploratory objective). In all analyses, censoring was treated as non-informative. The ‘as-started’ treatment effect (i.e. the real-world analogue of the ITT effect) was considered, which comprised the effect of initiating treatment with sotorasib monotherapy or docetaxel monotherapy irrespective of subsequent adherence, discontinuation, or switching.

For all study objectives, outcomes were formally compared between treatment groups using 2-tailed tests and a significance level of $\alpha = 0.05$. Baseline confounding was accounted for using PS weighting, as described in Appendix K; the target population for inference was the population represented by the sotorasib cohort, such that the ATT could be estimated. The ATT represents the average effect of treatment in the population of individuals who actually received the treatment of interest. The KM method and Cox PH regression were used to evaluate the effectiveness of sotorasib monotherapy versus docetaxel monotherapy for all study outcomes.

A correction for multiple testing was not performed, as the study had only one primary endpoint (i.e. OS). Subgroup and sensitivity analyses are exploratory in nature and therefore no correction factor for multiple testing was implemented.

For all study objectives, PS weighting was used to balance treatment groups with respect to important baseline covariates. The R *WeightIt* package was used for PS estimation and weighting, and the *cobalt* package was used for evaluation of covariate balance. SMRW was used for weighting; further details are provided in Appendix K.

KM Analysis

For all study objectives, the KM method was used to graphically depict the survival functions according to treatment group. In adjusted analyses, the KM analysis was performed using a weighted analysis set to account for baseline confounding; in unadjusted analyses, the KM analysis was performed using an unweighted analysis set. For all analyses, a two-sided log-rank test with a significance level of 0.05 was performed to compare treatment groups. The number of patients still at risk at discrete time points (e.g. every 3 months post-index date, up to 36 months) was tabulated below the curves. Median survival time and two-sided 95% CI were reported for each outcome, along with the first and third quartiles (Q1 and Q3). The probability of not experiencing the event of interest at each selected time point was estimated and reported along with the corresponding two-sided 95% CIs.

KM analyses were implemented using the R *survival* and/or *survminer* package(s).

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Cox regression

For all study objectives, the effect of sotorasib monotherapy versus docetaxel monotherapy was estimated using a Cox PH regression model. In adjusted analyses, the Cox model was fitted in the weighted analysis set to account for baseline confounding. Baseline confounders which remained imbalanced (i.e. standardised mean difference [SMD] ≥ 0.1) following weighting were included as covariates in the Cox model. An adjusted HR with associated 95% CI was reported as an estimate of the treatment effect. In unadjusted analyses, the Cox model was fitted in the unweighted analysis set without any confounders included as covariates, and an unadjusted HR with associated 95% CI was reported.

Cox regression modelling was implemented using the *coxph* function in the R *survival* package.

The PH assumption was assessed using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals, using the *plot.cox.zph* function in the same package. If the PH assumption is violated for the exposure, an interaction between the exposure and time (either continuous or categorical) was introduced to account for non-PH by allowing the HR to vary over time. If imbalanced variables were included as adjustment into the Cox model, these variables were removed and adjusted for through stratification. This was implemented in order to allow the baseline hazard to vary across levels of the stratifying variable(s), as direct inclusion of such variables could violate the assumption of correct model specification.

Estimation of standard error (SE)

PS weighting generates a pseudo-population in which some individuals contribute more to the analysis than others, depending on their assigned weights. This process can impact the effective sample size (ESS) and introduce correlation within the data, as observations are no longer equally weighted (92). As a result, SE estimates based on traditional methods may be biased. To account for this, robust SEs were used to calculate CIs for treatment effect estimates using the argument *robust=TRUE* in the *coxph* function. This approach adjusts for the variability introduced by the weighting process and provides more reliable estimates of statistical uncertainty.

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Estimation of ESS

The use of robust estimator methods for estimating CIs increases the variance in estimated effects (i.e. the ESS is reduced) (93). For each analysis, the ESS which resulted from the use of treatment weighting to adjust for baseline confounding was reported based on the formula:

$$ESS = \frac{(\sum_{j=1}^n w_j)^2}{\sum_{j=1}^n w_j^2}$$

where w_j is the weight for individual j . ESS was calculated using the *ESS* function in the *WeightIt* package.

Further details of statistical methods for estimation of PS, PS weighting, and evaluation of covariate balance between treatment groups are provided in Appendix K.

2.4.5.2.4 Sensitivity analyses

A summary of key sensitivity analyses is provided in Table 20.

Table 20: Summary of sensitivity analyses

Objective (Outcome)	Analysis Set	Comparison	Estimand
Primary (OS)	2L+	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+	Sotorasib monotherapy vs docetaxel monotherapy	All patients censored at treatment switching
	2L+	Sotorasib monotherapy vs docetaxel monotherapy	Docetaxel patients censored at treatment switching
	2L+ expanded stage	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ 6-month minimum potential follow-up	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ any <i>KRAS</i>	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ <i>KRAS G12C</i>	Sotorasib monotherapy vs docetaxel monotherapy	As-started

Objective (Outcome)	Analysis Set	Comparison	Estimand
Secondary (TTNTD)	2L+	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ expanded stage	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ 6-month minimum potential follow-up	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ any <i>KRAS</i>	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ <i>KRAS G12C</i>	Sotorasib monotherapy vs docetaxel monotherapy	As-started
Exploratory (TTDD)	2L+	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ expanded stage	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ 6-month minimum potential follow-up	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ any <i>KRAS</i>	Sotorasib monotherapy vs docetaxel monotherapy	As-started
	2L+ <i>KRAS G12C</i>	Sotorasib monotherapy vs docetaxel monotherapy	As-started

Abbreviations: 2L, second-line; ATT, average treatment effect in the treated; n/a; not applicable; SMRW, standardised mortality ratio weighting.

Bold indicates the main analysis for each objective; all other rows describe sensitivity analyses performed.

Note: Where confounding adjustment was applied, this used the ATT estimand with SMRW.

2.4.6 Participant flow in CAS RWE study

Between 1st January 2014 and 31st December 2022, 338,913 adult patients were diagnosed with NSCLC. Following the application of all study eligibility criteria, 394 patients were included in the sotorasib cohort. In the docetaxel cohort, 1,271 patients met the eligibility criteria. Patient attrition is outlined in Table 21 and Table 22.

Table 21: Patient attrition for the sotorasib cohort

Criterion	Patients, N	% of step
<i>Inclusion criteria</i>		
A. Diagnosis of NSCLC between 01 January 2013 and 31 December 2022	338,913	100%
B. Aged ≥18 years at NSCLC diagnosis date	338,858	99.98% of A
C. Eligible to have LoTs derived algorithmically	89,818	26.51% of B
D. Stage III or stage IV tumour at NSCLC diagnosis	71,974	80.13% of C

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Criterion	Patients, N	% of step
D1. Unresectable stage III	22,071	30.67% of C
D2. Resectable stage III	5,096	7.08% of C
D3. Stage IV	44,807	62.25% of C
E. Documented initiation of sotorasib monotherapy in 2L+ for locally advanced or metastatic NSCLC within the indexing period (from 01 March 2021 until 31 May 2024)	415	0.58% of D
<i>Exclusion criteria</i>		
F. Diagnosis of any other primary malignancy (excluding non-melanoma skin cancer) at any point prior to index date	403	97.11% of E
G. Record of any SACT more than 30 days prior to NSCLC diagnosis date	400	99.26% of F
H. Treated with sotorasib monotherapy or docetaxel monotherapy in the advanced setting at any point prior to index date	394	98.50% of G
<i>Final study cohort</i>		
I. Number of adult patients in CAS with de novo stage III or stage IV NSCLC selected for the sotorasib cohort	394	0.12% of A
<i>Subgroups</i>		
I1. Number of patients with prior PD-1/PD-L1 targeted immunotherapy	■	■
I2. Number of patients with no prior PD-1/PD-L1 targeted immunotherapy	■	■
I3. Number of patients with a record of prior brain metastasis	■	■
I4. Number of patients with no record of prior brain metastasis	■	■

Abbreviations: 2L+, second line and beyond; CAS, Cancer Analysis System; LoT, line of therapy; N, number; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SACT, systemic anti-cancer therapy.

Table 22: Patient attrition for the docetaxel cohort

Criterion	Patients, N	% of step
<i>Inclusion criteria</i>		
A. Diagnosis of NSCLC between 01 January 2013 and 31 December 2022	338,913	100%
B. Aged ≥18 years at NSCLC diagnosis date	338,858	99.98% of A
C. Eligible to have LoTs derived algorithmically	89,818	26.51% of B
D. Stage III or stage IV tumour at NSCLC diagnosis	71,974	80.13% of C
D1. Unresectable stage III	22,071	30.67% of C
D2. Resectable stage III	5,096	7.08% of C
D3. Stage IV	44,807	62.25% of C
E. Documented initiation of docetaxel monotherapy in 2L+ for locally advanced or metastatic NSCLC within the indexing period (from 01 January 2017 until 31 May 2024)	1,383	1.92% of D

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Criterion	Patients, N	% of step
F. Any record of treatment with platinum-doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy at any point prior to index date	1,370	99.06% of E
<i>Exclusion criteria</i>		
G. Any record of treatment with atezolizumab plus carboplatin and etoposide at any point prior to index date	1,370	100% of F
H. Diagnosis of any other primary malignancy (excluding non-melanoma skin cancer) at any point prior to index date	1,315	95.99% of G
I. Record of any SACT more than 30 days prior to NSCLC diagnosis date	1,281	97.41% of H
J. ECOG performance score of >2 within 7 days $\pm$ index date	1,281	100% of I
K. Treated with sotorasib monotherapy or docetaxel monotherapy in the advanced setting at any point prior to index date	1,271	99.22% of J
<i>Final study cohort</i>		
L. Number of adult patients in CAS with de novo stage III or stage IV NSCLC selected for the docetaxel cohort	1,271	0.38% of A
<i>Subgroups</i>		
L1. Number of patients with prior PD-1/PD-L1 targeted immunotherapy	■	■
L2. Number of patients with no prior PD-1/PD-L1 targeted immunotherapy	■	■
L3. Number of patients with a record of prior brain metastasis	■	■
L4. Number of patients with no record of prior brain metastasis	■	■

Abbreviations: 2L+, second line and beyond; CAS, Cancer Analysis System; ECOG, Eastern Cooperative Oncology Group; LoT, line of therapy; N, number; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; SACT, systemic anti-cancer therapy.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

CodeBreak 200 was a randomised, open-label Phase 3 trial conducted in accordance with Good Clinical Practice (GCP) guidelines. Patients were randomised using an interactive response technology system, and baseline demographics and disease characteristics were balanced at baseline. A summary of the quality assessment is provided in Table 24.

CodeBreak 100 was a single-arm, non-randomised study. Quality assessment was undertaken using the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool. CodeBreak 100 is at a low risk of bias in 6 out of the 7 domains considered by this tool, and at moderate risk of bias in 1 domain (see Appendix B).

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Quality assessment results for the CAS RWE study are provided in Table 24. The study design and analytical approaches were informed by the target trial emulation framework, which provides a formal methodology for designing studies aimed to estimate causal effects using real-world data and is the preferred approach of NICE.

Table 23: Quality assessment results for CodeBreakK 200

CodeBreakK 200	yes/no/not clear/N/A	Justification
Was randomisation carried out appropriately?	Yes	Patients were randomised using an interactive response technology system
Was the concealment of treatment allocation adequate?	N/A	CodeBreakK 200 was an open-label trial
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline demographics and disease characteristics were similar in the two treatment groups at baseline
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	CodeBreakK 200 was an open-label trial
Were there any unexpected imbalances in dropouts between groups?	Yes	23 (13%) of 174 patients who were randomly assigned to the docetaxel group did not receive treatment and discontinued the study, in comparison with two (1%) of 171 patients for the sotorasib group. This imbalance in the drop-out rates between treatment groups is a limitation due to the open-label design of this study
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Data reported in the CSR are aligned with the planned analyses outlined in the protocol.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Analyses in the overall population were conducted on the FAS (i.e. ITT), comprising all patients randomised to treatment. Sensitivity analyses were performed to assess the impact on the analysis of PFS due to any missing data/assessment

Abbreviations: CSR, clinical study report; FAS, full analysis; ITT, intent-to-treat; PFS, progression-free survival. Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

Table 24: Quality assessment results for CAS RWE study

CAS RWE	yes/no/not clear/N/A	Justification
Was the cohort recruited in an acceptable way?	Yes	Study data were collected from the CAS database, which contains data on most

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CAS RWE	yes/no/not clear/N/A	Justification
		cancer patients treated in National Health Service hospitals in England. • Clear inclusion criteria were reported to select the sotorasib and docetaxel cohorts from the database.
Was the exposure accurately measured to minimise bias?	Not clear	• Both exposures must have been delivered after at least one prior LoT in the advanced setting (i.e. in 2L+). • No restrictions on dose or duration of therapy were applied. • Exposures were identified according to information recorded in the SACT database (a component of CAS). • LoTs were derived from systemic treatments which were recorded in patient records, according to the algorithm described in the study protocol.
Was the outcome accurately measured to minimise bias?	Yes	OS, TTDD and TTNTD were all clearly defined, and details provided as to where the data were obtained.
Have the authors identified all important confounding factors?	Yes	Potential confounding variables were identified according to published literature and clinical expertise.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Confounding bias was mitigated through the application of key eligibility criteria for the receipt of sotorasib through the CDF to patients in the docetaxel cohort and the application of propensity score weighting to balance treatment cohorts with respect to known and available baseline confounders.
Was the follow-up of patients complete?	Yes	Patients were followed from their index date to the earliest date of death, loss to follow-up, or end of study period (i.e. 31st May 2024). As the indexing period for the sotorasib cohort was shorter due to sotorasib being more recently approved, the maximum potential duration of follow-up in the sotorasib cohort was shorter than in the docetaxel cohort. Therefore, to ensure that the opportunity for follow-up was the same for both treatment cohorts, the maximum period of follow-up was defined as 39 months post-index date, which was based on the maximum potential duration of follow-up for a patient in the sotorasib cohort. Consequently, patients in the docetaxel cohort with available follow-up exceeding 39 months were censored at 39 months.

CAS RWE	yes/no/not clear/N/A	Justification
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	Confidence interval and p values reported.

Abbreviations: 2L, second-line; CAS, Cancer Analysis System; CDF, cancer drugs fund; LoT, line of treatment; NSCLC, non-small cell lung cancer; OS, overall survival; SACT, systemic anti-cancer therapy; TTDD, time to treatment discontinuation or death; TTNTD, time to next treatment or death.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.

2.6 Clinical effectiveness results of the relevant studies

2.6.1 CodeBreak 200

2.6.1.1 Primary efficacy outcome: PFS

In total, 223 PFS events were reported by the data cut-off date for this analysis, including 122 subjects (71.3%) in the sotorasib group and 101 subjects (58.0%) in the docetaxel group. The median PFS was 5.62 months (95% CI: 4.27, 7.75) in the sotorasib group compared with 4.47 months (95% CI: 3.02, 5.68) in the docetaxel group. The HR for disease progression or death following treatment with sotorasib versus docetaxel was 0.663 (95% CI: 0.509, 0.864; p=0.002), demonstrating a statistically significant benefit in PFS and a 34% reduction in the risk of progression or death with sotorasib versus docetaxel. Results of the primary analysis of PFS are summarised in Table 25.

Table 25: Primary analysis of PFS as assessed by BICR (FAS)

	Docetaxel (N=174)	Sotorasib (N=171)
PFS events, n (%)	101 (58.0)	122 (71.3)
Progressive disease	68 (39.1)	100 (58.5)
Death	33 (19.0)	22 (12.9)
Censored, n (%)	73 (42.0)	49 (28.7)
Hazard ratio (95% CI)[†]	0.663 (0.509, 0.864)	
p-value (1-sided)[†]	0.002	
PFS, months[‡]		
n	174	171
Median (95% CI)	4.47 (3.02, 5.68)	5.62 (4.27, 7.75)
Min, Max (+ for censored)	0.0+, 21.6+	0.0+, 23.7+

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	Docetaxel (N=174)	Sotorasib (N=171)
Median follow-up time, months (95% CI)[§]	6.87 (5.42, 12.52)	15.24 (14.85, 17.31)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier; PFS, progression-free survival; PH, proportional hazards.

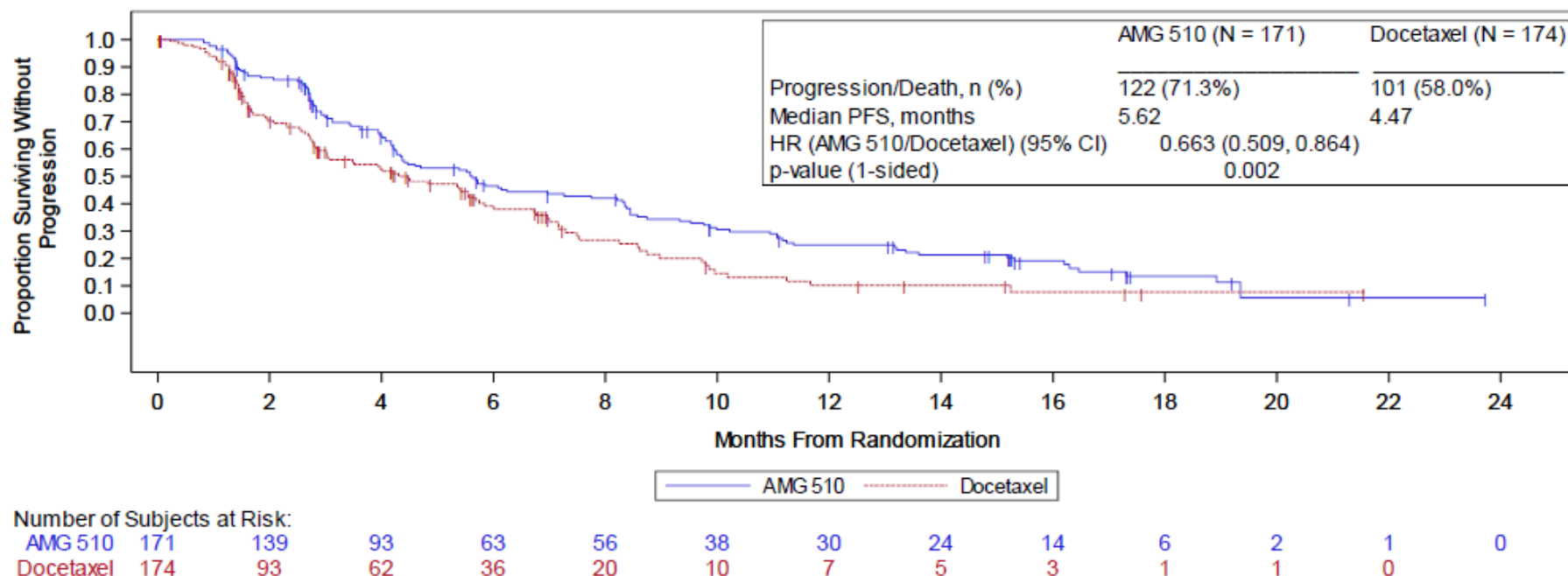
† Hazard ratios and 95% CIs are estimated using a stratified Cox PH model. A hazard ratio <1.0 indicates a lower average event rate and a longer PFS for sotorasib relative to docetaxel. P-value is calculated using a stratified log-rank test.

‡ Medians and percentiles are estimated using the KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.

§ Medians and percentiles of follow-up time are estimated using the reverse KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.

A KM plot of PFS as assessed by BICR is presented in Figure 7. The KM estimated PFS rates were 46.49% and 39.06% at 6 months and 24.84% and 10.12% at 12 months, for sotorasib versus docetaxel, respectively.

Figure 7: KM curve for PFS by BICR (FAS)



Abbreviations: AMG 510, sotorasib; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; FAS, full analysis set; KM, Kaplan-Meier; PD, progressive disease; PFS, progression-free survival; PH, proportional hazards. Censors indicated by vertical bar |. The survival curves and the median PFS are derived by KM method, while hazard ratios (95% CI) are reported from Cox PH model and p-value is calculated using log-rank test stratified by randomisation stratification factors. A hazard ratio <1.0 indicates a lower average event rate and a longer PFS for sotorasib relative to docetaxel.

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Results from the sensitivity analyses of PFS as assessed by BICR were consistent with that of the primary analysis, as outlined in Table 26.

Table 26: Sensitivity analyses of PFS

	HR (95% CI)	p-value
Unstratified analysis	0.692 (0.528, 0.908)	0.003
Initiation of new anticancer therapy treated as PFS event	0.599 (0.474, 0.757)	<0.001
LTFU/withdrawal of consent treated as PFS event	0.651 (0.501, 0.846)	<0.001
Per protocol population	0.686 (0.520, 0.905)	0.005
Scheduled assessment dates instead of actual assessment dates	0.658 (0.506, 0.855)	0.001
PFS assessed by investigators	0.645 (0.504, 0.824)	<0.001

Abbreviations: CI, confidence interval; LTFU, long-term follow-up; PFS, progression-free survival.

2.6.1.2 Secondary efficacy outcome: OS

A total of 203 deaths were reported by the data cut-off date, including 109 subjects (63.7%) in the sotorasib group and 94 subjects (54.0%) in the docetaxel group. The median OS was 10.64 months (95% CI: 8.94, 13.96) in the sotorasib group versus 11.30 months (95% CI: 9.00, 14.85) in the docetaxel group. The HR for OS following treatment with sotorasib versus docetaxel was 1.010 (95% CI: 0.766, 1.331; p=0.53).

Results from the sensitivity analyses of OS were consistent with that of the primary analysis for the unstratified analysis (HR: 1.009, 95% CI: 0.766, 1.331; p=0.53), and the per protocol population (HR: 1.048, 95% CI: 0.785, 1.399; p=0.62), but differed for the initiation of new anticancer therapy treated as PFS event, where a significant difference in favour of sotorasib was observed (HR: 0.642, 95% CI: 0.500, 0.823; p<0.001). The OS sensitivity analysis based on the two-stage approach adjusting only for per-protocol crossover resulted in a HR of 0.885 (0.172, 1.328). A post-hoc two-stage analysis adjusting for all crossover (i.e. per-protocol crossover and off-protocol crossover to commercial sotorasib) yielded an OS HR of 0.820 (95% CI: 0.315, 1.309).

Results of the OS analysis are shown in Table 27.

Table 27: Analysis of OS (FAS)

	Docetaxel (N=174)	Sotorasib (N=171)
Death, n (%)	94 (54.0)	109 (63.7)
Censored, n (%)	80 (46.0)	62 (36.3)
Hazard ratio (95% CI) [†]	1.010 (0.766, 1.331)	
p-value (1-sided) [†]	0.53	
OS, months [‡]		
n	174	171
Median (95% CI)	11.30 (9.00, 14.85)	10.64 (8.94, 13.96)
Min, max (+ for censored)	0.0+, 24.1+	0.8, 24.0+
Follow-up time, months [§]	16.33 (16.07, 17.08)	17.71 (16.95, 19.15)

Abbreviations: CNS, central nervous system; FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazards.

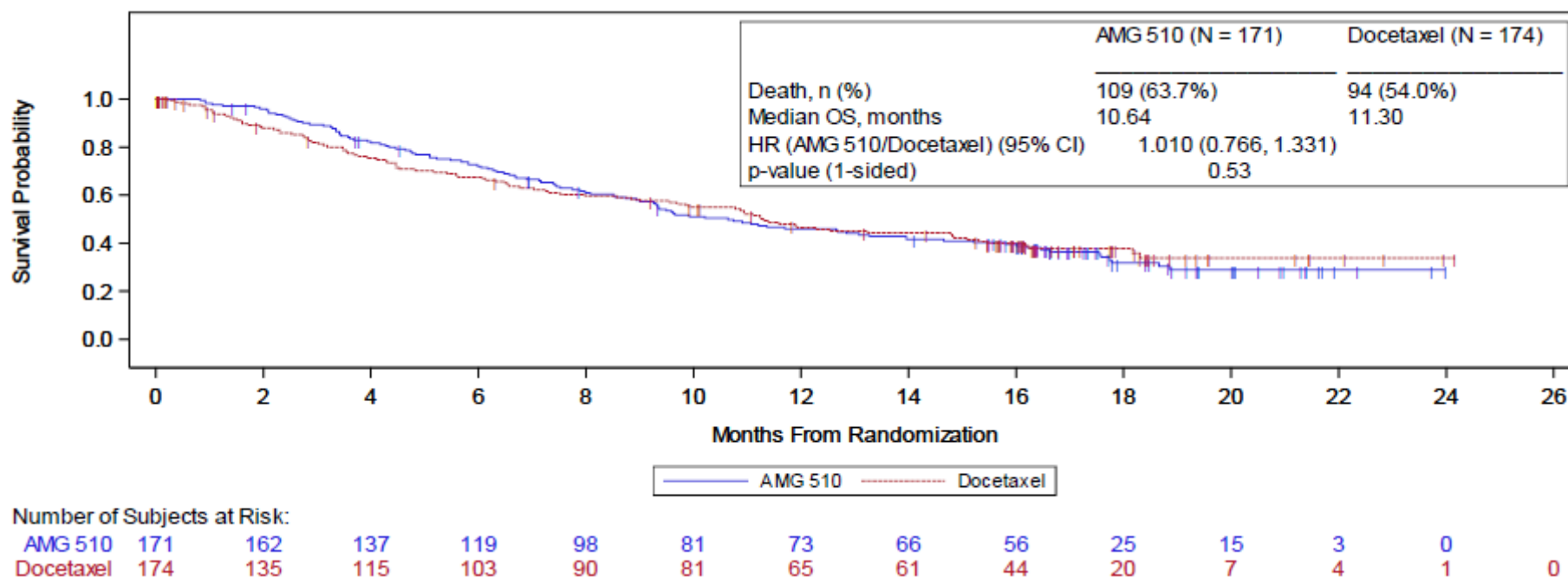
[†] Hazard ratios and 95% CIs are estimated using a stratified Cox PH model. A hazard ratio <1.0 indicates a lower average death rate and a longer OS for sotorasib relative to docetaxel. P-value is calculated using a stratified log-rank test.

[‡] Medians and percentiles are estimated using the KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.

[§] Medians and percentiles of follow-up time are estimated using the reverse KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.

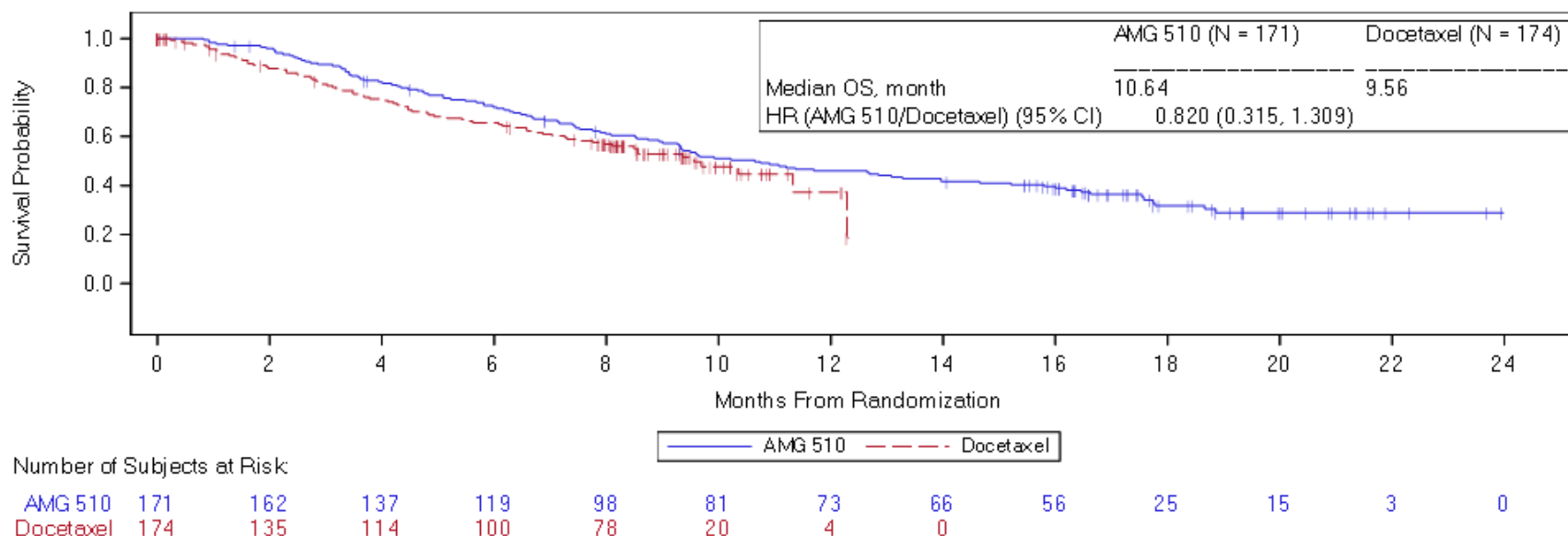
A KM plot of OS is presented in Figure 8. The KM plot for the two-stage crossover adjusted OS is presented in Figure 9.

Figure 8: KM curve for OS (FAS)



Abbreviations: AMG 510, sotorasib; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazards. Censors indicated by vertical bar |. The survival curves and the median OS are derived by KM method, while hazard ratios (95% CI) are reported from Cox PH model and p-value is calculated using log-rank test stratified by randomisation stratification factors. A hazard ratio <1.0 indicates a lower average event rate and a longer OS for sotorasib relative to docetaxel.

Figure 9: KM curve for OS (two-stage crossover adjusted including patients who received commercial sotorasib)



Abbreviations: AMG 510, sotorasib; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazards. Censors indicated by vertical bar (|). The survival curves and the median OS are derived by KM method, while hazard ratios (95% CI) are reported from Cox PH model and p-value is calculated using log-rank test stratified by randomisation stratification factors. A hazard ratio <1.0 indicates a lower average event rate and a longer OS for sotorasib relative to docetaxel.

2.6.1.3 Secondary efficacy outcome: ORR

An objective response was achieved for 48 subjects (CR for 2 subjects, PR for 46 subjects) in the sotorasib group, and for 23 subjects (all PR) in the docetaxel group. The ORR was 28.1% (95% CI: 21.5, 35.4) in the sotorasib group compared with 13.2% (95% CI: 8.6, 19.2) in the docetaxel group (OR of 2.600; 95% CI: 1.483, 4.557; $p < 0.001$).

Results from the sensitivity analyses of ORR were consistent with those of the primary analysis: response as assessed by the investigator (OR of 2.299; 95% CI: 1.323, 3.997; $p = 0.001$), and in the per protocol set response as assessed by BICR (OR of 2.504; 95% CI: 1.416, 4.427; $p < 0.001$).

2.6.1.4 Secondary efficacy outcome: DOR

Forty-eight subjects (28.1%) in the sotorasib group and 23 subjects (13.2%) had a confirmed best overall response of CR or PR. The median (95% CI) DOR was 8.64 (7.06, 17.97) months in the sotorasib group compared with 6.80 (4.27, 8.28) months in the docetaxel group.

Results from the sensitivity analyses for DOR were consistent with that of the main analysis: for the response as assessed by the investigator, the median (95% CI) DOR was 8.34 (7.13, 10.35) months in the sotorasib group and 4.27 (2.96, 11.53) in the docetaxel group; and for the response as assessed by BICR using the per protocol set, the DOR was 8.64 (6.93, 12.25) months in the sotorasib group and 6.80 (4.27, 8.28) in the docetaxel group.

2.6.1.5 Secondary efficacy outcome: TTR

Among the 48 responders (2 CR, 46 PR) in the sotorasib group, the median (range) time to response was 1.41 (1.2, 8.3) months. Among the 23 responders (all PR) in the docetaxel group, the median (range) time to response was 2.76 (1.3, 11.3) months.

Results from the sensitivity analyses for time to response were consistent with that of the main analysis: for the response as assessed by the investigator, the median (range) time to response was 1.48 (1.2, 11.0) months in the sotorasib group and 2.76 (1.3, 9.4) in the docetaxel group; and for the response as assessed by BICR

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using the per protocol set, the time to response was 1.41 (1.2, 8.3) months in the sotorasib group and 2.76 (1.3, 11.3) in the docetaxel group.

2.6.1.6 Secondary efficacy outcome: DCR

In total, 141 subjects in the sotorasib group and 105 subjects in the docetaxel group achieved disease control. CR was reported for 2 subjects (1.2%) in the sotorasib group and 0 subjects in the docetaxel group, PR for 46 subjects (26.9%) and 23 subjects (13.2%), respectively, and stable disease for 93 subjects (54.4%) and 82 subjects (47.1%), respectively. The DCR (95% CI) was 82.5% (75.9, 87.8) in the sotorasib group compared with 60.3% (52.7, 67.7) in the docetaxel group (OR of 3.077, 95% CI: 1.862, 5.085; $p < 0.001$).

Results from the sensitivity analyses for DCR were consistent with that of the main analysis: for the response as assessed by the investigator, the DCR was 81.3% (74.6, 86.8) in the sotorasib group and 54.6% (46.9, 62.1) in the docetaxel group (OR of 3.695, 95% CI: 2.240, 6.094; $p < 0.001$); and for the response as assessed by BICR using the per protocol set, the DCR was 81.8% (74.9, 87.4) in the sotorasib group and 61.3% (53.4, 68.9) in the docetaxel group (OR of 2.803, 95% CI: 1.670, 4.704; $p < 0.001$).

2.6.1.7 Patient-reported outcomes (PROs)

2.6.1.7.1 Key PROs

The key PROs were change from baseline (Cycle 1 Day 1) to Week 12 in:

- Global health status and physical functioning as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-Item Core Module (EORTC QLQ-C30)
- Dyspnoea as measured by a four item dyspnoea domain from EORTC QLQ-C30 and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module (EORTC QLQ-LC13)
- Cough and chest pain as measured by EORTC QLQ-LC13

The key PRO endpoints were not statistically tested, because the hierarchical testing was stopped at the non-statistically significant OS endpoint. The results on PRO endpoints are considered descriptive in nature.

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The key PRO endpoints were stabilised for subjects in the sotorasib group, whereas there was clinically meaningful worsening in the docetaxel group.

For global health status and physical functioning (for which negative results equate to worsening) and dyspnoea (for which positive results equate to worsening), within group least squares (LS) mean (SE) changes from baseline to Week 12 were:

- 0.03 (1.45) vs -6.90 (1.58) for global health status/QoL
- 0.10 (1.48) vs -8.68 (1.62) for physical functioning
- -0.57 (1.41) vs 9.52 (1.58) for dyspnoea (composite)

These correspond to LS mean change differences from baseline to Week 12 (mixed model for repeated measurement [MMRM] analyses) which were all in favour of sotorasib, with corresponding p-values unadjusted for multiplicity below 0.001:

- 6.93 (95% CI: 3.66, 10.19) for global health status
- 8.78 (95% CI: 5.39, 12.17) for physical functioning
- -10.09 (95% CI: -13.39, -6.78) for dyspnoea (composite)

The generalised estimating equations (GEE) analysis for cough suggests a likelihood of having improved symptoms at Week 12 (OR of sotorasib versus docetaxel 3.21; 95% CI: 1.55, 6.65; p=0.002). Numerical improvements (not statistically significant) in chest pain symptoms were also observed for sotorasib versus docetaxel (OR 1.56; 95% CI: 0.82, 2.96; p=0.18).

2.6.1.7.2 Secondary PRO outcomes

Secondary PRO measures included:

- Time to deterioration for the subscales for EORTC QLQ-C30 and EORTC QLQ-LC13
- Summary scores at each assessment and changes from baseline of visual analogue scale (VAS) scores as measured by EQ-5D-5L
- Change from baseline to week 12 for the remaining subscales for 29EORTC QLQ-C30 and EORTC QLQ-LC13

Time to deterioration

Overall, sotorasib showed a clinically meaningful difference compared with docetaxel in delaying time to deterioration in global health status (HR: 0.694, 95% CI: 0.530, 0.909), physical functioning (HR: 0.692, 95% CI: 0.521, 0.920), dyspnoea (composite) (HR: 0.629, 95% CI: 0.479, 0.825), and cough (HR: 0.553, 95% CI: 0.381, 0.803). Furthermore, a trend was observed for chest pain (HR: 0.839, 95% CI: 0.595, 1.183).

In terms of weeks to deterioration, the median time was increased with sotorasib compared with docetaxel for global health status from 6.55 to 9.25 weeks, for physical functioning from 9.40 to 15.09 weeks, for dyspnoea (composite) from 6.55 to 12.10 weeks, for cough from 15.23 to 49.26 weeks, and for chest pain from 27.33 to 34.88 weeks.

EQ-5D-5L VAS

QoL as measured by the VAS of the EQ-5D-5L questionnaire was comparable at baseline in both treatment groups. Mean (SD) was 67.6 (19.9) in the sotorasib group and 68.3 (20.3) in the docetaxel group. Overall, VAS changes were favourable for sotorasib when compared with docetaxel. Immediately after administration of investigational product, i.e. at Day 5, mean (SD) change from baseline in EQ-5D-5L VAS scores were 1.5 (15.9) in the sotorasib group compared with -8.4 (20.8) in the docetaxel group. Also, long term, i.e. all follow-up cycles up to Week 12, noteworthy changes were observed; at Week 12, mean (SD) changes from baseline in VAS scores were 2.2 (15.6) in the sotorasib group compared with -5.8 (18.2) in the docetaxel group.

Change from baseline to Week 12 in EORTC QLQ-C30 and EORTC QLQ-LC13 subscales

Change from baseline to Week 12 in the EORTC QLQ-C30 and EORTC QLQ-LC13 subscales were broadly consistent with the changes from baseline to Week 12 in the key secondary endpoints, as outlined in Section 2.6.1.7.1.

2.6.1.7.3 Exploratory PRO outcomes

The Functional Assessment of Cancer Therapy-General, item 5 (FACT-G GP5) scale was used to assess bother from side effects of treatment, and Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) scores were collected to assess the severity, frequency, and interference of treatment-related symptoms.

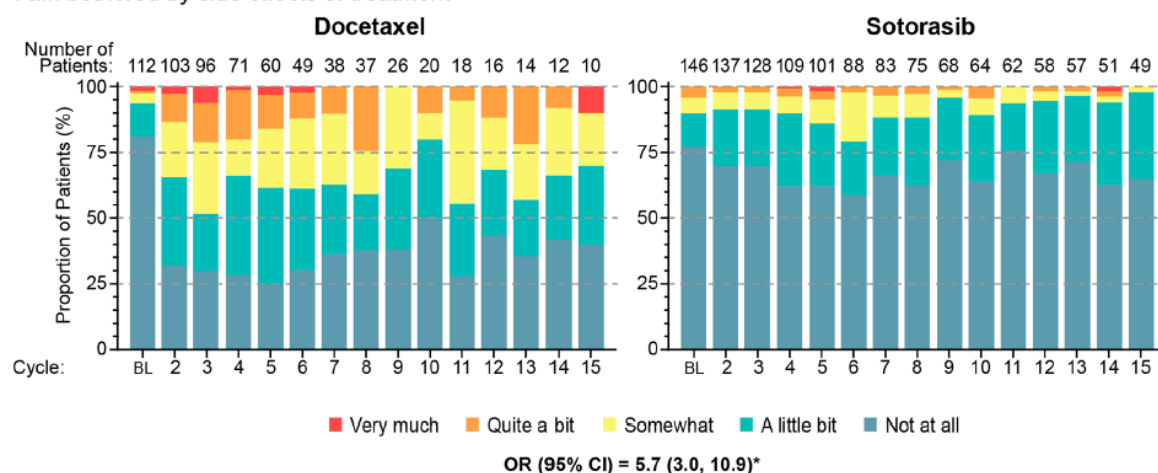
FACT-G GP5

Patients treated with sotorasib compared with those treated with docetaxel were less bothered by the side effects of treatment. The FACT-G GP5 score suggested that sotorasib was better tolerated compared with docetaxel, with the OR at Week 12 (Cycle 5 Day 1) of selecting a superior category while being treated with sotorasib at 5.7 (95% CI: 3.0, 10.9; $p < 0.001$) (Figure 10). The OR corresponds to the likelihood of patients selecting a more favourable response category. Similar results were observed at other cycles and overall.

Figure 10: Treatment side effects over time by FACT-G GP5

FACT-G GP5

"I am bothered by side effects of treatment"



Abbreviations: BL, baseline; CI, confidence interval; FACT-G GP5, Functional Assessment of Cancer Therapy Tool General Form, single item "I am bothered by side effects of treatment", rated on a 5-point Likert scale; GEE, generalised estimating equation; OR, odds ratio.

Patients completed the FACT-G GP5 on day 1 (administered by tablet in the clinic) of each cycle and at the safety follow-up. *OR of change from baseline to week 12, based on GEE model.

Source: Waterhouse et al. 2024 (69).

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PRO-CTCAE

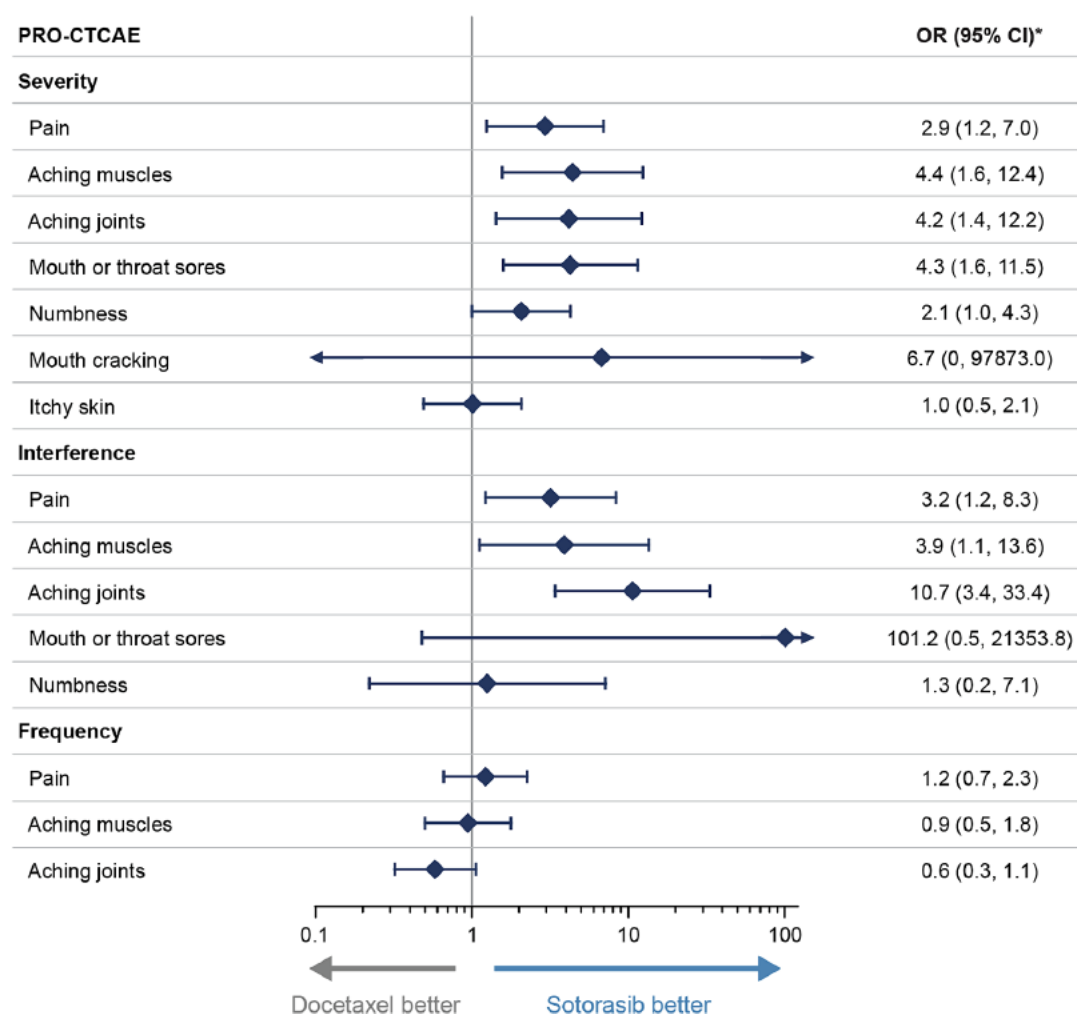
Overall, PRO-CTCAE scores suggested that sotorasib was better tolerated compared with docetaxel (Figure 11). In particular, for docetaxel, the symptoms showed a higher severity and stronger interference with daily/usual activities. However, in terms of frequency of symptoms, both trial groups were similar.

Severity: The impact of treatment on severity of symptoms suggested better outcomes with sotorasib compared with docetaxel. At Week 12 (Cycle 5 Day 1), compared with docetaxel, sotorasib improved the severity of pain (OR: 2.9, 95% CI: 1.2, 7.0; $p=0.014$), aching muscles (OR: 4.4, 95% CI: 1.6, 12.4; $p=0.005$), aching joints (OR: 4.2, 95% CI: 1.4, 12.2; $p=0.009$), mouth or throat sores (OR: 4.3, 95% CI: 1.6, 11.5; $p=0.004$), numbness (OR: 2.1, 95% CI: 1.0, 4.3; $p=0.050$), and mouth cracking (OR: 6.7, 95% CI: 0.0, 97873.0; $p=0.700$). In addition, based on PRO-CTCAE, sotorasib patients were less likely to lose fingernails (OR: 0.13, 95% CI: 0.07, 0.25), have bumps on the nails (OR: 0.16, 95% CI: 0.08, 0.30), or have a change in nail colour (OR: 0.06, 95% CI: 0.03, 0.12). The severity of itchy skin was similar between sotorasib and docetaxel treatment groups (OR: 1.0, 95% CI: 0.5, 2.1; $p=0.990$) at Week 12, with similar results observed at other cycles and overall.

Interference: Patients treated with sotorasib reported less interference in daily/usual activities for pain (OR: 3.2, 95% CI: 1.2, 8.3; $p=0.018$), aching muscles (OR: 3.9, 95% CI: 1.1, 13.6; $p=0.033$), aching joints (OR: 10.7, 95% CI: 3.4, 33.4; $p<0.001$), mouth or throat sores (OR: 101.2, 95% CI: 0.5, 21353.8; $p=0.091$), and numbness (OR: 1.3, 95% CI: 0.2, 7.1; $p=0.80$) at Week 12. Similar results were observed at other cycles and overall.

Frequency: The frequency of pain (OR: 1.2, 95% CI: 0.7, 2.3; $p=0.520$), aching muscles (OR: 0.9, 95% CI: 0.5, 1.8; $p=0.850$), and aching joints (OR: 0.6, 95% CI: 0.3, 1.1; $p=0.760$) were similar between treatment groups. Generally similar results were observed in other cycles and overall.

Figure 11: Impact of treatment on symptoms by PRO-CTCAE (including severity, interference, and frequency) after 12 weeks of treatment



Abbreviations: CI, confidence interval; OR, odds ratio; PRO-CTCAE, Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events.

The analysis set included all randomised patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements (sotorasib, n=48; docetaxel, n=113). The displayed PRO-CTCAE list is comprehensive: there were no further assessments on severity, interference, or frequency of symptoms beyond the list presented here. *OR and 95% CIs were estimated using a generalised estimating equations model.

Arrows indicate continuation of 95% CI past the OR graph range. An OR >1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel.

Source: Waterhouse et al. 2024 (69).

2.6.1.8 Conclusion

CodeBreak 200 met its primary endpoint. Treatment with sotorasib resulted in a 34% reduction in the hazard of progression or death when compared with docetaxel (HR: 0.66 [95% CI: 0.51, 0.86], $p=0.002$), corresponding to a 1.1 month improvement in PFS, in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with the *KRAS G12C* mutation. More than twice as many subjects

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in the sotorasib group were alive without progression at a 1-year landmark compared with subjects in the docetaxel group (1-year PFS was 24.8% for sotorasib vs 10.1% for docetaxel). The PFS benefit observed with sotorasib treatment was consistent across all relevant subgroups, including history of CNS involvement and liver metastasis at baseline.

In addition, ORR, DOR, TTR, and DCR were improved for sotorasib versus docetaxel:

- ORR was statistically significantly improved for sotorasib versus docetaxel (28.1% [95% CI: 21.5, 35.4] vs 13.2% [95% CI: 8.6, 19.2], respectively; $p < 0.001$)
- The median DOR was 8.6 months with sotorasib versus 6.8 months with docetaxel
- The median TTR for subjects was 1.4 months in the sotorasib group versus 2.8 months in the docetaxel group
- DCR was 82.5% with sotorasib versus 60.3% for docetaxel

In the primary analysis, OS was not significantly different between the sotorasib group (median 10.6 months) and the docetaxel group (median 11.3 months). However, adjusted analyses accounting for all crossover yielded an OS HR of 0.820 (95% CI: 0.315, 1.309). These adjusted results, although not statistically significant due to limited power, support a numerically favourable OS trend for sotorasib and align with CAS RWE findings.

Treatment with sotorasib demonstrated better QoL and reduced symptom burden compared with docetaxel. While QoL measurements for subjects in the sotorasib group remained stable, for subjects in the docetaxel group, QoL measurements significantly worsened, both directly after administration and long-term treatment. Patients treated with sotorasib reported less severe symptoms and were less bothered by treatment side effects than those receiving docetaxel.

CodeBreak 200 establishes sotorasib as the first oral *KRAS*^{G12C}-targeted therapy in a randomised Phase 3 trial to have a higher PFS and ORR, compared with IV

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docetaxel, for treatment of patients with advanced NSCLC with the *KRAS G12C* mutation who had been previously treated with other anticancer drugs.

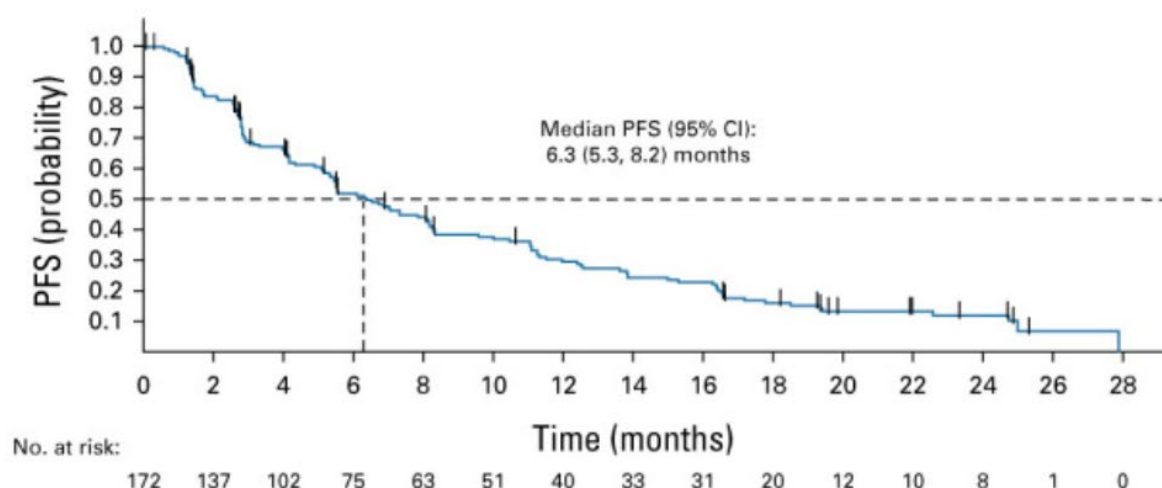
2.6.2 CodeBreakK 100 long-term follow-up

2.6.2.1 Efficacy outcomes

As of 22nd February 2022, of the 174 patients treated with sotorasib, ORR in CodeBreakK 100 was 41% (95% CI: 33.3, 48.4). Of patients with confirmed response, an estimated 72.8% (95% CI: 60.0, 82.2) and 50.6% (37.4, 62.4) remained in response at 6 and 12 months, respectively. Median DOR was 12.3 months (95% CI: 7.1, 15.0).

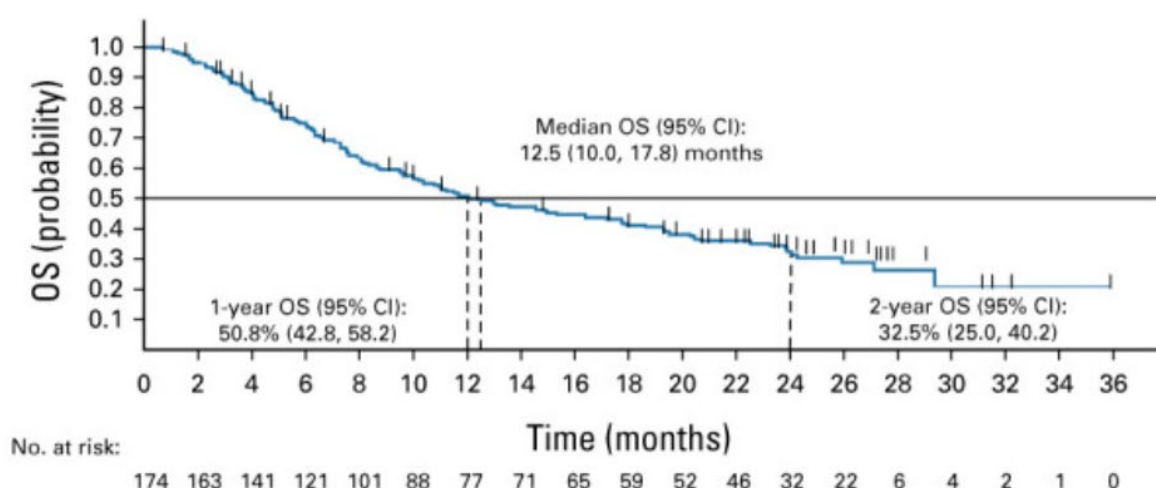
Median PFS was 6.3 months (95% CI: 5.3, 8.2; Figure 12), while median OS was 12.5 months (10.0, 17.8). The KM OS estimates were 51% (95% CI: 42.8, 58.2) and 33% (95% CI: 25.0, 40.2) at 12 and 24 months, respectively (Figure 13). At data cut-off, nine of 70 (13%) patients with response remained on study without progression, including five receiving sotorasib for ≥ 2 years with continued response.

Figure 12: KM plot of PFS from long-term CodeBreakK 100 follow-up



Abbreviations: CI, confidence interval; KM, Kaplan-Meier; PFS, progression-free survival.

Figure 13: KM plot of OS from long-term CodeBreakK 100 follow-up



Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival.

2.6.3 CAS RWE study

The median follow-up time from index date was 8.62 months (Q1-Q3: 4.47-13.90) for the sotorasib cohort and 6.11 months (Q1-Q3: 3.22-10.87) for the docetaxel cohort. Prior to SMRW, large differences in the PS distributions were 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 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). The ESS was 394 patients in the sotorasib treatment group and 392 patients in the docetaxel treatment group.

2.6.3.1 Primary efficacy outcome: OS

Prior to SMRW, unadjusted median OS in the 2L+ analysis set was [REDACTED] months (95% CI: [REDACTED]) in the sotorasib treatment group and [REDACTED] months (95% CI: [REDACTED]) in the docetaxel treatment group (p [REDACTED]). Treatment with sotorasib was associated with a [REDACTED]% decreased risk of death (HR: [REDACTED]; 95% CI: [REDACTED]; $p < [REDACTED]$) compared with docetaxel monotherapy. Full unadjusted results can be found in Appendix K.

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Following SMRW, adjusted median OS in the 2L+ analysis set was 10.18 months (95% CI: 9.10, 12.02) in the sotorasib treatment group and 6.87 months (95% CI: 6.01, 7.82) in the docetaxel treatment group ($p < 0.001$) (Table 28). The weighted KM plot for OS in the 2L+ analysis set is provided in Figure 14. Treatment with sotorasib was associated with a 36.7% decreased risk of death (HR: 0.633; 95% CI: 0.536, 0.749; $p < 0.001$) compared with docetaxel monotherapy.

Table 28: KM results for OS in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)

		Docetaxel (N=363)	Sotorasib (N=394)
Total	Number of patients, n	363	394
	Number of events, n	■	■
	Number of censored patients, n	■	■
	Median (95% CI)	6.87 (6.01, 7.82)	10.18 (9.10, 12.02)
	Q1-Q3	■	■
3 months	Number of patients	■	■
	Probability (95% CI)	■	■
6 months	Number of patients	■	■
	Probability (95% CI)	■	■
9 months	Number of patients	■	■
	Probability (95% CI)	■	■
12 months	Number of patients	■	■
	Probability (95% CI)	■	■
24 months	Number of patients	■	■
	Probability (95% CI)	■	■
36 months	Number of patients	■	■
	Probability (95% CI)	■	■
Hazard ratio (95% CI)†		0.633 (0.536, 0.749)	
p-value		<0.001	

Abbreviations: ATT, average treatment effect in the treated; CI, confidence interval; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; OS, overall survival; SMRW, standardised mortality ratio weighting.
† Based on Cox regression analysis. Adjusted for confounding using SMRW or IPTW (as applicable). If other covariates may be unbalanced that were not considered in the propensity score model, these will be adjusted for in the Cox model. CIs for the treatment effect estimate calculated using robust standard errors.
* Numbers from 1-5 are masked, in accordance with NHS England policy to minimise the risk of patient identification.

Figure 14: KM plot for OS in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)



Abbreviations: ATT, average treatment effect in the treated; KM, Kaplan-Meier; OS, overall survival; SMRW, standardised mortality ratio weighting.

2.6.3.2 Secondary efficacy outcome: TTNTD

Prior to SMRW, the unadjusted median TTNTD in the 2L+ analysis set was [REDACTED] months (95% CI: [REDACTED]) for the sotorasib group and [REDACTED] months (95% CI: [REDACTED]) for the docetaxel group (p[REDACTED]). Treatment with sotorasib was associated with a [REDACTED]% decreased risk of initiation of a new LoT or death (HR: [REDACTED]; 95% CI:

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██████████; p ██████████) compared with docetaxel monotherapy. Full unadjusted results can be found in Appendix K.

Following SMRW, the adjusted median TTNTD in the 2L+ analysis set was 8.51 months (95% CI: 7.33, 9.43) for the sotorasib group and 5.62 months (95% CI: 5.06, 6.18) for the docetaxel group (p<0.001) (Table 29). The weighted KM survival plot for TTNTD in the 2L+ analysis set is provided in Figure 15. Treatment with sotorasib was associated with a 43.3% decreased risk of initiation of a new LoT or death (HR: 0.567; 95% CI: 0.485, 0.663; p<0.001) compared with docetaxel monotherapy.

Table 29: KM results for TTNTD in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)

		Docetaxel (N=363)	Sotorasib (N=394)
Total	Number of patients, n	363	394
	Number of events, n	██████████	██████████
	Number of censored patients, n	██████████	██████████
	Median (95% CI)	5.62 (5.06, 6.18)	8.51 (7.33, 9.43)
	Q1-Q3	██████████	██████████
3 months	Number of patients	██████████	██████████
	Probability (95% CI)	██████████	██████████
6 months	Number of patients	██████████	██████████
	Probability (95% CI)	██████████	██████████
9 months	Number of patients	██████████	██████████
	Probability (95% CI)	██████████	██████████
12 months	Number of patients	██████████	██████████
	Probability (95% CI)	██████████	██████████
24 months	Number of patients	██████████	██████████
	Probability (95% CI)	██████████	██████████
36 months	Number of patients	██████████	██████████
	Probability (95% CI)	██████████	██████████
Hazard ratio (95% CI)†		0.567 (0.485, 0.663)	
p-value		<0.001	

Abbreviations: ATT, average treatment effect in the treated; CI, confidence interval; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; SMRW, standardised mortality ratio weighting; TTNTD, time to next treatment or death.

† Based on Cox regression analysis. Adjusted for confounding using SMRW or IPTW (as applicable). If other covariates may be unbalanced that were not considered in the propensity score model, these will be adjusted for in the Cox model. CIs for the treatment effect estimate calculated using robust standard errors.

* Numbers from 1-5 are masked, in accordance with NHS England policy to minimise the risk of patient identification.

Figure 15: KM plot for TTNTD in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)



Abbreviations: ATT, average treatment effect in the treated; KM, Kaplan-Meier; SMRW, standardised mortality ratio weighting; TTNTD, time to next treatment or death.

2.6.3.3 Exploratory outcome: TTDD

Prior to SMRW, unadjusted median TTDD in the 2L+ analysis set was [REDACTED] months (95% CI: [REDACTED]) in the sotorasib treatment group and [REDACTED] months (95% CI: [REDACTED]) in the docetaxel treatment group (p[REDACTED]). Treatment with sotorasib was associated with a [REDACTED]% decreased risk of treatment discontinuation or death (HR:

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█████; 95% CI: █████; p(█████) compared with docetaxel monotherapy. Full unadjusted results can be found in Appendix K.

Following SMRW, adjusted median TTDD in the 2L+ analysis set was 5.06 months (95% CI: 4.34, 6.11) in the sotorasib treatment group and 2.30 months (95% CI: 2.07, 2.76) in the docetaxel treatment group (p<0.001). The weighted KM survival plot for TTDD in the 2L+ analysis set is given in Figure 16. Treatment with sotorasib was associated with a 74.8% decreased risk of treatment discontinuation or death (HR: 0.252; 95% CI: 0.212, 0.300; p<0.001) compared with docetaxel monotherapy.

Table 30: KM results for TTDD in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)

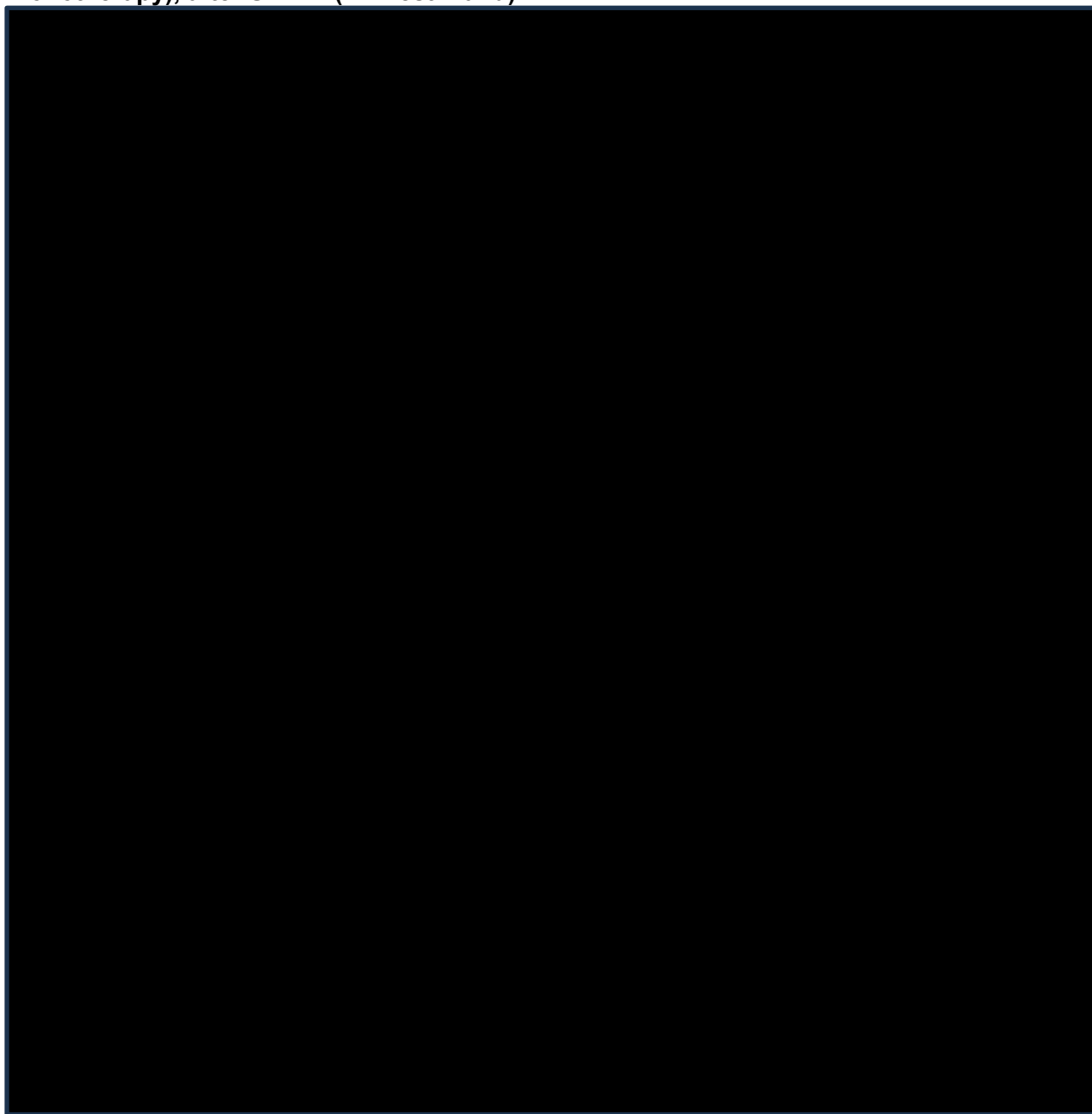
		Docetaxel (N=363)	Sotorasib (N=394)
Total	Number of patients, n	363	394
	Number of events, n	████	████
	Number of censored patients, n	████	████
	Median (95% CI)	2.30 (2.07, 2.76)	5.06 (4.34, 6.11)
	Q1-Q3	██████	██████
3 months	Number of patients	████	████
	Probability (95% CI)	██████████	██████████
6 months	Number of patients	████	████
	Probability (95% CI)	██████████	██████████
9 months	Number of patients	████	████
	Probability (95% CI)	██████████	██████████
12 months	Number of patients	████	████
	Probability (95% CI)	██████████	██████████
24 months	Number of patients	████	████
	Probability (95% CI)	██████████	██████████
36 months	Number of patients	████	████
	Probability (95% CI)	██████████	██████████
Hazard ratio (95% CI)†		0.252 (0.212, 0.300)	
p-value		<0.001	

Abbreviations: ATT, average treatment effect in the treated; CI, confidence interval; IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; NA, not applicable; SMRW, standardised mortality ratio weighting; TTDD, time to treatment discontinuation or death.

† Based on Cox regression analysis. Adjusted for confounding using SMRW or IPTW (as applicable). If other covariates may be unbalanced that were not considered in the propensity score model, these will be adjusted for in the Cox model. CIs for the treatment effect estimate calculated using robust standard errors.

* Numbers from 1-5 are masked, in accordance with NHS England policy to minimise the risk of patient identification.

Figure 16: KM plot for TTDD in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)



Abbreviations: ATT, average treatment effect in the treated; KM, Kaplan-Meier; SMRW, standardised mortality ratio weighting; TTDD, time to treatment discontinuation or death.

2.6.3.4 Sensitivity analyses

A summary of key sensitivity analyses for the comparison of sotorasib versus docetaxel monotherapy for all study outcomes is provided in Appendix K.

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- **OS:** Across all adjusted sensitivity analyses performed, median OS ranged from [REDACTED] to [REDACTED] months in the sotorasib treatment group and from [REDACTED] to [REDACTED] months in the docetaxel treatment group, while the HR ranged from [REDACTED] to [REDACTED].
- **TTNTD:** Adjusted TTNTD ranged from [REDACTED] to [REDACTED] months in the sotorasib treatment group and from [REDACTED] to [REDACTED] months in the docetaxel treatment group, while the HR ranged from [REDACTED] to [REDACTED].
- **TTDD:** Adjusted TTDD ranged from [REDACTED] to [REDACTED] months in the sotorasib treatment group and was [REDACTED] in the docetaxel treatment group, while the HR ranged from [REDACTED] to [REDACTED].

2.6.3.5 Conclusion

Among patients with locally advanced or metastatic NSCLC who have previously been treated with platinum-doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy, sotorasib monotherapy was significantly more effective than docetaxel monotherapy in 2L+ for prolonging OS, TTNTD, and TTDD. Treatment with sotorasib was associated with a 36.7% lower risk of death, a 43.3% lower risk of death or new LoT initiation, and a 74.8% lower risk of death or treatment discontinuation compared with docetaxel monotherapy (after SMRW adjustment). Sotorasib prolonged median OS by approximately 3.25 months, median TTNTD by approximately 3 months, and median TTDD by 2.75 months.

2.7 Subsequent treatments used in the relevant studies

2.7.1 CodeBreakK 200

A summary of subsequent treatments used in CodeBreakK 200 is provided in Table 31.

Table 31: Summary of subsequent anti-cancer therapy (FAS)

	Docetaxel (N=174) n (%)	Sotorasib (N=171) n (%)
Any subsequent anti-cancer therapy including crossover	73 (42.0)	62 (36.3)
Chemotherapy	21 (12.1)	36 (21.1)
KRAS ^{G12C} inhibitor	59 (33.9)	6 (3.5)

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	Docetaxel (N=174) n (%)	Sotorasib (N=171) n (%)
Immunotherapy	10 (5.7)	16 (9.4)
Checkpoint inhibitor	10 (5.7)	14 (8.2)
Other	18 (10.3)	25 (14.6)

Abbreviations: eCRF, electronic case record form; FAS, full analysis set.

This table summarises subjects based on all entries collected on the anti-cancer therapy (post-treatment) eCRF form, and 46 subjects who crossed over from docetaxel to sotorasib per protocol, categorised under "KRAS G12C inhibitor". One subject can be counted under multiple categories.

2.8 Subgroup analysis

2.8.1 CodeBreakK 200

2.8.1.1 Methodology

In addition to the stratification factors for randomisation, number of prior lines of therapy in advanced disease (1 versus 2 versus >2), race (Asian versus non-Asian), history of CNS involvement (yes versus no), the following subgroup analyses of primary and selected secondary endpoints were planned to investigate the consistency of treatment effects:

- region (North America and Europe versus rest of world) best response on prior therapy primary refractory (progression on first scan), suboptimal response (stable disease), recurrent (initial response with subsequent growth)
- age (<65 vs ≥65)
- sex (male vs female)
- race (white, black, Asian, other)
- ECOG status (0 vs 1)
- liver metastasis at baseline (yes versus no)
- stage (locally advanced and unresectable versus metastatic)
- smoking history (yes versus no)
- histology (squamous versus non-squamous)
- presence of specific co-mutation at baseline (yes versus no)
- brain metastasis at baseline (yes versus no)
- bone metastasis at baseline (yes versus no)

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- PD-L1 protein expression (<1% vs ≥1%, and <50% vs ≥50%)
- *STK11* mutation
- *KEAP1* mutation

In the event the number of subjects in a subgroup was insufficient (i.e. <10% of the whole population), relevant subgroups may have been combined.

The primary endpoint of PFS was analysed within each of the subgroups. To determine whether the treatment effect was consistent across subgroups, the estimate of the HRs (with 95% CI) for PFS between the treatment groups was calculated. Subgroup analysis for OS was performed using the same method described for PFS as appropriate.

The inferential comparison between treatment groups for ORR and estimates of ORR with 95% CI were performed using the same methods as outlined for the primary analysis (see Section 2.4.1.2.2).

2.8.1.2 Results

The PFS benefit observed in the sotorasib group versus the docetaxel group was consistent across all relevant subgroups, including history of CNS involvement and liver metastasis at baseline. Likewise, results from the subgroup analyses of OS and ORR were generally consistent with those of the primary analyses. Key subgroup analyses of PFS are provided in Table 32, with further results in Appendix C, including subgroup analyses for OS and ORR.

Table 32: Key subgroup analyses of PFS

Subgroup	Number of patients		HR for disease progression or death (95% CI)
	Docetaxel	Sotorasib	
All randomised subjects	174	171	0.663 (0.509, 0.864)
Europe	126	126	0.675 (0.497, 0.916)
History of CNS involvement	60	58	0.530 (0.342, 0.821)
No history of CNS involvement	114	113	0.735 (0.528, 1.025)
History of liver metastasis	35	30	0.471 (0.260, 0.853)
No history of liver metastasis	139	141	0.667 (0.493, 0.902)

Subgroup	Number of patients		HR for disease progression or death (95% CI)
	Docetaxel	Sotorasib	
One prior line of therapy in advanced disease	78	77	0.695 (0.466, 1.036)
Two prior lines of therapy in advanced disease	69	65	0.608 (0.399, 0.924)
More than two prior lines of therapy in advanced disease	27	29	0.740 (0.374, 1.463)

Abbreviations: CI, confidence interval; CNS, central nervous system; PFS, progression-free survival.

2.8.2 CAS RWE study

2.8.2.1 Methodology

The following subgroups of the 2L+ analysis set were included for the analyses of OS (primary objective), TTNTD (secondary objective), and TTDD (exploratory objective):

1. Receipt of prior PD-1/PD-L1 immunotherapy
 - a. Prior PD-1/PD-L1 targeted immunotherapy: Patients included if they have any record of receiving PD-1/PD-L1 targeted immunotherapy for locally advanced or metastatic NSCLC prior to index date
 - b. No prior PD-1/PD-L1 targeted immunotherapy: Patients included if they have no record of receiving PD-1/PD-L1 targeted immunotherapy for locally advanced or metastatic NSCLC prior to index date
2. Prior brain metastases:
 - a. Record of prior brain metastases: Patients included if they have any record of brain metastasis prior to index date, according to ICD-10 diagnosis and OPCS-4 procedure codes
 - b. No record of prior brain metastases: Patients included if they have no record of brain metastasis prior to index date, according to ICD-10 diagnosis and OPCS-4 procedure codes

PS estimation was done within each subgroup separately to ensure that covariate balance was achieved within the subgroups. All subgroup analyses were contingent upon available sample size. A subgroup analysis was performed if there were ≥ 30 patients and ≥ 10 outcome events within the subgroup.

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2.8.2.2 Results

Compared with docetaxel monotherapy, treatment with sotorasib decreased the risk of death by:

- █% (HR: █; 95% CI: █; p █) among patients who received prior PD-1/PD-L1 targeted immunotherapy
- █% (HR: █; 95% CI: █; p █) among patients who did not receive prior PD-1/PD-L1 targeted immunotherapy
- █% (HR: █; 95% CI: █; p █) among patients with a prior record of brain metastasis
- █% (HR: █; 95% CI: █; p █) among patients without a prior record of brain metastasis

Further results from subgroup analyses are provided in Appendix C.

2.9 Meta-analysis

CodeBreak 200 is the only RCT providing comparative data for sotorasib versus docetaxel in patients with *KRAS G12C*-mutated NSCLC. As docetaxel is the only relevant comparator for sotorasib (see Section 1.3.2), meta-analysis was not required.

2.10 Indirect and mixed treatment comparisons

As the evidence base for sotorasib provides direct head-to-head data versus the only relevant comparator, docetaxel, no indirect treatment comparisons were performed.

2.11 Adverse reactions

The CAS RWE study did not collect any safety data (see Section 2.3.3 for study design). Adverse reactions from CodeBreak 200 and CodeBreak 100 long-term follow-up are presented in Sections 2.11.1 and 2.11.2, respectively.

2.11.1 CodeBreak 200

Unless otherwise stated, all AEs summarised in text are treatment-emergent, defined as events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or

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before the first dose of sotorasib if subjects crossed over from docetaxel to sotorasib, whichever occurred earlier. Safety analyses were conducted using the SAS (N=169 sotorasib, N=151 docetaxel).

2.11.1.1 Extent of exposure

In the sotorasib group (median [range]), the duration of treatment was 19.86 (0.4, 101.3) weeks administered over 7.0 (1, 34) cycles, and the relative dose intensity was 100% (23.7, 100.0). In the docetaxel group (median [range]), the duration of treatment was 12.0 (3.0, 101.0) weeks administered over 4.0 (1, 33) cycles, and the relative dose intensity was 94.8% (48.9, 105.6).

2.11.1.2 Overall treatment-emergent adverse events

A summary of AEs is provided in Table 33. A total of 166 subjects (98.2%) in the sotorasib group and 148 subjects (98.0%) in the docetaxel group had at least one AE; of these subjects, 119 subjects (70.4%) in the sotorasib group and 130 subjects (86.1%) in the docetaxel group had AEs that were considered treatment related by the investigator.

Grade ≥ 3 AEs were reported for 121 subjects (71.6%) in the sotorasib group (treatment related for 56 subjects [33.1%]) and for 91 subjects (60.3%) in the docetaxel group (treatment related for 61 subjects [40.4%]). AEs that led to the discontinuation of investigational product occurred in 28 subjects (16.6%) in the sotorasib group and 24 subjects (15.9%) in the docetaxel group, of which 16 subjects (9.5%) in the sotorasib group and 17 subjects (11.3%) in the docetaxel group had AEs that were considered treatment related.

Serious adverse events (SAEs) were reported in 91 subjects (53.8%) in the sotorasib group and 67 subjects (44.4%) in the docetaxel group, of which 18 subjects (10.7%) in the sotorasib group and 34 subjects (22.5%) in the docetaxel group had SAEs that were considered treatment related. Fatal AEs occurred in 37 subjects (21.9%) in the sotorasib group and 18 subjects (11.9%) in the docetaxel group; for 1 subject (0.6%) in the sotorasib group and 2 subjects (1.3%) in the docetaxel group, the fatal event was considered treatment related.

Table 33: Summary of TEAEs (SAS)

	Docetaxel (N=151) n (%)	Sotorasib (N=169) n (%)
All TEAEs	148 (98.0)	166 (98.2)
Grade ≥ 2	136 (90.1)	152 (89.9)
Grade ≥ 3	91 (60.3)	121 (71.6)
Grade ≥ 4	35 (23.2)	48 (28.4)
SAEs	67 (44.4)	91 (53.8)
Leading to discontinuation of IP	24 (15.9)	28 (16.6)
Leading to dose reduction	43 (28.5)	26 (15.4)
Leading to dose interruption	42 (27.8)	86 (50.9)
Fatal AEs	18 (11.9)	37 (21.9)
Treatment-related TEAEs	130 (86.1)	119 (70.4)
Grade ≥ 2	114 (75.5)	89 (52.7)
Grade ≥ 3	61 (40.4)	56 (33.1)
Grade ≥ 4	19 (12.6)	10 (5.9)
SAEs	34 (22.5)	18 (10.7)
Leading to discontinuation of IP	17 (11.3)	16 (9.5)
Leading to dose reduction	40 (26.5)	26 (15.4)
Leading to dose interruption	23 (15.2)	60 (35.5)
Fatal AEs	2 (1.3)	1 (0.6)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; IP, investigational product; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

AEs coded using MedDRA (version 25.0) and graded using CTCAE (version 5.0). TEAEs in this table are events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if subjects crossed over from docetaxel to sotorasib, whichever occurred earlier. For subjects with multiple events under the same category, only the worst grade was reported. Grade 5 fatal AEs may have started before data cut-off and resulted in death after data cut-off. These events are summarised in this table, but deaths after data cut-off are not included in analysis.

† Treatment-related AEs are AEs considered related to at least one investigational product by the investigator.

2.11.1.2.1 Exposure-adjusted event rates

Given the differences with the longer exposure to sotorasib compared with docetaxel, exposure-adjusted event rates per 100 subject years for AEs were also evaluated in an ad hoc analysis (see Appendix J). The exposure-adjusted event rate for all AEs was 1055.4 in the sotorasib group and 2443.8 in the docetaxel group. Exposure-adjusted event rates in the sotorasib group and docetaxel group were 177.4 and 271.2, respectively, for grade ≥ 3 AEs; 26.8 and 48.9, respectively, for AEs leading to discontinuation of investigational product; and 102.2 and 169.9, respectively, for SAEs. The exposure-adjusted event rate for fatal AEs was 35.4 in the sotorasib group and 36.0 in the docetaxel group.

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The exposure-adjusted event rate for all AEs considered related to investigational product by the investigator was 297.3 in the sotorasib group and 1327.1 in the docetaxel group. Exposure-adjusted event rates for treatment-related AEs in the sotorasib group and docetaxel group were 71.6 and 160.9, respectively, for grade ≥ 3 treatment-related AEs; 15.3 and 34.4, respectively, for treatment-related AEs leading to discontinuation of investigational product; and 17.9 and 77.3, respectively, for treatment-related SAEs. The exposure-adjusted event rate for treatment-related fatal AEs was 1.0 in the sotorasib group and 4.0 in the docetaxel group.

2.11.1.3 Frequently reported AEs

2.11.1.3.1 AEs

The most frequently reported AEs ($>20\%$ of subjects in either group), were diarrhoea (70 subjects [41.4%]), nausea (44 subjects [26.0%]), and decreased appetite (39 subjects [23.1%]) in the sotorasib group; and fatigue (45 subjects [29.8%]), diarrhoea (39 subjects [25.8%]), nausea (37 subjects [24.5%]), anaemia (35 subjects [23.2%]), and alopecia (35 subjects [23.2%]) in the docetaxel group.

2.11.1.3.2 Treatment-related AEs

The most common treatment-related AEs ($>10\%$ of subjects in either group) were diarrhoea (57 subjects [33.7%]), nausea (24 subjects [14.2%]), decreased appetite (18 subjects [10.7%]), and alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased (17 subjects [10.1%] each) in the sotorasib group; and fatigue (38 [25.2%]), alopecia (31 subjects [20.5%]), nausea (30 subjects [19.9%]), diarrhoea (28 subjects [18.5%]), anaemia (27 subjects [17.9%]), decreased appetite (21 [13.9%]), stomatitis (17 subjects [11.3%]), and asthenia and constipation (16 subjects [10.6%] each) in the docetaxel group.

2.11.1.3.3 Grade ≥ 3 AEs

The most frequently reported grade ≥ 3 AEs ($>5\%$ in either group) were diarrhoea (23 subjects [13.6%]), NSCLC (17 subjects [10.1%]), ALT increased (14 subjects [8.3%]), and AST increased (10 subjects [5.9%]) in the sotorasib group; and neutropenia (13 subjects [8.6%]), anaemia (10 subjects [6.6%]), fatigue and pneumonia (9 subjects [6.0%] each), and febrile neutropenia (8 subjects [5.3%]) in the docetaxel group (Table 34).

Table 34: Grade ≥3 AEs by preferred term reported for ≥3% of subjects in either treatment group (SAS)

	Docetaxel (N=151) n (%)	Sotorasib (N=169) n (%)
Number of subjects reporting treatment-emergent grade 3 or higher AEs	91 (60.3)	121 (71.6)
Diarrhoea	4 (2.6)	23 (13.6)
Non-small cell lung cancer	5 (3.3)	17 (10.1)
Alanine aminotransferase increased	0 (0.0)	14 (8.3)
Aspartate aminotransferase increased	0 (0.0)	10 (5.9)
Anaemia	10 (6.6)	8 (4.7)
Dyspnoea	5 (3.3)	8 (4.7)
Blood alkaline phosphatase increased	0 (0.0)	6 (3.6)
Decreased appetite	0 (0.0)	6 (3.6)
Abdominal pain	2 (1.3)	5 (3.0)
Hypokalaemia	1 (0.7)	5 (3.0)
Fatigue	9 (6.0)	4 (2.4)
Asthenia	6 (4.0)	4 (2.4)
Pneumonia	9 (6.0)	1 (0.6)
Neutropenia	13 (8.6)	0 (0.0)
Febrile neutropenia	8 (5.3)	0 (0.0)
Neutrophil count decreased	5 (3.3)	0 (0.0)
Number of subjects reporting treatment-emergent treatment-related grade 3 or higher AEs	61 (40.4)	56 (33.1)
Diarrhoea	3 (2.0)	20 (11.8)
Alanine aminotransferase increased	0 (0.0)	13 (7.7)
Aspartate aminotransferase increased	0 (0.0)	9 (5.3)
Blood alkaline phosphatase increased	0 (0.0)	5 (3.0)
Neutropenia	13 (8.6)	0 (0.0)
Fatigue	9 (6.0)	1 (0.6)
Febrile neutropenia	8 (5.3)	0 (0.0)
Anaemia	5 (3.3)	1 (0.6)
Neutrophil count decreased	5 (3.3)	0 (0.0)
Pneumonia	5 (3.3)	0 (0.0)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAS, safety analysis set.

2.11.1.4 Withdrawals due to AEs

In total, 28 subjects (16.6%) in the sotorasib group and 24 subjects (15.9%) in the docetaxel group had an AE that led to discontinuation of investigational product, and the exposure-adjusted event rates were 26.8 and 48.9, respectively.

AEs that led to discontinuation of investigational product (reported for ≥ 3 subjects in either group) were ALT increased (6 subjects [3.6%] in sotorasib group vs 0 [0.0%] in docetaxel group), NSCLC (5 subjects [3.0%] vs 2 [1.3%]), and blood bilirubin increased (4 subjects [2.4%] vs 0 [0.0%]) and fatigue (0 subjects [0.0%] vs 3 [2.0%]).

2.11.1.5 Serious AEs

SAEs were reported for 91 subjects (53.8%) in the sotorasib group and 67 subjects (44.4%) in the docetaxel group, and the exposure-adjusted event rates were 102.2 and 169.9, respectively. The most common SAEs (≥ 3 subjects in either group) were NSCLC (18 subjects [10.7%] in sotorasib group vs 5 [3.3%] in docetaxel group), diarrhoea (5 subjects [3.0%] vs 2 [1.3%]), pyrexia (3 subjects [1.8%] vs 2 [1.3%]), abdominal pain (3 subjects [1.8%] vs 1 [0.7%]), chest pain (3 subjects [1.8%] vs 0 [0.0%]), pneumonia (1 subject [0.6%] vs 10 [6.6%]), febrile neutropenia (0 subjects [0.0%] vs 7 [4.6%]), anaemia (1 subject [0.6%] vs 5 [3.3%]), dyspnoea (2 subjects [1.2%] vs 4 [2.6%]) and respiratory failure (1 subject [0.6%] vs 4 [2.6%]), and sepsis (0 subjects [0.0%] vs 3 [2.0%]).

Treatment-related SAEs were reported for 18 subjects (10.7%) in the sotorasib and 34 subjects (22.5%) in the docetaxel group, and the exposure-adjusted event rates were 17.9 and 77.3, respectively.

The most frequently reported treatment-related SAEs (≥ 2 subjects in either group) were diarrhoea (3 subjects [1.8%]), drug-induced liver injury and hypertransaminasaemia (2 subjects [1.2%] each) in the sotorasib group; and febrile neutropenia (7 subjects [4.6%]), pneumonia (5 subjects [3.3%]), anaemia (3 subjects [2.0%]), and diarrhoea, fatigue, malaise, pneumonitis, sepsis, and stomatitis (2 subjects [1.3%] each) in the docetaxel group.

2.11.1.6 Fatal AEs

Fatal AEs were reported for 37 subjects (21.9%) in the sotorasib group and 18 subjects (11.9%) in the docetaxel group, and the exposure-adjusted event rates were 35.4 and 36.0, respectively.

The most frequently reported fatal AEs in both groups were related to disease progression and included NSCLC (17 subjects [10.1%]), and lung adenocarcinoma, lung neoplasm malignant (2 subjects [1.2%]), and NSCLC metastatic (2 subjects [1.2%]) in the sotorasib group; and NSCLC (5 subjects [3.3%]) and respiratory failure (2 subjects [1.3%]) in the docetaxel group.

Treatment-related fatal AEs were interstitial lung disease (1 subject [0.6%]) in the sotorasib group and ileus (1 subject [0.7%]) and multiple organ dysfunction syndrome (1 subject [0.7%]) in the docetaxel group. The exposure-adjusted fatal AE rates were 1.0 and 4.0 in the sotorasib and docetaxel groups, respectively.

2.11.1.7 Events of interest (EOI)

Subject incidences for adverse EOIs – hepatotoxicity, pneumonitis, and renal toxicity – were summarised according to the search strategy categories using Standardised MedDRA Queries (SMQs). Preferred terms consistent with hepatic EOIs were identified using hepatic disorders SMQ (broad and narrow) search criteria; pneumonitis EOIs were identified using interstitial lung disease (broad and narrow) search criteria; and renal EOIs were identified using acute renal failure SMQ (broad and narrow) and chronic kidney disease SMQ (broad and narrow) search criteria.

Using the narrow search strategy, hepatotoxicity EOIs were reported for 41 subjects (24.3%) in the sotorasib group and 7 subjects (4.6%) in the docetaxel group, pneumonitis EOIs for 4 subjects in each group (2.4% and 2.6%, respectively), and renal toxicity EOIs for 10 subjects (5.9%) in the sotorasib group (none in the docetaxel group).

Using the broad search strategy, hepatotoxicity EOIs were reported for 46 subjects (27.2%) in the sotorasib group and 14 subjects (9.3%) in the docetaxel group, pneumonitis EOIs for 4 subjects in each group (2.4% and 2.6%, respectively), and

renal toxicity EOs for 31 subjects (18.3%) in the sotorasib group and 18 subjects (11.9%) in the docetaxel group.

2.11.2 CodeBreaK 100

Any-grade treatment-related AEs were observed in 121 (70%) patients, with grade 3 in 34 (20%), grade 4 in 2 (1%), and no fatal treatment-related AEs. Treatment-related AEs led to treatment reduction or interruption in 39 (22%) and treatment discontinuation in 11 (6%). The most common treatment-related AEs were diarrhoea (53 [30%]), increased alanine aminotransferase level (31 [18%]), and increased aspartate aminotransferase level (31 [18%]). Median (range) time to grade ≥ 3 diarrhoea and hepatotoxicity onset was 6.1 (1.7, 11.1) and 9.1 (3.1, 18.7) weeks. All grade ≥ 3 (median [range] duration, weeks) diarrhoea resolved (2.9 [0.3, 6.0]); grade ≥ 3 hepatotoxicity resolved in all but three of 19 (16%; 5.5 [0.4, 39.1]). Trends toward increased hepatotoxicity in patients receiving checkpoint inhibitors $\leq$ versus >3 months before sotorasib initiation were observed.

Of 45 patients who continued sotorasib beyond 1 year, 11 (24%) had any-grade treatment-related AEs after 1 year on treatment (new-onset treatment-related AEs), without trends in AE type. One grade 3 new-onset treatment-related AE (2%; haemolytic anaemia) resolved in 5 days (sotorasib discontinued after disease progression). No grade 4 or 5 new-onset treatment-related AEs occurred. New-onset treatment-related AEs led to dose reduction in one (2%) patient without treatment discontinuation.

2.11.3 Safety overview

The most common AEs reported in the sotorasib and docetaxel groups of CodeBreaK 200 were consistent with those previously observed with the individual study treatments or with events expected to occur in the study population independent of drug exposure. Crude subject incidences of grade ≥ 3 AEs, serious events, and fatal events were higher in the sotorasib group compared with the docetaxel group. However, ad hoc analyses of exposure-adjusted event rates were lower in the sotorasib group for all event categories, except for dose interruption. Patients treated with sotorasib reported less severe symptoms and were less bothered by treatment side effects than those receiving docetaxel (see Section

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2.6.1.7.3). In addition, long-term follow-up of CodeBreak 100 detected no new safety signals. Overall, sotorasib had an acceptable safety profile.

2.12 *Ongoing studies*

CodeBreak 100 and CodeBreak 200 are still ongoing, however no additional data read out is expected in the next 12 months. There are no other ongoing clinical trials of sotorasib in adult patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC, who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy.

2.13 *Interpretation of clinical effectiveness and safety evidence*

2.13.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Sotorasib received conditional marketing authorisation in the UK in September 2021, and subsequently entered the CDF in 2022, following positive data from the Phase 1/2 single-arm CodeBreak 100 trial. Additional data collection to support full marketing authorisation was planned through the Phase 3 multicentre, randomised, open-label, active-controlled CodeBreak 200 trial, which compared sotorasib with docetaxel in patients with locally advanced/ unresectable or metastatic *KRAS G12C*-mutated NSCLC. Similarly, the Managed Access Agreement for sotorasib noted CodeBreak 200 as a primary source of further data collection, alongside longer-term data from CodeBreak 100. RWE gained via the CDF was anticipated as a secondary data source.

Due to changes to the trial based on regulatory feedback as a result of positive data from CodeBreak 100 (see Section 2.3.1.7), CodeBreak 200 was no longer powered to detect a benefit in OS, as outlined further below. Consequently, we have utilised the comprehensive RWE collected whilst sotorasib has been available through the CDF to support this submission. These data help to validate the PFS results from CodeBreak 200, and demonstrate a clear benefit for patients treated with sotorasib versus docetaxel, with respect to OS.

At the data cut-off for the primary analysis, CodeBreak 200 enrolled 345 patients (N=174 sotorasib; N=171 docetaxel) across Europe (including UK), North America, Asia, Australia, and South America. The trial met its primary endpoint; treatment with sotorasib resulted in a 34% reduction in the hazard of progression or death when compared with docetaxel (HR: 0.66 [95% CI: 0.51, 0.86], $p=0.002$), corresponding to a 1.1 month improvement in PFS, in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with the *KRAS G12C* mutation. More than twice as many subjects in the sotorasib group were alive without progression at a 1-year landmark compared with subjects in the docetaxel group (1-year PFS was 24.8% for sotorasib versus 10.1% for docetaxel). PFS benefit with sotorasib treatment was consistent across all relevant subgroups, including history of CNS involvement and liver metastasis at baseline. Treatment with sotorasib demonstrated better QoL and reduced symptom burden compared with docetaxel, and had an acceptable safety profile. Patients treated with sotorasib reported less severe symptoms and were less bothered by treatment side effects than those receiving docetaxel.

Further supporting the efficacy and safety of sotorasib in this population, 2-year follow-up analysis of single-arm CodeBreak 100 trial showed that sotorasib treatment provided long-term efficacy and was well tolerated, with no new safety signals detected. In total, 174 patients across Australia, Austria, Brazil, Canada, France, Germany, Greece, Hungary, Japan, Korea, Portugal, Romania, Spain, Switzerland, United States received sotorasib. ORR was 41% (95% CI: 33.3, 48.4), with a median DOR of 12.3 months (95% CI: 7.1, 15.0), and across 172 efficacy-evaluable patients, 40 (23%) had long-term clinical benefit (PFS ≥ 12 months).

Overall, the CAS RWE study identified 1,665 eligible patients with *de novo* stage III or stage IV NSCLC, of which 394 initiated sotorasib monotherapy in 2L+ and 1,271 initiated docetaxel monotherapy in 2L+. The study demonstrated that sotorasib monotherapy was significantly more effective than docetaxel monotherapy in 2L+ for prolonging OS, TTNTD, and TTDD among patients with locally advanced or metastatic NSCLC who have previously been treated with platinum-doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy. Treatment with sotorasib was associated with a 36.7% lower risk of death (), a 43.3% lower risk of

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death or new LoT initiation, and a 74.8% lower risk of death or treatment discontinuation compared with docetaxel monotherapy. Sotorasib prolonged median OS by approximately 3.25 months (10.18 vs 6.87 months), median TTNTD by approximately 3 months (8.51 vs 5.62 months), and median TTDD by 2.75 months (5.06 vs 2.30 months).

These real-world findings are broadly consistent with results from the CodeBreak 100 trial, which reported a median OS of 12.5 months (95% CI: 10.0, NE) and median PFS of 6.8 months (95% CI: 5.1, 8.2) for patients treated with sotorasib. The results also align with those observed in the sotorasib arm of the CodeBreak 200 trial (median OS: 10.6 months [95% CI: 8.9, 14.0]; median PFS: 5.6 months [95% CI: 4.3, 7.8]). In contrast, outcomes for patients who received docetaxel monotherapy in the CAS RWE study were generally poorer than those reported for docetaxel in CodeBreak 200 (though more closely aligned to figures reported for patients receiving docetaxel in other clinical trials in similar populations – see Section 2.13.3). The CAS RWE study therefore shows further improved survival benefits of sotorasib compared with docetaxel monotherapy relative to CodeBreak 200. A summary of the clinical evidence base for sotorasib is provided in Table 35.

Table 35: Summary of clinical evidence base for sotorasib versus docetaxel

Study	Design	Overall survival					Progression-free survival				
		Sotorasib		Docetaxel			Sotorasib		Docetaxel		
		N [†]	OS, months (95% CI)	N [†]	OS, months (95% CI)	HR (95% CI)	N [†]	PFS, months (95% CI)	N [†]	PFS, months (95% CI)	HR (95% CI)
CodeBreak 200	Phase 3 RCT of sotorasib vs docetaxel	171	10.64 (8.94, 13.96)	174	11.3 (9.00, 14.85)	0.820 (0.315, 1.309) [¶]	171	5.62 (4.27, 7.75)	174	4.47 (3.02, 5.68)	0.663 (0.509, 0.864), p=0.002
CodeBreak 100	Single-arm Phase 1/2 trial of sotorasib	174	12.5 (10.0, NE)	NA	NA	NA	174	6.8 (5.1, 8.2)	NA	NA	NA
CAS RWE study	Retrospective RWE study of CAS database in England	394	10.18 (9.10, 12.02) [‡]	1,271	6.87 (6.01, 7.82) [‡]	0.633 (0.536, 0.749), p<0.001	394	8.51 (7.33, 9.43) ^{‡, §}	1,271	5.62 (5.06, 6.18) ^{‡, §}	0.252; (0.212, 0.300), p<0.001 [§]
Flatiron US RWE (see Appendix L)	Retrospective RWE study of Flatiron US EHR dataset	164 ^{††}	10.2 (8.0, 14.6) ^{††}	116 ^{††}	7.2 (5.1, 10.6) ^{††}	0.65 (0.49, 0.87) ^{††}	NA	NA	NA	NA	NA
		102 ^{‡‡}	10.2 (7.6, 16.3) ^{‡‡, §§}	58 ^{‡‡}	6.0 (4.2, 11.0) ^{‡‡, §§}	0.62 (0.41, 0.93) ^{‡‡, §§}	NA	NA	NA	NA	NA

Abbreviations: CAS, Cancer Analysis System; CI, confidence interval; EHR, electronic health records; NA, not applicable; OS, overall survival; PFS, progression-free survival; PS, propensity score; RWE, real-world evidence; SMRW, standardised mortality ratio weighting; TTNTD, time to next treatment or death.

† Number of patients treated. ‡ After SMRW. § TTNTD used as a proxy for PFS. ¶ Based on two-stage analysis adjusting for all crossover (i.e. per-protocol crossover and off-protocol crossover to commercial sotorasib). †† 2L+ setting. ‡‡ 2L setting. §§ After PS weighting.

As discussed in Section 1.3.1, treatment of *KRAS G12C*-mutated NSCLC with non-targeted agents is associated with very poor outcomes. As a specifically targeted oral therapy for the *KRAS G12C* mutation, sotorasib offers the potential for improved clinical outcomes, tolerability, convenience and HRQoL compared with previous highly toxic, non-targeted, standard of care therapy with docetaxel. Its early use in line with its licensed indication as a second- or subsequent-line therapy can delay the need to use less effective, IV cytotoxic chemotherapy. It is therefore of crucial importance to ensure continued access to sotorasib in this patient population.

2.13.2 Strengths and limitations of the clinical evidence base for the technology

2.13.2.1 CodeBreaK 200

2.13.2.1.1 RCT demonstrating PFS benefit versus relevant comparator

CodeBreaK 200 was a RCT, conducted in accordance with International Council for Harmonisation GCP guidelines (68). It provides direct head-to-head data versus docetaxel, the relevant comparator for patients with *KRAS G12C*-mutated NSCLC, in line with treatment guidelines and clinical expert opinion.

CodeBreaK 200 met its primary endpoint and demonstrated a statistically significant improvement in PFS with sotorasib relative to docetaxel. Sensitivity and subgroup analyses were conducted and were generally consistent with the primary analysis, demonstrating the robustness of the PFS result (68).

2.13.2.1.2 Challenging to make conclusions on OS benefit

CodeBreaK 200 found no differences in OS between the two treatment groups. Notably, 23 (13%) of 174 patients who were randomly assigned to the docetaxel group did not receive treatment and discontinued the study, in comparison with two (1%) of 171 patients for the sotorasib group (34). This imbalance in the drop-out rates between treatment groups is a major limitation due to the open-label design of this study. In the ITT analysis for OS, of the patients assigned to the docetaxel group who did not receive treatment, five (22%) of these 23 patients died and 17 (74%) patients were censored at the date of consent withdrawal or the last date known to be alive, whichever was later. These 23 patients had a poorer prognosis compared with the patients who did receive treatment with docetaxel (i.e. higher incidence of

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history of CNS involvement, liver metastases, ECOG PS of 1, and refractory to previous therapy).

The study was initially planned to enrol 650 patients and powered for both PFS and OS. Following the observed clinical benefits of sotorasib in the CodeBreak 100 Phase 2 trial and per regulatory feedback, the protocol was amended in February 2021, to decrease the sample size to approximately 330 patients, which was only powered for PFS, to limit the overall number of patients treated with docetaxel. Additionally, crossover from docetaxel to sotorasib upon centrally confirmed radiological progression was allowed. In total, 59 (34%) patients in the docetaxel group subsequently received a KRAS^{G12C} inhibitor. This crossover further limited the ability of the trial to detect an OS benefit. Although analyses were conducted to adjust for crossover, which showed a numerical OS benefit for sotorasib, these resulted in large CIs with high levels of uncertainty.

Overall, given these limitations, a definitive conclusion on OS benefit with sotorasib is difficult to be drawn from the CodeBreak 2rw00 trial. The importance of the CAS RWE study as a clinically relevant alternative source of OS data is described in Section 2.13.2.2.

2.13.2.2 CAS RWE study

The CAS RWE study was designed taking into account input from NICE and NHS England, to support a robust evidence package and validation of real-world outcomes with sotorasib.

2.13.2.2.1 Comprehensive, validated data source

The CAS RWE study was based on a comprehensive dataset containing data on nearly all cancer patients treated in NHS hospitals in England. The data are therefore directly relevant to clinical practice in England, with no generalisability issues. The CAS database is considered a valid and reliable source of data relating to patient characteristics, systemic treatments, and outcomes among patients with NSCLC in England, and has been used in many published studies (94-96). Data are captured in a structured format and are subject to validation checks to ensure accuracy (97). Mortality data are updated regularly from the ONS, which is the largest independent producer of official statistics in the UK and consequently can be Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

considered a reliable and comprehensive source for death registrations in England. Extracts of death registrations are received daily and are passed through a series of automatic validation processes and internal consistency checks to eliminate any errors made during the recording of deaths, and to ensure the annual dataset is complete (97).

2.13.2.2.2 Consistent source of data for treatment arms

The analysis utilised data from the CAS database for both sotorasib and docetaxel treatment arms in a trial-emulation approach. The use of a consistent data source and individual patient-level data for both treatment arms with PS weighting prevented the need for a matching adjusted indirect comparison (MAIC), which would introduce additional uncertainties. PS weighting ensured that docetaxel patients whose baseline characteristics matched those of the sotorasib patients most closely were allocated higher weights in the analysis, enabling a closer estimate of the true treatment effects of sotorasib and docetaxel than would be possible if these methods were not used. The CAS database is also used by NHS Digital for treatments entering the CDF to gain a real-world estimation of treatment effects.

2.13.2.2.3 Weighting to address potential confounding

Confounding was addressed through SMRW (for all main analyses) and IPTW (for sensitivity analyses only). The set of covariates to include in the PS modelling were informed by published literature and clinical expertise. However, there is the potential for uncontrolled confounding due to unobserved or misclassified variables. For instance, CAS lacks information on smoking status, which is known to affect prognosis (98). The use of historical data within the docetaxel cohort may also lead to unobserved differences with respect to the sotorasib cohort if care practices have changed over time. To mitigate the potential effects of changes over time impacting study results, the indexing period for the docetaxel cohort was restricted to post-2016. Subgroup analyses relating to prior receipt of PD-1/PD-L1 targeted immunotherapy were also performed for primary and secondary study objectives.

2.13.2.2.4 LoT algorithm

Information relating to disease progression is not recorded in the CAS database. Consequently, treatments recorded in the CAS database were combined into LoTs according to an algorithm. Although the algorithm was developed in accordance with Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

treatment guidance from ESMO (58, 99) and NICE (59), and in collaboration with clinical experts to minimise misclassification of LoTs, a degree of misclassification may be expected as all treatment decisions cannot be perfectly captured by a single set of progression rules. The use of a LoT algorithm could also result in exposure misclassification. For instance, the algorithm could incorrectly classify a patient as receiving docetaxel monotherapy when they instead received combination therapy. This misclassification could be expected to be differential across treatment cohorts, since sotorasib may only be delivered as monotherapy. For both treatment cohorts, LoT numbering could also be affected, whereby a patient is correctly classified as receiving either sotorasib or docetaxel monotherapy but at the incorrect LoT number, which could affect covariate adjustment. To help mitigate these risks, the study population used for all main analyses was restricted to patients with *de novo* stage III or stage IV NSCLC, as the risk of LoT misclassification in this patient population is expected to be lower than in patients with stage I or stage II NSCLC who eventually progress to treatment for locally advanced or metastatic disease. The use of a LoT algorithm could also result in misclassification of the outcomes TTDD and TTNTD, since the end date of the index LoT and the start date of the next LoT will be algorithmically defined. Misclassification is expected to be higher for the outcome TTDD compared to TTNTD, since treatment end dates are not recorded but treatment start dates are. Consequently, TTDD was included as an exploratory endpoint only with TTNTD as a secondary endpoint. The primary endpoint (OS) is not expected to be affected. Any outcome misclassification is not expected to be differential across treatment cohorts.

2.13.2.2.5 Selection bias

A key limitation of the CAS RWE study related 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.

Firstly, although all patients in the sotorasib cohort were expected to have *KRAS G12C*-mutated NSCLC, the docetaxel cohort comprised patients irrespective of *KRAS* mutation status, with over [REDACTED] of patients having no recorded *KRAS G12C*

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mutation status, reflecting historical testing practices prior to *KRAS*-targeted treatment availability given that *KRAS* mutations were not routinely tested for prior to the introduction of *KRAS* inhibitors. The decision to include patients irrespective of *KRAS* mutation status was taken due to feasibility considerations, as an initial descriptive pilot study in the CAS database found that only approximately 20 study-eligible patients with *KRAS* G12C mutation and approximately 40 study-eligible patients with any *KRAS* mutation received docetaxel monotherapy in 2L+. Literature suggests that different *KRAS* mutations (i.e. G12C versus non-G12C mutations) do not have a significantly different impact on OS (41, 46-48). However, evidence for the prognostic importance of *KRAS* mutations is more mixed. For instance, one systematic review and meta-analysis found that *KRAS* mutations predict worse OS and PFS compared to *KRAS* wildtype among chemotherapy-treated patients (42), while another found no effect on OS or PFS in RCTs but a negative prognostic effect in observational studies (25). Nevertheless, it is important to note that in the case of *KRAS* mutations resulting in poorer prognosis, this would be expected to bias results in favour of docetaxel, making the observed OS benefit for sotorasib conservative. In the present study, across both cohorts, testing records for genetic mutations were low. It is worth noting, however, that the low proportion of patients with genetic testing records likely reflects not only limitations in testing capabilities and capacity across the NHS, but also limitations in capture of this information within the CAS MDx dataset. In the sotorasib cohort, given the terms of the Managed Access Agreement, it can reasonably be assumed that all patients were tested for (and confirmed to be positive for) *KRAS* G12C mutation, despite less than half having a record of this in CAS. Notably, █ patients (██%) in the sotorasib cohort had a negative test result for *KRAS* mutation, and a further █ patients (██%) had a negative test result for the specific G12C mutation despite having a positive test result for the *KRAS* mutation generally, indicating that more recent test results may not have been captured. Consequently, the true rates of testing for genetic mutations in England is likely to be higher than those reported in this study. The small proportion of patients in the docetaxel cohort with a record of *KRAS* G12C mutation is not unexpected given that *KRAS* mutations were not routinely tested for prior to the introduction of *KRAS* inhibitors, and that patients with a confirmed G12C

mutation would be more likely to receive sotorasib than docetaxel monotherapy in 2L+ after sotorasib became available.

Descriptive results from the CAS RWE study did not find evidence for any differential effect of *KRAS* mutation status among patients who received docetaxel monotherapy. However, the low prevalence of confirmed *KRAS* mutations in the docetaxel cohort makes it difficult to draw definitive conclusions. Taken together, these findings therefore suggest that there is the potential for bias due to the inclusion of patients without a *KRAS G12C* mutation in the docetaxel cohort, but the magnitude and direction of such bias is unknown.

Secondly, patients in the sotorasib cohort were expected to have no known brain metastases or be symptomatically stable at index date if they did have brain metastases. However, because CAS does not directly or routinely capture information on metastases or symptom stability, it was not possible to replicate this criterion in the docetaxel cohort. Consequently, the docetaxel cohort may include a higher proportion of patients with brain metastases, which could create bias in the estimated effects which favour sotorasib. However, this potential bias was likely mitigated by the exclusion of patients with ECOG >2 from the docetaxel cohort, which may have indirectly limited the inclusion of patients with poor symptom control or active CNS disease. In addition, a smaller proportion of patients in the docetaxel cohort had any evidence of prior brain metastasis (i.e. [REDACTED]) compared with the sotorasib cohort ([REDACTED]), although this could be at least partially due to improved metastasis detection over time. PS weighting further balanced the distribution of both ECOG and prior brain metastasis between treatment groups. Subgroup analyses among patients with evidence of prior brain metastasis also demonstrated [REDACTED]. Taken together, these factors suggest that any bias arising from the potential inclusion of patients with active brain metastases in the docetaxel cohort is likely minimal and unlikely to materially affect the study's findings.

Several sensitivity analyses were performed due to the aforementioned limitations around emulation of all eligibility criteria for sotorasib in the docetaxel monotherapy cohort. Additional sensitivity analyses were conducted to describe the (unadjusted)

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effect of sotorasib versus docetaxel monotherapy separately in the subgroups of patients with any *KRAS* mutation and specifically *KRAS G12C* mutation. Results were broadly consistent with the primary analysis, though OS and TTNTD were [REDACTED] ([REDACTED] months [95% CI: [REDACTED]] and [REDACTED] [95% CI: [REDACTED]], respectively) in the docetaxel arm when restricted to patients with any *KRAS* mutation. This effect was not maintained when restricting to patients with a *KRAS G12C* mutation, however the sample size was insufficient to detect a significant difference. Primary and secondary objectives were also evaluated in the subgroups of patients with or without a prior record of brain metastasis. Among patients with a record of prior brain metastasis, [REDACTED] [REDACTED]. Compared with docetaxel monotherapy, patients treated with sotorasib had a [REDACTED] in the risk of death in patients with prior brain metastasis (HR: [REDACTED]; 95% CI: [REDACTED]; p [REDACTED]) and a [REDACTED] in the risk of death in patients without (HR: [REDACTED]; 95% CI: [REDACTED]; p [REDACTED]). Study results also suggested a [REDACTED].

2.13.2.2.6 Proxies for PFS

While PFS was not captured in the CAS RWE study, TTDD or TTNTD may be considered as proxies, given that patients in clinical practice would likely be treated until progression. However, TTDD analyses may be less reliable than OS and TTNTD analyses. As treatment end dates are not recorded in the CAS database, the date of treatment discontinuation had to be derived for all patients using the recorded start date of treatment and number of cycles received. Consequently, a degree of outcome misclassification can be expected in TTDD analyses, but this is expected to have affected both treatment cohorts equally. Additionally, analyses of TTDD indicated that the treatment group (i.e. sotorasib or docetaxel monotherapy) violated the PH assumption. Indeed, there was a much higher rate of treatment discontinuation for patients who received docetaxel compared with sotorasib, which might be expected due to their different mechanisms of action. While this limitation is unlikely to affect KM analyses or estimates for median TTDD, it could affect the accuracy of reported HRs obtained from Cox models.

2.13.3 Conclusion

The efficacy and safety of sotorasib in patients with *KRAS G12C*-mutated NSCLC has been demonstrated in a clinical trial setting in CodeBreak 200 (comparative data versus docetaxel) and CodeBreak 100 (single-arm data for sotorasib), while real-world effectiveness in UK clinical practice comes from the CAS RWE study in which evidence for both sotorasib and docetaxel are available.

Among patients who received sotorasib, in the CAS RWE study, median OS (after SMRW) was 10.18 months and median TTNTD was 8.51 months, findings which are broadly consistent with results from the Phase 1/2 CodeBreak 100 trial (median OS: 12.5 months; median PFS: 6.8 months for patients treated with sotorasib (100)), and the Phase 3 CodeBreak 200 trial (median OS: 10.6 months; median PFS: 5.6 months in the sotorasib arm). The results are also broadly consistent with other published studies; a real-world study of long-term outcomes for patients with advanced *KRAS G12C*-mutated NSCLC treated with sotorasib from the global expanded access program reported a median OS of 9.5 months (95% CI: 8.6, 12.0) and a median real-world PFS of 6.3 months (95% CI: 5.0, 7.3) (101), with outcomes reported from other single-country real-world studies also in broad alignment (71, 102-106).

Notably, OS for patients who received docetaxel monotherapy in the CAS RWE study was generally poorer than for the docetaxel arm in CodeBreak 200 but more closely aligned to figures reported for patients receiving docetaxel in other clinical trials in similar patient populations. The Phase 3 SELECT-1 trial in patients with previously treated *KRAS*-mutated NSCLC reported a median OS of 7.9 months (IQR: 3.8-20.1) and median PFS of 2.8 months (IQR: 1.4-5.5) for patients treated with docetaxel monotherapy (with placebo) (32), while the Phase 3 KRYSTAL-12 trial in patients with previously treated *KRAS G12C*-mutated NSCLC reported a median PFS of 3.84 months (95% CI: 2.73, 4.73) for patients treated with docetaxel monotherapy (107). The Phase 3 TAX 317 trial also reported a median OS of 7.5 months among patients with advanced NSCLC treated in 2L with docetaxel monotherapy (108).

Looking at the comparative data, in the CAS RWE study, sotorasib was associated with an approximate 3.25 months increase in OS and 3 month increase in TTNTD relative to docetaxel. Sotorasib decreased the risk of death by 36.7% relative to docetaxel (HR: 0.633; 95% CI: 0.536, 0.749; $p < 0.001$), and decreased the risk of death or new LoT by 43.3% (HR: 0.567; 95% CI: 0.485, 0.663; $p < 0.001$). These results are closely aligned to those of a real-world study of US electronic health record data from the Flatiron database, which reported an adjusted median OS of 10.2 months (95% CI: 8.0, 14.6) for patients treated with sotorasib and 7.2 months (95% CI: 5.1, 10.6) for patients treated with docetaxel monotherapy or combination therapy in 2L+, resulting in a 35% lower risk of death (HR: 0.65; 95% CI: 0.49, 0.87) for patients treated with sotorasib (71).

Given the limitations of the CodeBreak 200 trial, the CAS RWE results are used as inputs in the base case of the economic model. Clinical data from CodeBreak 200 are included as a scenario analysis.

To our knowledge, this is the first NICE submission where RWE forms the primary evidence base for both treatment and comparator. However, the CAS dataset includes nearly all patients treated in NHS hospitals in England. This, combined with robust statistical methods (e.g. SMRW/IPTW) and external validation from other real-world studies, provides a comprehensive and generalisable evidence base for sotorasib in patients with *KRAS G12C*-mutated NSCLC.

3 Cost effectiveness

3.1 *Published cost-effectiveness studies*

3.1.1 Identification of studies

Details regarding an SLR of the non-clinical literature, including full search strategies, inclusion and exclusion criteria, the PRISMA flow diagram and the list of studies, are presented in Appendix E. The sections within this dossier present the overview of studies relevant to the current submission.

An additional targeted review of prior NICE technology appraisals was conducted to ensure all relevant information to inform the economic model was captured. The search function on the NICE website was used to search for technology appraisal guidance using the term: 'KRAS NSCLC'. No other eligibility criteria were applied.

3.1.2 Description of identified studies

The searches identified six published economic evaluations including comparisons with sotorasib, as outlined in Table 36. One study utilised the data from CodeBreak 100 clinical trial (109), the source used in the original submission for sotorasib, whereas four studies (110-113) utilised data from the CodeBreak 200 trial which is used as supporting evidence for the current submission. One study did not report the source of clinical data (114). However, the economic evaluations identified are not relevant to the UK setting due to inclusion of non-UK patient data and country-specific unit costs.

The search for prior NICE technology appraisals identified two appraisals which were considered relevant to the scope of this submission (see Table 37). Those include TA781 (9), including the originally submitted model for sotorasib to NICE, and the ongoing NICE evaluation of adagrasib (115). Both treatments were evaluated for patients in previously treated *KRAS G12C* mutation-positive advanced NSCLC and were used to inform the current submission.

Table 36: Summary list of published cost-effectiveness studies

Study	Country	Summary of model	Interventions (intervention / comparator)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Notes
Berardi 2023 (114)	NR	Cost of response	Adagrasib / sotorasib	N/A	N/A	N/A	Abstract only. Assumes superior efficacy for adagrasib over sotorasib, not accounting for different baseline risk in North-American cohort.
El Saadany 2025 (110)	Switzerland	PSM	Sotorasib / docetaxel	- Sotorasib: 1.28 - Docetaxel: 1.28	- Sotorasib full dose (CHF): 138,894 - Sotorasib quarter dose (CHF): 82,741 - Docetaxel (CHF): 80,383	- Sotorasib full dose: 10,361,420 - Sotorasib quarter dose: 453,721	Based on published ITT CodeBreak 200 trial results, without any crossover adjustment
Jiang 2023 (111)	USA and China	PSM for the USA, microsimulation for China	Sotorasib / docetaxel	- Sotorasib: - USA, 0.07 - China, 0.54 - Docetaxel: NR	- USA (\$): - Sotorasib: 227,786 - Docetaxel: 118,704 - China (\$): - Sotorasib: 272,190 - Docetaxel: 17,737	- USA: 1,501,852 - China: 469,106	Based on published ITT CodeBreak 200 trial results without any crossover adjustment

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Study	Country	Summary of model	Interventions (intervention / comparator)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)	Notes
Karim 2024 (109)	USA	PSM	Sotorasib / adagrasib	Sotorasib: 1.35 Adagrasib: 1.60	Sotorasib: 274,879 Adagrasib: 327,878	Sotorasib a dominant intervention	Abstract only; data from MAIC based on CodeBreakK 100 and KRYSTAL-1
Keeping 2024 (112)	USA	Unclear	Sotorasib / adagrasib	NR	NR	NR	Abstract only focused on hepatotoxicity management; data from MAIC based on CodeBreakK 200 and KRYSTAL-1
Zhu 2024 (113)	China and USA	Markov model	Sotorasib / docetaxel	- USA: – Sotorasib, 0.35 – Docetaxel, - 7.39 - China: – Sotorasib, 0.44 – Docetaxel, 0.35	- USA (\$): – Sotorasib, 487,585.57 – Docetaxel, 363,794.84 - China (\$): – Sotorasib, 84,372.59 – Docetaxel, 74,809.61	- USA (\$): 102,701.84 - China (\$): \$15,976.5	Utilised the data from CodeBreakK 200 trial; the study results lack face validity due to concerns regarding calculation of QALYs, particularly from the US perspective

Abbreviations: ICER, incremental cost-effectiveness ratio; MAIC, matching adjusted indirect comparison; N/A, not available; NR, not reported; PSM, partitioned survival model; QALY, quality-adjusted life year.

Table 37: NICE technology appraisals in *KRAS*-mutated NSCLC

Identifier	Appraisal	Publication date
TA781 (9)	Sotorasib for previously treated <i>KRAS</i> G12C mutation-positive advanced non-small-cell lung cancer	30 th March 2022
GID-TA11432 (115)	Adagrasib for previously treated <i>KRAS</i> G12C mutation-positive advanced non-small-cell lung cancer	In progress

Abbreviations: NSCLC, non-small cell lung cancer.

3.2 *Economic analysis*

The TA781 submission was the most relevant cost-effectiveness study identified in the SLR, published specifically in NSCLC with the *KRAS G12C* mutation (or *KRAS* mutation in general). Therefore, this submission uses the same modelling approach as in TA781, accounting for modifications and corrections highlighted by the Evidence Review Group (ERG) and the NICE committee (see Table 38).

Table 38: Uncertainties in the original submission for sotorasib (TA781)

Uncertainty	Details	Mitigation	Section(s) of dossier
Use of unanchored indirect treatment comparison	The original submission utilised the results from the unanchored MAIC to estimate the clinical effectiveness for sotorasib and docetaxel in the base case. The company also presented the results utilising the Flatiron RWE study. The ERG and committee highlighted uncertainty in this approach but considered it appropriate for decision-making in light of no head-to-head data for sotorasib and docetaxel.	Two data sources are available that provide the relative efficacy of sotorasib vs docetaxel, that are not based on an anchored approach: Firstly, the CB200 data is available. This analysis, however, does not provide robust OS data, due to sample size, crossover, and high stochastic uncertainty. Secondly, based on the CAS data collected, a comparative effectiveness study (real-world) has been conducted. This study also does not rely on an unanchored approach.	Section 3.3
The utility and disutility values used in the economic model	The original submission used time-to-death utilities in the base case and health-state utilities as a sensitivity analysis. The ERG was not opposed the company's approach, but preferred a health-state approach as the utilities derived from CodeBreak 100 were comprised of a small sample size. Despite the uncertainties in using time-to-death approach, both approaches were considered in the decision making.	The current submission includes a much larger sample of patients from CodeBreak 200 reducing the uncertainty in the estimates. As the ERG was not opposed to time-to-death utility approach in the original submission, the base case utilises time-to-death utilities with a health-state approach explored in a sensitivity analysis. The time-to-death approach is also able to explain a higher degree of the sum of squares of errors compared to the health state approach.	Section 3.4.4, 3.7.2 (Table 70)
The magnitude of any treatment waning	The original submission did not apply treatment waning in the model as it considered the impact of discontinuation on the survival curves to be implemented into the hazard function. The ERG disagreed that sotorasib would have a continued benefit and highlighted immature evidence. In the ERG base case, a preferred approach was to apply treatment effect waning at 2 years and gradually decrease the HR to 1 over 5 years.	The clinical evidence from the CAS RWE study (the base case of the current submission), CodeBreak 200 and Flatiron (sensitivity analysis) provides more robust evidence base with the length of follow-up that captures any decline in treatment effectiveness.	Section 3.2.2 (Table 39)

Uncertainty	Details	Mitigation	Section(s) of dossier
Whether the technology meets the end of life 3-month extension criterion	During the original submission, it was agreed that sotorasib meets the end-of-life criteria. However, there were uncertainties with the unanchored indirect treatment comparison methods.	The end-of-life criteria do not apply to the current submission. Instead, the assessment of the severity of the condition is performed and incorporated into the model calculations.	Section 3.6

Abbreviations: ERG, Evidence Review Group; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PS, propensity score; RWE, real-world evidence.

The cost-effectiveness analysis was undertaken from the perspective of the NHS, comparing sotorasib with docetaxel for the treatment of patients with NSCLC with the *KRAS G12C* mutation. A partitioned survival model (PSM) was developed with a lifetime time horizon and a discount rate of 3.5% for cost and health outcomes. The analyses were conducted from an NHS and personal social services (PSS) perspective in England and Wales and are consistent with NICE guidelines.

The economic evaluation conducted adheres to the methodological requirements set out in the NICE health technology evaluations manual last updated in May 2025 (116).

3.2.1 Patient population

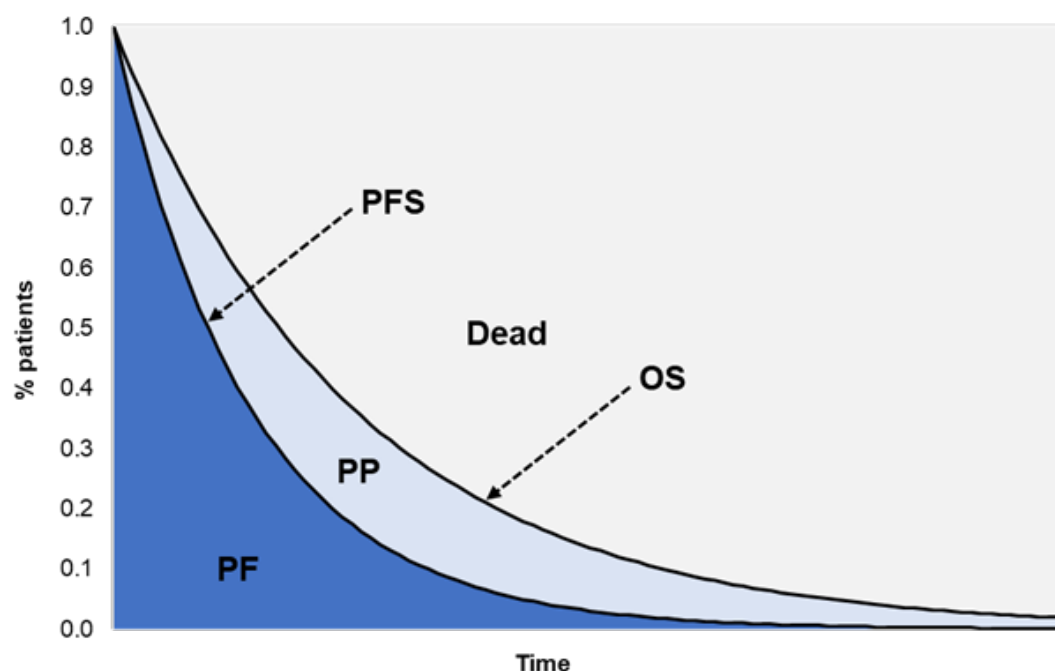
In line with the final scope of this appraisal, the population in TA781, and the anticipated marketing authorisation, the patient population for the economic analysis is adult patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy. The patient population is also aligned with that in the Phase 3 CodeBreak 200 RCT, and the sotorasib arm of the CAS RWE study, as described in Section 3.3.1.

Subgroup analyses were not included in the cost-effectiveness analysis given there were no subgroups observed with substantially different efficacy to the whole population in CAS RWE, as described in Section 2.8.2.

3.2.2 Model structure

A PSM with three distinct health states (progression-free [PF], progressed disease [PD] and dead) was developed in Microsoft Excel® (Figure 17). All patients entered the model in the progression-free state and were at risk of progression of disease or death. Transitions to the death state occurred from either the progression-free or progressed disease health states. Death was an 'absorbing state', where once entered, patients reside for the remainder of the model time horizon.

Figure 17: Partitioned survival analysis model



Abbreviations: OS, overall survival; PF, progression free; PFS, progression-free survival; PP, post progression.

This model structure is fully aligned with the primary objectives of treatment in oncology and NSCLC, namely avoiding disease progression and prolonging life. Furthermore, the structure and health states selected are typical of modelling in oncology and have been used in previous NSCLC technology appraisals conducted by NICE, including the original submission for sotorasib (TA781).

The state occupancy of patients for each cycle was estimated using the TTNTD data as a proxy for PFS and OS data from the CAS RWE study. Time on treatment was considered in the model and measures the time patients spend receiving treatment while in the progression-free state. Because patients may discontinue treatment before their disease progresses (e.g. due to unacceptable toxicity or physician or patient decision), it was important for the model to reflect the impact of time on treatment on medication and administration costs as well as QoL. The proportion of patients on treatment was modelled separately and was capped by the PFS curve, so that the proportion of patients on treatment was always equal to or lower than the proportion of patients in progression-free state.

The model used a weekly cycle with a half-cycle correction and a lifetime time horizon of 20 years.

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Table 39: Features of the economic analysis

Factor	TA781 (9)	GID-TA11432 [†] (115)	Current evaluation	
			Features	Justification
Population	Adults with previously treated <i>KRAS G12C</i> -mutated, locally advanced or metastatic NSCLC	Adult patients with advanced NSCLC with <i>KRAS G12C</i> mutation detected in tumour tissue previously treated with systemic therapy	Adult patients with <i>KRAS G12C</i> -mutated locally advanced or metastatic NSCLC, who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy	In line with marketing authorisation
Model structure and framework	Three-state partitioned survival analysis (progression free, progressed, death)	Three-state partitioned survival analysis (progression free, progressed, death)	Three-state partitioned survival analysis (progression free, progressed, death)	Reflects the three most relevant disease health states which capture the clinical events experienced by patients with NSCLC
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	Consistent with the NICE reference case (116)
Annual discount rate	3.5% for costs and QALYs	3.5% for costs and QALYs	3.5% for costs and QALYs	Consistent with the NICE reference case (116)
Time horizon	Lifetime (20 years)	Lifetime (20 years)	Lifetime (20 years)	20 years is considered sufficiently long so that most patients (>99%) would have died by the end of the model time horizon. The model is therefore able to reflect all differences in costs and outcomes in line with the NICE reference case (116)
Cycle length	1 week	1 week	1 week	In line with previous appraisals; the cycle length is considered short enough to ensure accuracy in model calculations
Measure of health effects	QALYs	QALYs	QALYs	Consistent with the NICE reference case (65)
Treatment waning	Limit to the treatment effect at the 2-year time point,	Not considered	Not considered	Treatment waning was a key uncertainty in the original TA781

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Factor	TA781 (9)	GID-TA11432† (115)	Current evaluation	
			Features	Justification
effect	with a subsequent gradual waning of the effect over 5 years.			submission (see Table 1 and Table 38). Treatment waning is not considered in the current submission as the length of patient follow-up in the main source of clinical effectiveness is sufficient to capture any decline in treatment effectiveness
Source of utility values	CodeBreak 100 and published literature	KRYSTAL-12 (base case) and published literature (scenario analysis)	CodeBreak 200	The use of time-to-death utilities was a key uncertainty in the original TA781 submission (see Table 1 and Table 38). The evaluation will use utility values derived from EQ-5D-5L data collected in CodeBreak 200 in line with the NICE reference case (116). It was not possible to collect utilities during the CAS RWE study
Source of costs	UK standard costs sources: NHS Reference costs and eMIT/MIMs	• eMIT (generic treatment) • BNF (branded treatment) • NHS National Cost Collection (administration, AE management, and resource use) • PSSRU unit costs (resource use)	UK standard costs sources: NHS Reference costs, eMIT, BNF, PSSRU as well as TA781 and published literature	Standard sources for informing UK-based economic evaluations, and in line with the NICE reference case (116)

Abbreviations: AE, adverse event; CAS, Cancer Analysis System; eMIT, electronic drugs and pharmaceutical electronic market information tool; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; RWE, real world evidence; TA, technology appraisal.

† Please note that, at the time of this submission, adagrasib is currently undergoing evaluation by NICE.

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3.2.3 Intervention technology and comparators

Sotorasib (LUMYKRAS™) was the first KRAS^{G12C} inhibitor to be submitted for marketing authorisation in 2021. Since then, adagrasib has become available and currently going through the NICE appraisal process with an unknown expected guidance publication date at the time of this submission (115).

Sotorasib is a once-daily oral therapy (960 mg, administered as eight 120 mg tablets or four 240 mg tablets), that has received a conditional marketing authorisation in the UK by the MHRA since September 2021 as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy, unless contraindicated (15).

Sotorasib is administered until disease progression or until no further clinical benefit is expected, which is aligned with the Phase 3 CodeBreak 200 trial (68) and the CAS RWE study (77).

The current NHS clinical pathway for treating patients with *KRAS G12C*-mutated NSCLC is detailed in Section 1.3.2. The only relevant comparator for the economic analysis is docetaxel monotherapy, with the rationale for selection presented in Section 1.3.3. Briefly, based on the RWE from the CAS database, only ~5% (n<5) of patients with *KRAS*-mutated NSCLC received docetaxel + nintedanib in the 2L+ setting between 2017 and 2021. As the use of this combination treatment is low in UK clinical practice, this comparator was not included in the economic analysis.

3.3 Clinical parameters and variables

3.3.1 Population baseline characteristics

The baseline patient characteristics in the economic model are sourced from the CodeBreak 200 trial and are comparable to those reported in the CAS RWE study (Table 40). Where no data were available from the CAS study (i.e. weight and body surface area), CodeBreak 200 data were used.

Table 40: Baseline characteristics in the CEM

Patient characteristic	Value	Source	Value	Source
Age at baseline (years)	63.50	CodeBreak 200 Phase 3 NSCLC cohort FAS (see Section 2.3.1.8)	■	CAS RWE (see Section 2.3.3.9)
Gender (female)	40.9%		■	
Weight (kg)	72.02		■	
Body surface area (m ²)	1.81		■	

Abbreviations: CEM, cost-effectiveness model; CAS, cancer analysis system; FAS, full analysis set; kg, kilogram; NA, not applicable; RWE, real world evidence.

3.3.2 Overview of the modelled clinical efficacy and safety

Efficacy inputs for the PFS, OS, and TTDD data for sotorasib and docetaxel come from the CAS RWE study. Since PFS data were not collected, TTNTD was used as a proxy. Data from CodeBreak 200 and Flatiron US RWE study were used in scenario analyses (see Section 3.9.3).

The clinical parameters in the model are summarised in Table 41 and detailed further throughout this section.

Table 41: Overview of clinical and safety data used to inform the model

Component	Application in model	Source
OS (Section 3.3.4)	Used to fit parametric survival curves to capture lifetime OS estimates - Base case curve selections: - Sotorasib: Log-logistic - Docetaxel: Log-logistic	Base case: CAS RWE study Scenario analyses: - OS crossover adjusted data from CodeBreak 200 - Flatiron - UK life tables
TTNTD (PFS) (Section 3.3.5)	Used to fit parametric survival curves to capture lifetime PFS estimates - Base case curve selections: - Sotorasib: Gamma - Docetaxel: Gamma	Base case: CAS RWE study Scenario analyses: - CodeBreak 200
TTDD (Section 3.3.6)	Used to fit parametric survival curves to capture time on first-line treatment - Base case curve selections: - Sotorasib: - Docetaxel:	Base case: CAS RWE study Scenario analyses: - CodeBreak 200

Component	Application in model	Source
AE incidence (Section 3.4.5)	Informed the proportion of patients who incur costs and disutilities associated with each AE (disutilities applied in a scenario analysis only)	CodeBreakK 200

Abbreviations: AE, adverse event; CAS, Cancer Analysis System; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence; TTDD, time to treatment discontinuation or death; TTNTD, time to next treatment or death.

3.3.3 Incorporation of CAS RWE study into the economic model

3.3.3.1 Digitisation of KM plots and generation of pseudo patient-level data

As patient-level data were not available for the time-to-event outcomes from the CAS RWE study, it was necessary to digitise KM plots (after propensity score weighting, as described in Section 2.4.5.2 and Appendix K) for OS, TTDD, and TTNTD to generate pseudo patient-level data to allow the fitting of parametric models. Plots were digitised using automeris (formerly WebPlotDigitizer) (117). Pseudo patient-level data were then generated from X-Y co-ordinates from the digitised plots and their corresponding risk tables using the IPDfromKM R package (118).

3.3.3.2 Approach used for masking of patient numbers

In the CAS RWE study, if there were few (≤ 5) patients at risk at a given time point, the patient numbers were masked in the risk table. If no patients were at risk at a given time point, the number of patients was not masked. It was assumed that where a patient number was masked, this represented three patients (the median of five patients rounded up to the nearest whole patient).

3.3.3.3 Parametric modelling methods

The guidance published in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 was used in order to fit and select the most appropriate parametric modelling method (119). As the KM data for the outcomes of interest were incomplete, it was necessary to fit parametric models to extrapolate the outcomes over the time horizon of the economic model. As per NICE TSD 14, jointly-fitted parametric models were explored first, and the validity of the PH assumption was assessed by Schoenfeld residual and log-cumulative hazard plots. If PH could not be rejected, then jointly-fitted models were used; if there was no, or limited,

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evidence for PH, independently-fitted models (i.e. parametric models fitted to the intervention and comparator separately) were used instead.

Seven forms of parametric models were fitted to the digitised KM data. These were:

- Exponential
- Gamma
- Generalised gamma
- Gompertz
- Log-logistic
- Log-normal
- Weibull

The models were fitted in both jointly-fitted and independent forms, with the option to select between these methods included in the economic model.

3.3.3.4 Choice of parametric distributions

The choice of the parametric distributions put forward in the base case were informed by clinical opinion, visual fit, and statistical goodness-of-fit as determined by the Akaike information criterion (AIC) and Bayesian information criterion (BIC).

3.3.4 Modelling of overall survival from CAS RWE

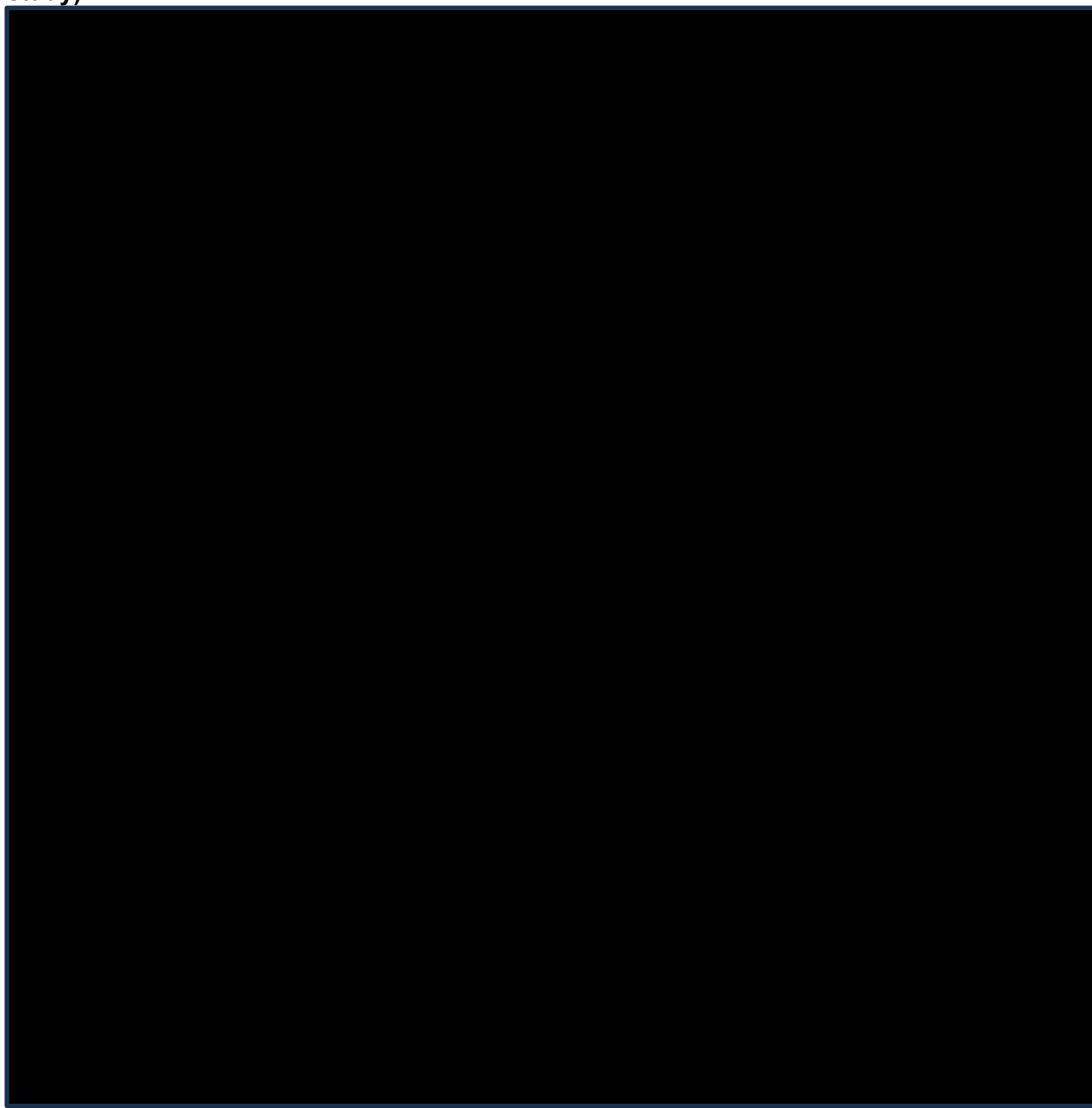
OS for both sotorasib and docetaxel was modelled based on parametric curves fitted to the pseudo patient-level data from the CAS RWE study. A summary of the observed trial data and corresponding KM curves are presented in Table 42 and Figure 18.

Table 42: Summary of weighted overall survival data from the CAS study

	Sotorasib (N=394)	Docetaxel (N=363)
Total deaths, n (%)	████████	████████
Censored, n (%)	████████	████████
Median OS (95% CI) (months)	10.18 (9.10, 12.02)	6.87 (6.01, 7.82)

Abbreviations: CAS, cancer analysis system; CI, confidence interval; OS, overall survival.

Figure 18: Original KM OS plot for sotorasib and docetaxel after SMRW (CAS RWE study)

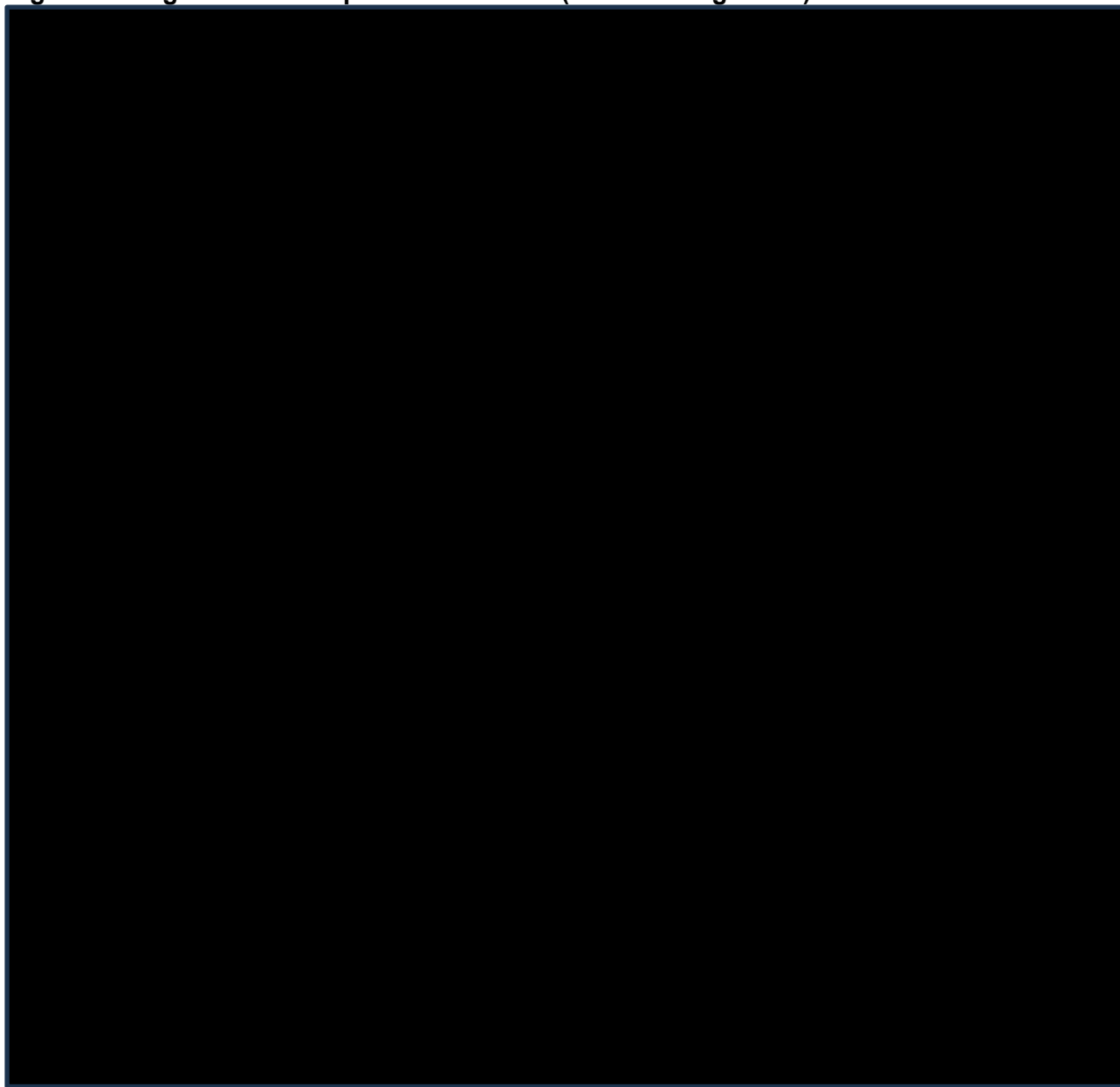


Abbreviations: CAS, Cancer Analysis System; KM, Kaplan-Meier; OS, overall survival; RWE, real-world evidence; SMRW, standardised mortality ratio weighting.

The digitised KM OS curves for sotorasib and docetaxel with their accompanying CIs are shown below in Figure 19 and Figure 20.

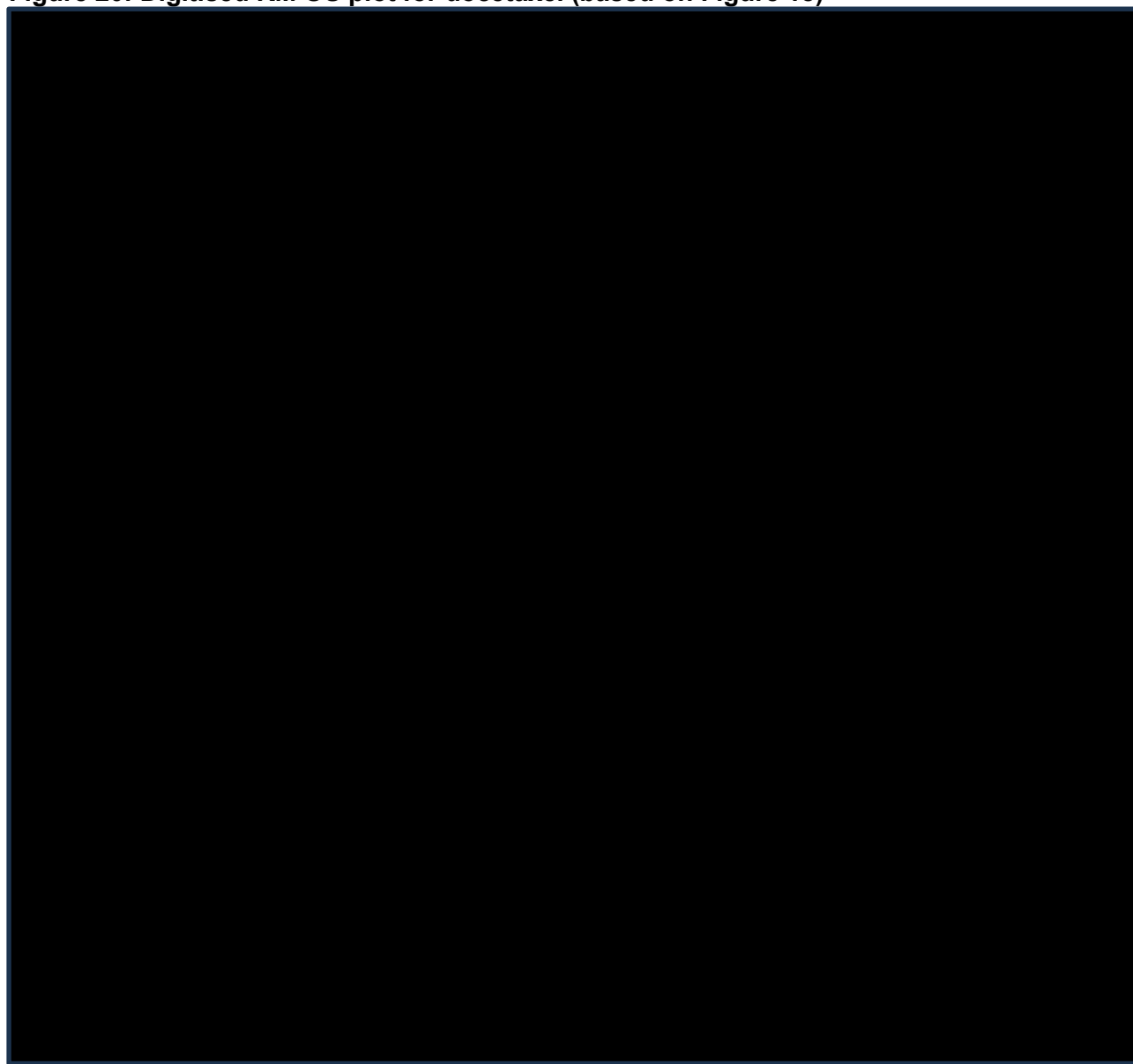
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Figure 19: Digitised KM OS plot for sotorasib (based on Figure 18)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.
Note: X axis time units in months.

Figure 20: Digitised KM OS plot for docetaxel (based on Figure 18)



Abbreviations: KM, Kaplan-Meier; OS, overall survival.
Note: X axis time units in months.

Standard parametric distributions were fitted to the adjusted time-to-event data with joint fitting and independent fitting conducted using R (ver. 4.4.2) and the *flexsurv* package.

3.3.4.1 Diagnostic assessment

3.3.4.1.1 Statistical goodness-of-fit

Goodness-of-fit statistics using AIC and BIC are presented for jointly fitted and independent models (Table 43). For individually fitted curves, the log-logistic

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distribution was the best statistically fitting curve with the lowest AIC and BIC across both sotorasib and docetaxel and the relative performance of each distribution was similar between arms.

For the jointly fitted curves, AIC and BIC indicate that the best fitting curve was the log-logistic model, as for the independently-fitted models. There was a notable (>2) deterioration in the performance of other distributions based on the statistical AIC and BIC criteria.

Table 43: Goodness-of-fit statistics for independent and jointly fitted models for OS

Model	Independent fit – sotorasib		Independent fit – docetaxel		Jointly-fitted	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1811.85	1815.83	2011.22	2015.11	3823.07	3832.33
Gamma	1806.35	1814.30	2008.02	2015.81	3812.61	3826.50
Generalised gamma	1805.10	1817.03	1990.26	2001.94	3793.61	3812.13
Gompertz	1813.79	1821.74	2009.42	2017.21	3823.02	3836.91
Log-normal	1814.48	1822.44	1991.60	1999.39	3807.09	3820.98
Log-logistic	1797.85	1805.80	1982.12	1989.91	3779.10	3792.98
Weibull	1808.45	1816.40	2011.68	2019.47	3819.20	3833.09

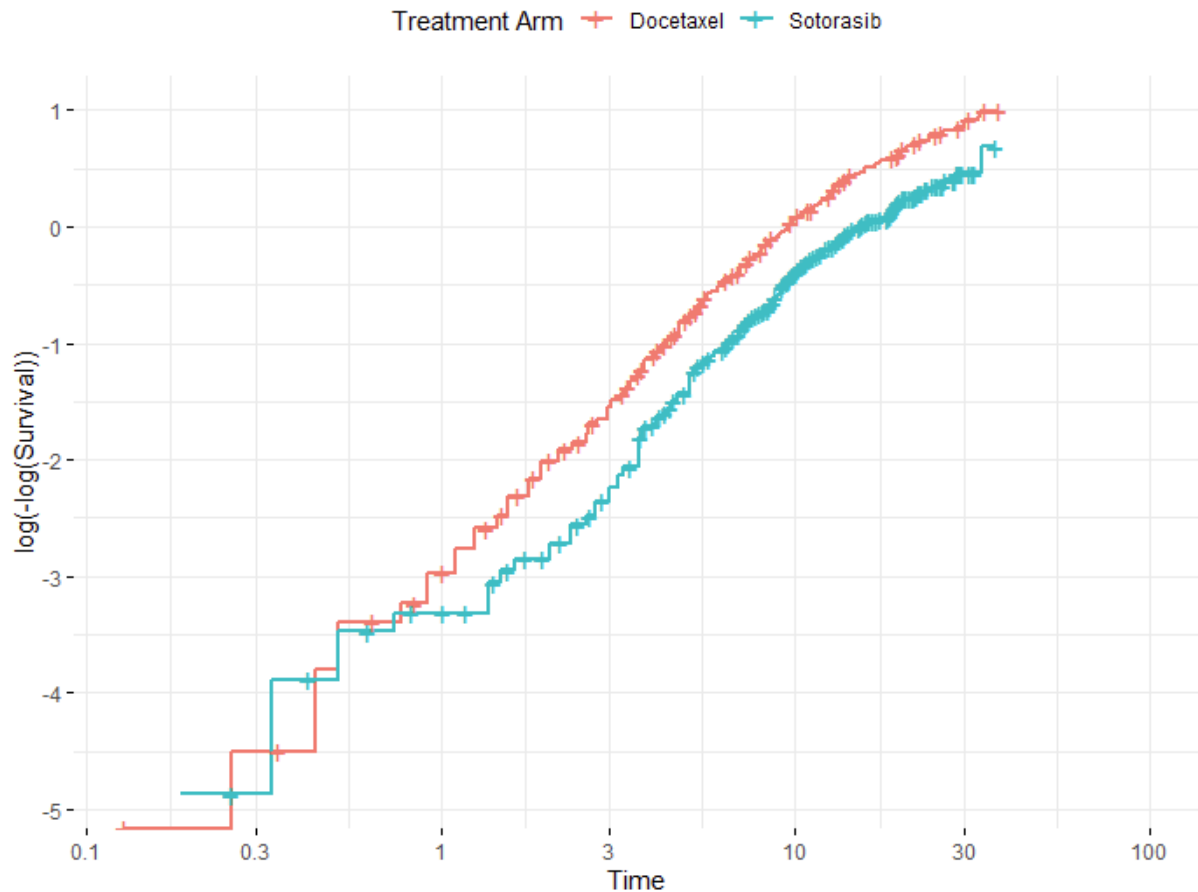
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival. Bold text indicates the best-fitting models.

3.3.4.1.2 Assessment of PH

To further inform the most appropriate distribution to extrapolate OS, the assumption of PH between the two treatments was assessed using the log-cumulative hazards plot (Figure 21) and a Schoenfeld residuals plot (Figure 22). The log-cumulative hazards and the Schoenfeld residuals plot for sotorasib and docetaxel indicated that the PH assumption may be considered valid up to approximately 26 months, where the low number of patients at risk in both arms (~13 for sotorasib and ~27 for docetaxel) makes the assessment of PH beyond 26 months of follow-up difficult. The strongly parallel lines of the log-cumulative hazard plots for the majority of the follow-up period support the validity of the PH assumption. With respect to the Schoenfeld residuals, at most times the point-wise confidence intervals included zero (Figure 22). The overall Schoenfeld individual test resulted in a p-value of 0.32, indicating that there is no evidence against the PH assumption. Considering the slope

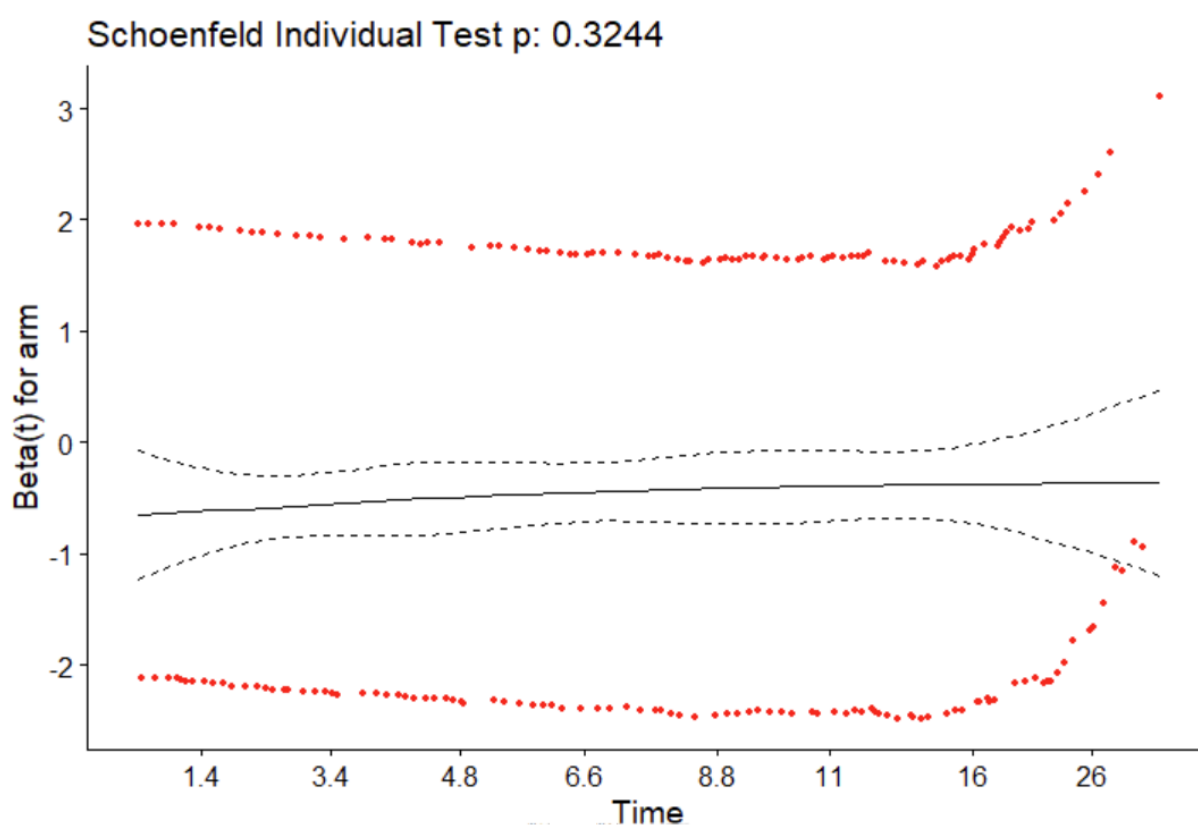
observed and the sample size used in the analysis, the validity of the PH assumption was considered uncertain but not strongly violated.

Figure 21: Log-cumulative hazards plot for OS



Abbreviations: OS, overall survival.
Note: X axis time units in months.

Figure 22: Schoenfeld residuals plot for OS



Abbreviations: OS, overall survival.
Note: X axis time units in months.

3.3.4.2 Visual inspection

Despite the log-logistic model having the best statistical fit as per AIC and BIC, and the best visual fit to the observed KM data, the log-logistic distribution generated a long tail which was not considered likely given the severity of NSCLC in the 2L+ setting (Figure 23). Similarly long tails were observed for the log-normal and Gompertz distributions (Figure 24 and Figure 25). After the log-logistic model, the model with the next-best statistical goodness-of-fit was generalised gamma, which did not have as good a visual fit to the observed data as the log-logistic model, but generated more plausible tails (Figure 26). The remaining models (exponential, Weibull, and gamma) had poor visual fit and were also the least well-fitting according to AIC and BIC (Figure 27 to Figure 29). A clinical expert performed an informal validation of the extrapolations and stated that all seven parametric extrapolations could be considered feasible, with 5-year OS expected to be in the low single digit

(1-2%) percentages for patients on docetaxel; sotorasib would be expected to have slightly higher survival rates (120).

Figure 23: Observed and estimated OS from the CAS RWE study using the jointly-fitted log-logistic model



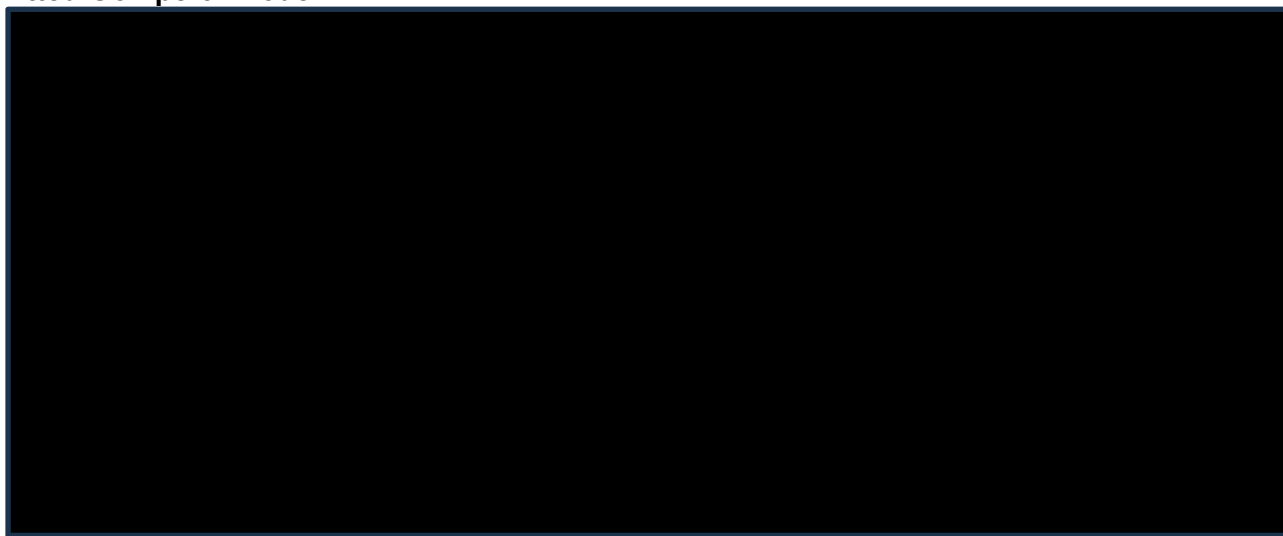
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real-world evidence.

Figure 24: Observed and estimated OS from the CAS RWE study using the jointly-fitted log-normal model



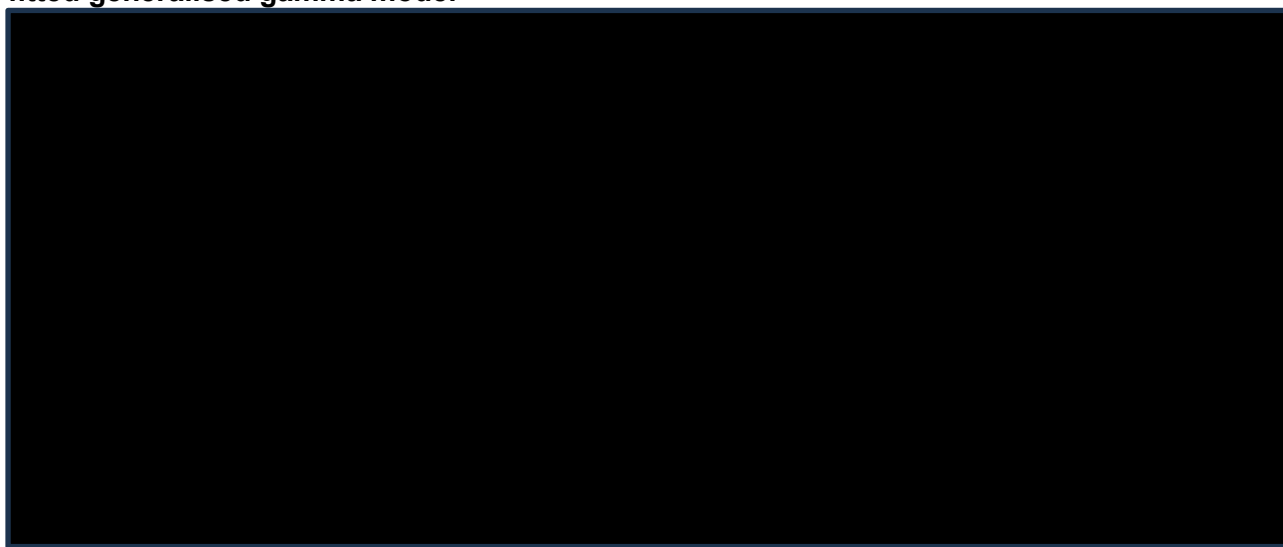
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real-world evidence.

Figure 25: Observed and estimated OS from the CAS RWE study using the jointly-fitted Gompertz model



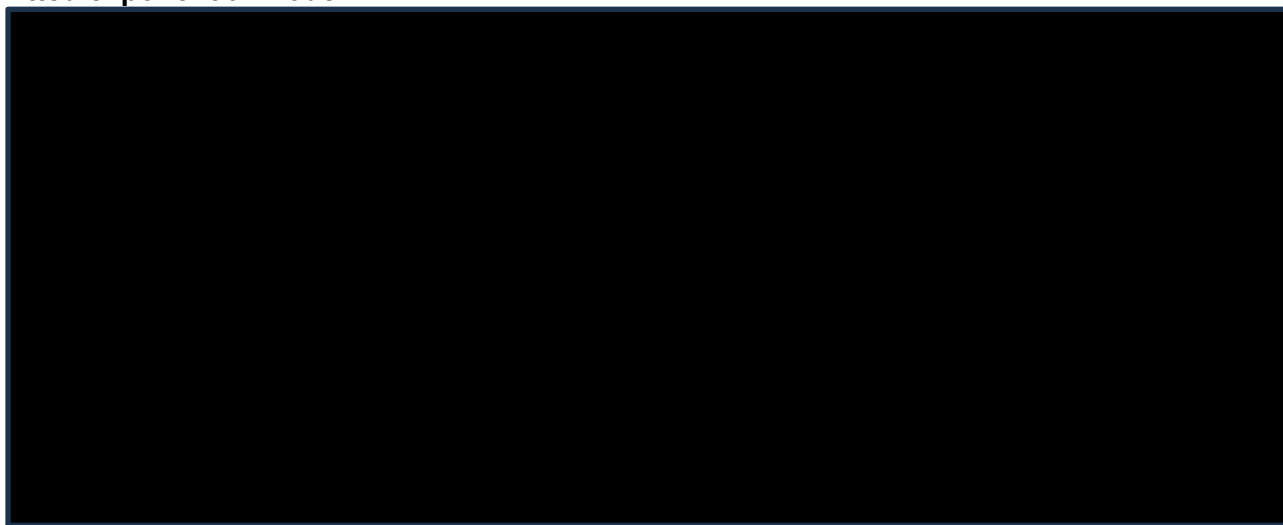
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real-world evidence.

Figure 26: Observed and estimated OS from the CAS RWE study using the jointly-fitted generalised gamma model



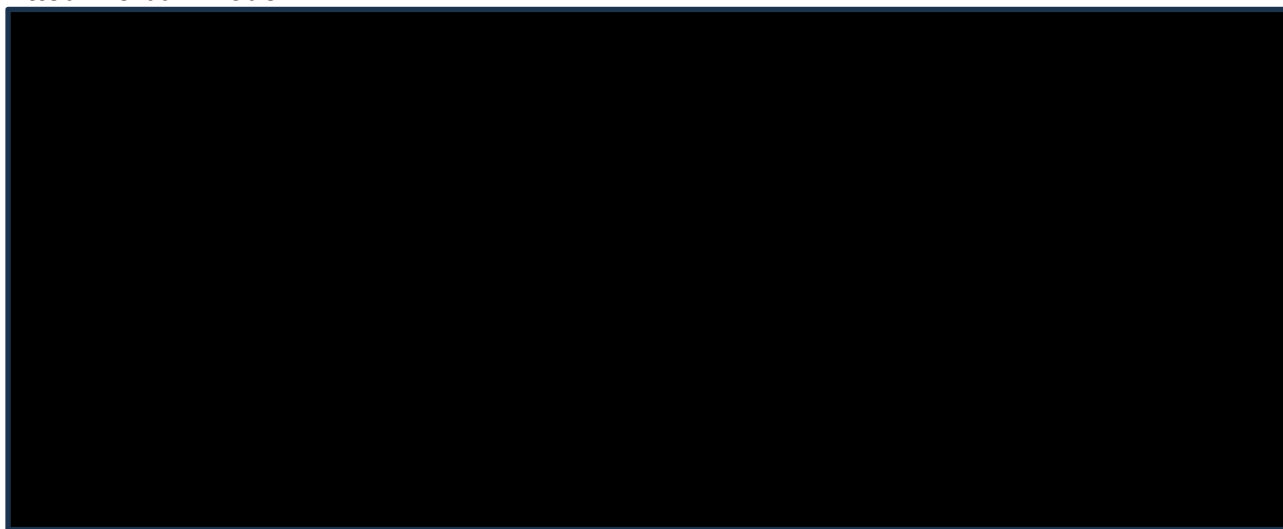
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real-world evidence.

Figure 27: Observed and estimated OS from the CAS RWE study using the jointly-fitted exponential model



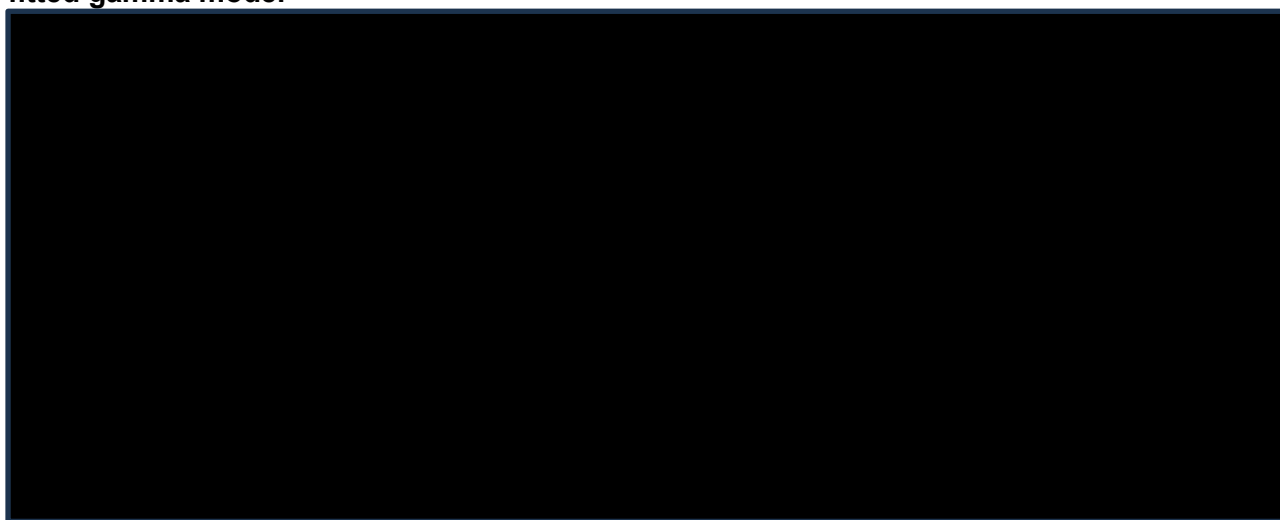
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real-world evidence.

Figure 28: Observed and estimated OS from the CAS RWE study using the jointly-fitted Weibull model



Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real-world evidence.

Figure 29: Observed and estimated OS from the CAS RWE study using the jointly-fitted gamma model



Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real-world evidence.

3.3.4.3 *Base case distribution selection for OS*

Considering the statistical goodness-of-fit and visual fit of the parametric models, generalised gamma was selected as the base-case distribution for OS. An alternative scenario was explored in which the log-logistic model was applied, due to the high statistical and visual fit to the observed CAS RWE OS data.

3.3.5 **Modelling of time to next treatment or death (TTNTD) (proxy for PFS) from CAS RWE**

TTNTD was used as a proxy for PFS, as PFS was not available in the CAS database as described in Section 2.13.2.2.6. As for OS, the TTNTD data were modelled based on parametric curves fitted to the pseudo patient-level data from the CAS RWE study. A summary of the observed trial data and corresponding KM curves are presented in Table 44 and Figure 30.

Table 44: Summary of weighted TTNTD data from the CAS study

	Sotorasib (N=394)	Docetaxel (N=363)
Total events, n (%)	██████	██████
Censored, n (%)	██████	██████
Median TTNTD (95% CI) (months)	8.51 (7.33, 9.43)	5.62 (5.06, 6.18)

Abbreviations: CAS, cancer analysis system; CI, confidence interval, TTNTD, time to next treatment or death.

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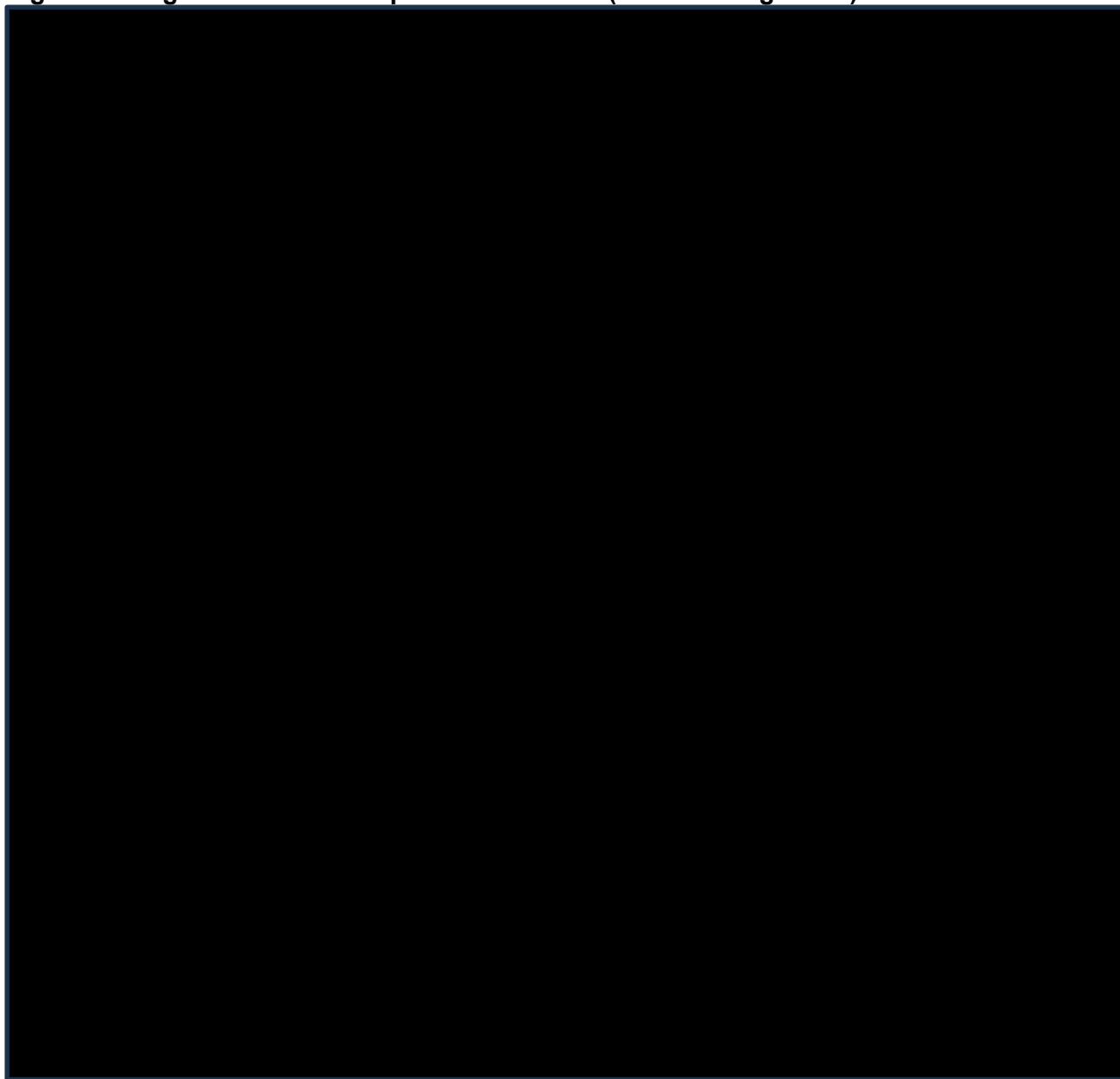
Figure 30: Original KM TTNTD plot for sotorasib and docetaxel after SMRW (CAS RWE study)



Abbreviations: CAS, Cancer Analysis System; KM, Kaplan-Meier; RWE, real-world evidence; SMRW, standardised mortality ratio weighting; TTNTD, time to next treatment or death.

The digitised KM TTNTD curves for sotorasib and docetaxel with their accompanying CIs are shown below in Figure 31 and Figure 32.

Figure 31: Digitised KM TTNTD plot for sotorasib (based on Figure 30)



Abbreviations: KM, Kaplan-Meier; TTNTD, time to next treatment or death.
Note: X axis time units in months.

Figure 32: Digitised KM TTNTD plot for docetaxel (based on Figure 30)



Abbreviations: KM, Kaplan-Meier; TTNTD, time to next treatment or death.
Note: X axis time units in months.

As for OS, standard parametric distributions were fitted to the adjusted time-to-event data with joint fitting and independent fitting conducted using R (ver. 4.4.2) and the *flexsurv* package.

3.3.5.1 Diagnostic assessment

3.3.5.1.1 Statistical goodness-of-fit

As for OS, goodness-of-fit statistics using AIC and BIC are presented for jointly fitted and independent models (Table 45).

Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

Table 45: Goodness-of-fit statistics for independent and jointly fitted models for TTNTD

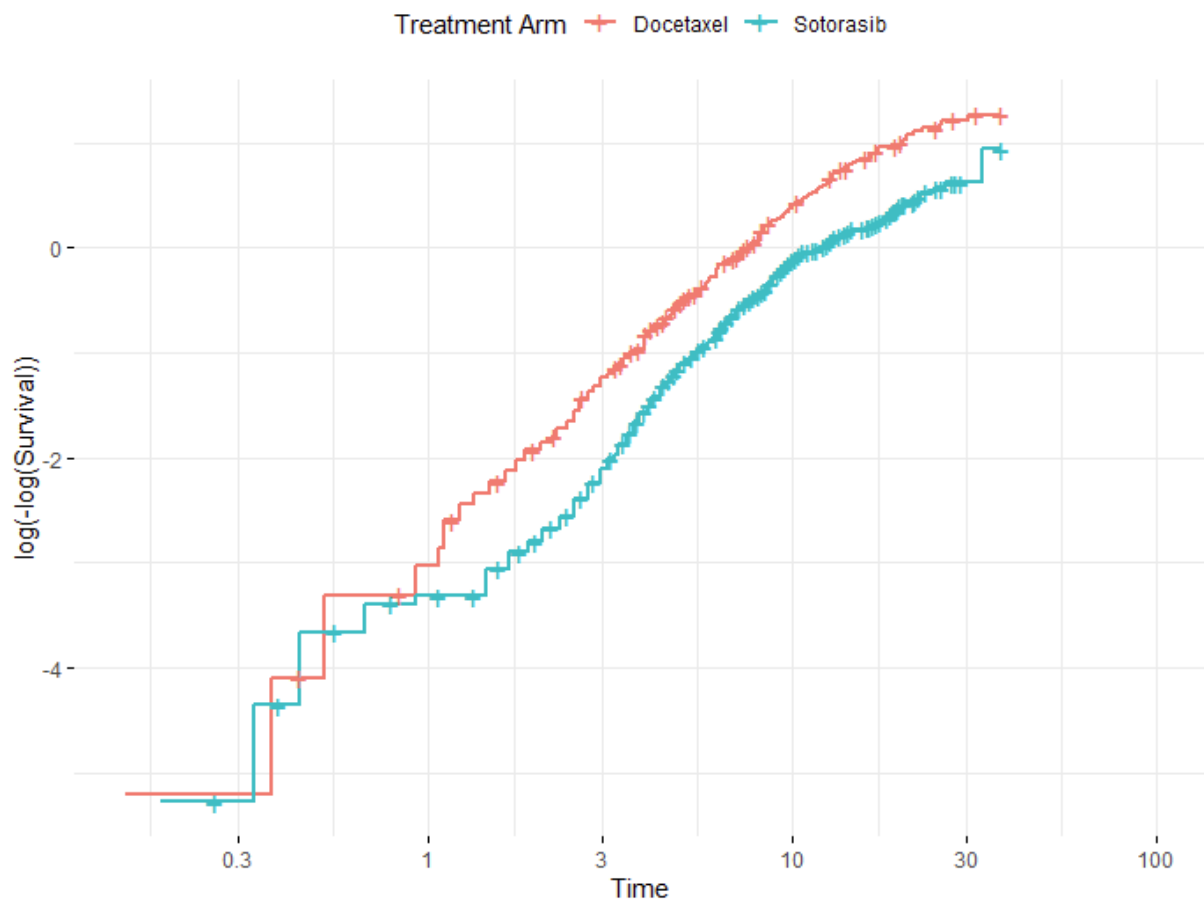
Model	Independent fit – sotorasib		Independent fit – docetaxel		Jointly-fitted	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1887.40	1891.37	1939.02	1942.91	3826.41	3835.67
Gamma	1873.97	1881.93	1915.58	1923.37	3787.98	3801.86
Generalised gamma	1868.54	1880.47	1908.05	1919.73	3774.49	3793.00
Gompertz	1889.15	1897.10	1940.67	1948.46	3827.82	3841.71
Log-normal	1874.51	1882.46	1917.57	1925.36	3794.77	3808.66
Log-logistic	1857.64	1865.60	1903.25	1911.04	3761.95	3775.84
Weibull	1878.79	1886.74	1924.17	1931.96	3801.01	3814.90

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion. Bold text indicates the best-fitting models.

3.3.5.1.2 Assessment of PH

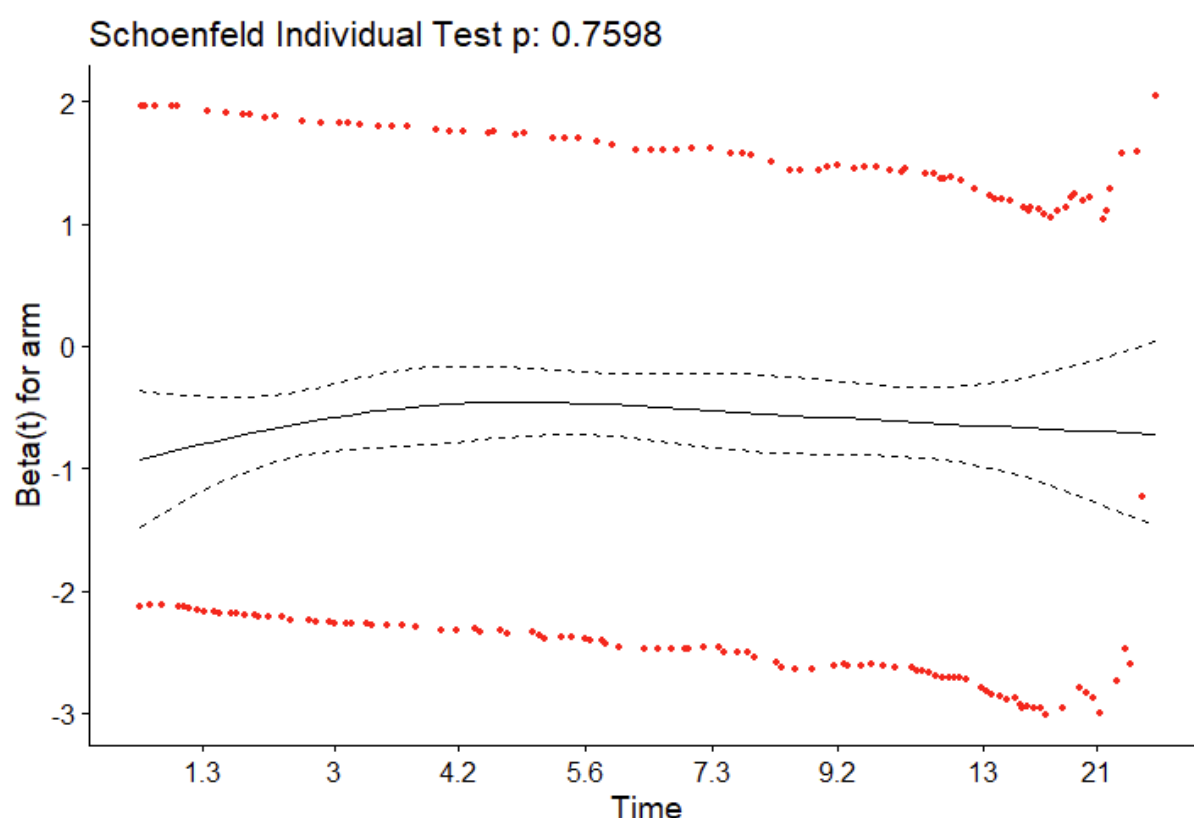
The same approach as used for OS was repeated to determine the appropriate distribution to assess TTNTD as a proxy for PFS in the PSM. A log-cumulative hazard plot (Figure 33) and Schoenfeld residual plot (Figure 34) were generated to assess the applicability of the PH assumption. As for OS, the strongly parallel and straight log-cumulative hazards plots indicate that the assumption of PH for TTNTD between sotorasib and docetaxel is appropriate. The Schoenfeld residual plot corroborates this finding, with a generally flat line and a Schoenfeld individual test result of $p=0.76$. There is no evidence to suggest that the PH assumption is violated.

Figure 33: Log-cumulative hazard plots for TTNTD



Abbreviations: TTNTD, time to next treatment or death.
Note: X axis time units in months.

Figure 34: Schoenfeld residuals plot for TTNTD

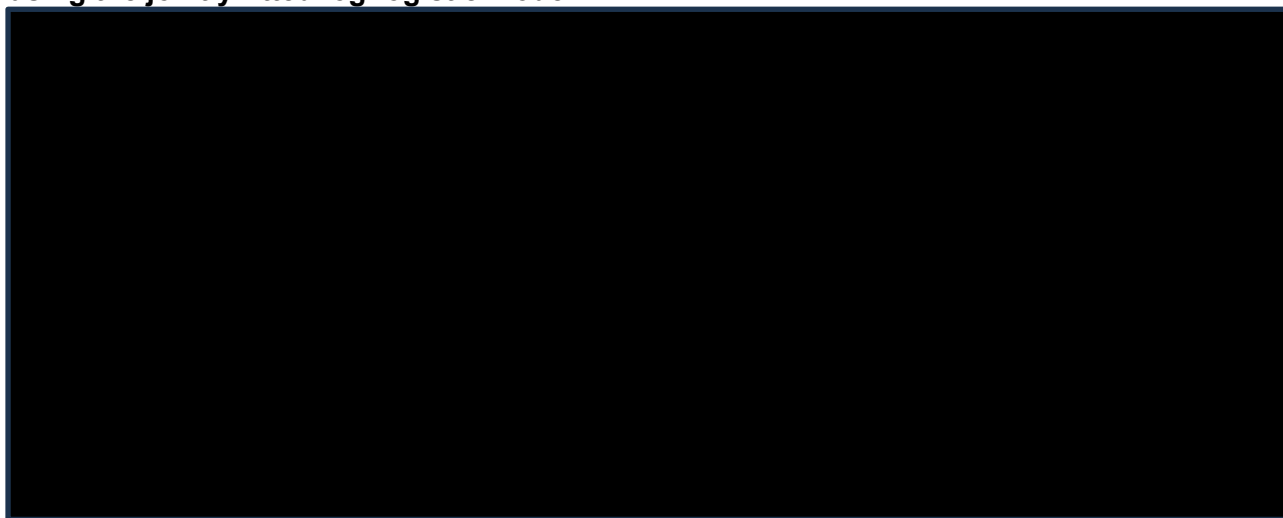


Abbreviations: TTNTD, time to next treatment or death.
Note: X axis time units in months.

3.3.5.2 Visual inspection

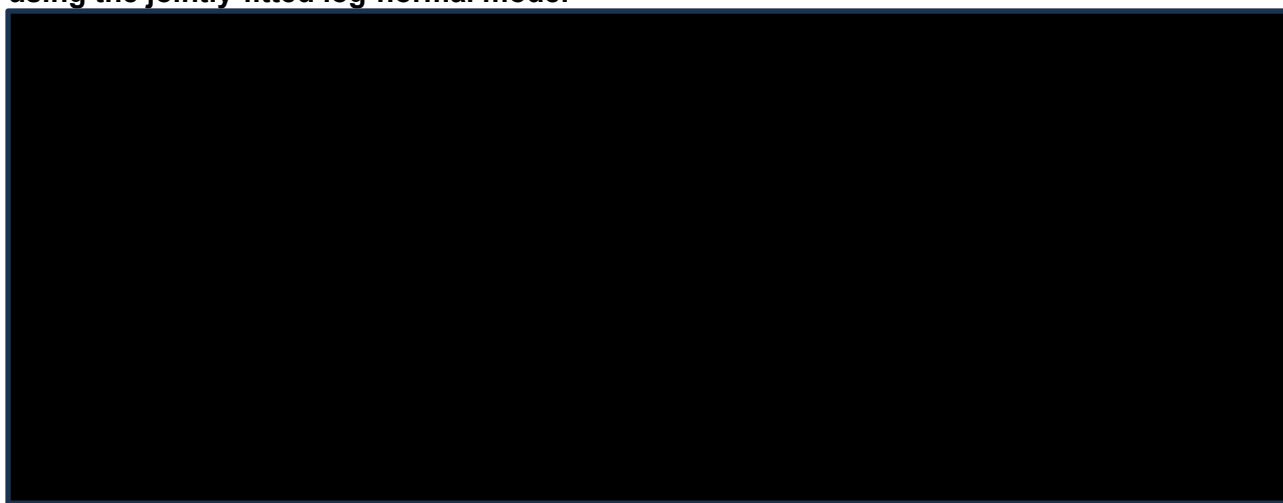
As for OS (Section 3.3.4.2), the log-logistic model was the best-fitting as per AIC and BIC but had similar issues in terms of it estimating a long tail which may have limited plausibility, despite good visual fit to the observed data (Figure 35). The log-normal distribution (Figure 36) also predicted a long tail in a similar pattern to the OS parametric extrapolations. The Gompertz model appeared to fit relatively well visually despite its poorer statistical goodness-of-fit (Figure 37). The generalised gamma model appeared to fit to the observed data well (Figure 38) and was also the second-best fitting parametric model, similarly to OS. The remaining models (exponential, Weibull and gamma), as for OS, had poorer visual fit than the other models and also had the worst statistical fit (Figure 39, Figure 40, and Figure 41 respectively). The TTNTD curves were informally validated by a clinical expert who stated that all curves appeared to be equally plausible (120).

Figure 35: Observed and estimated TTNTD (proxy for PFS) from the CAS RWE study using the jointly-fitted log-logistic model



Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real-world evidence; TTNTD, time to next treatment or death.

Figure 36: Observed and estimated TTNTD (proxy for PFS) from the CAS RWE study using the jointly-fitted log-normal model



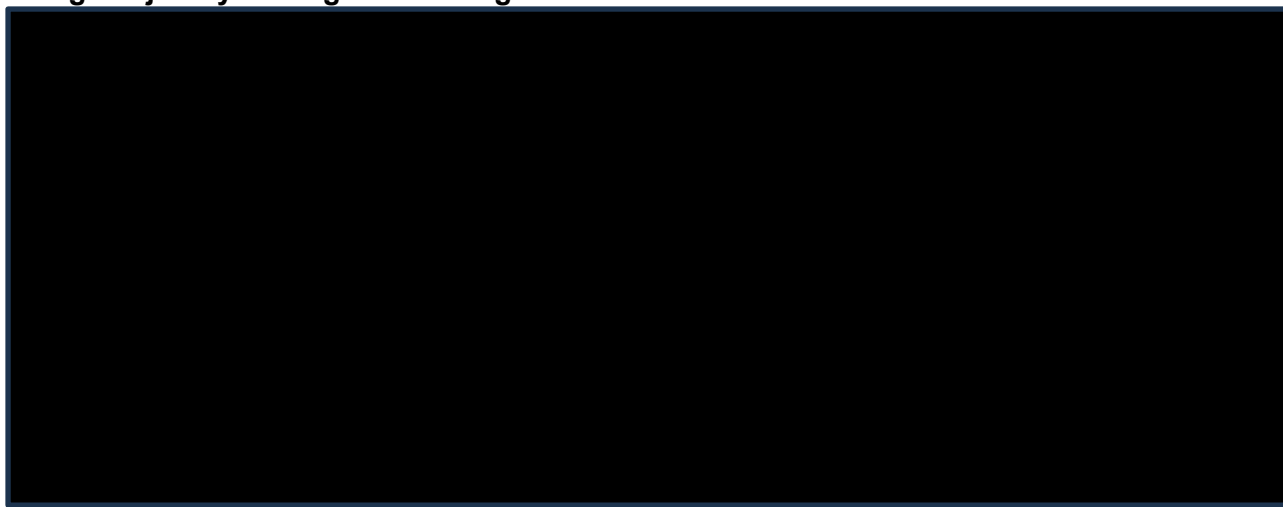
Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real-world evidence; TTNTD, time to next treatment or death.

Figure 37: Observed and estimated TTNTD (proxy for PFS) from the CAS RWE study using the jointly-fitted Gompertz model



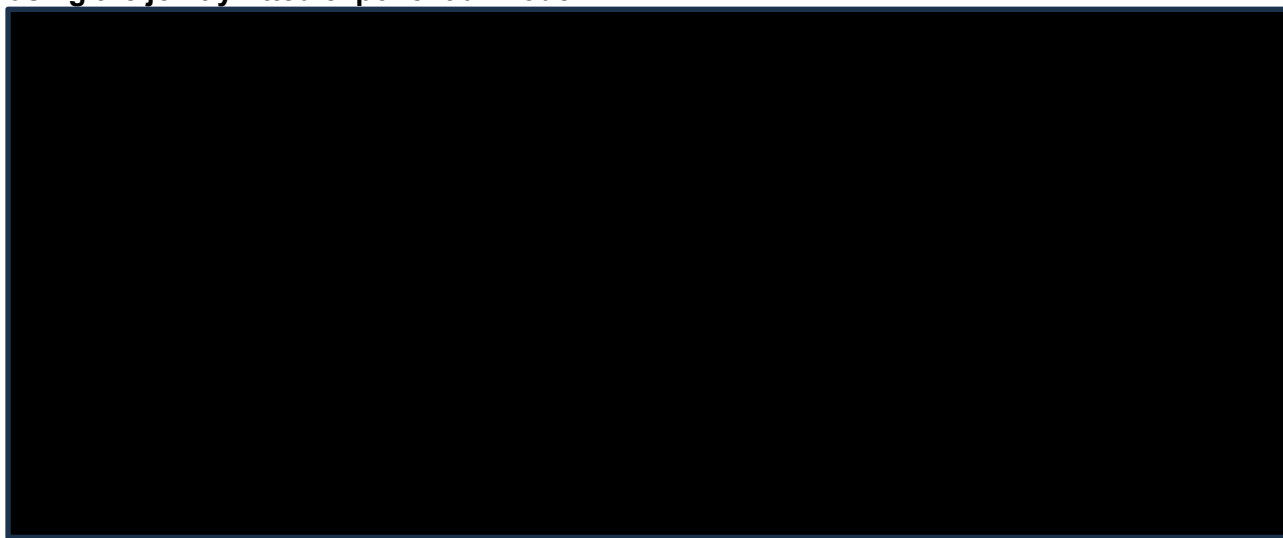
Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real-world evidence; TTNTD, time to next treatment or death.

Figure 38: Observed and estimated TTNTD (proxy for PFS) from the CAS RWE study using the jointly-fitted generalised gamma model



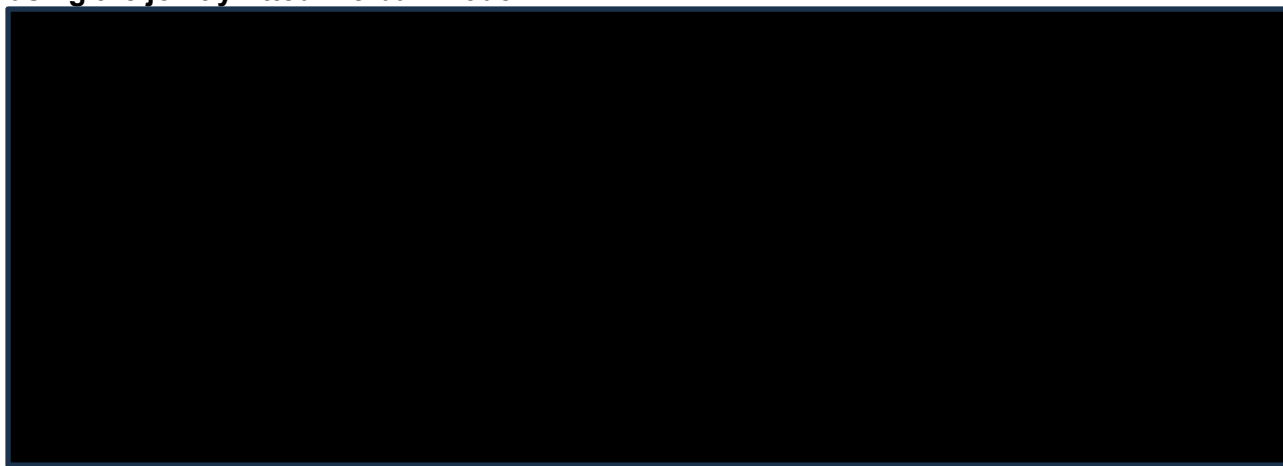
Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real-world evidence; TTNTD, time to next treatment or death.

Figure 39: Observed and estimated TTNTD (proxy for PFS) from the CAS RWE study using the jointly-fitted exponential model



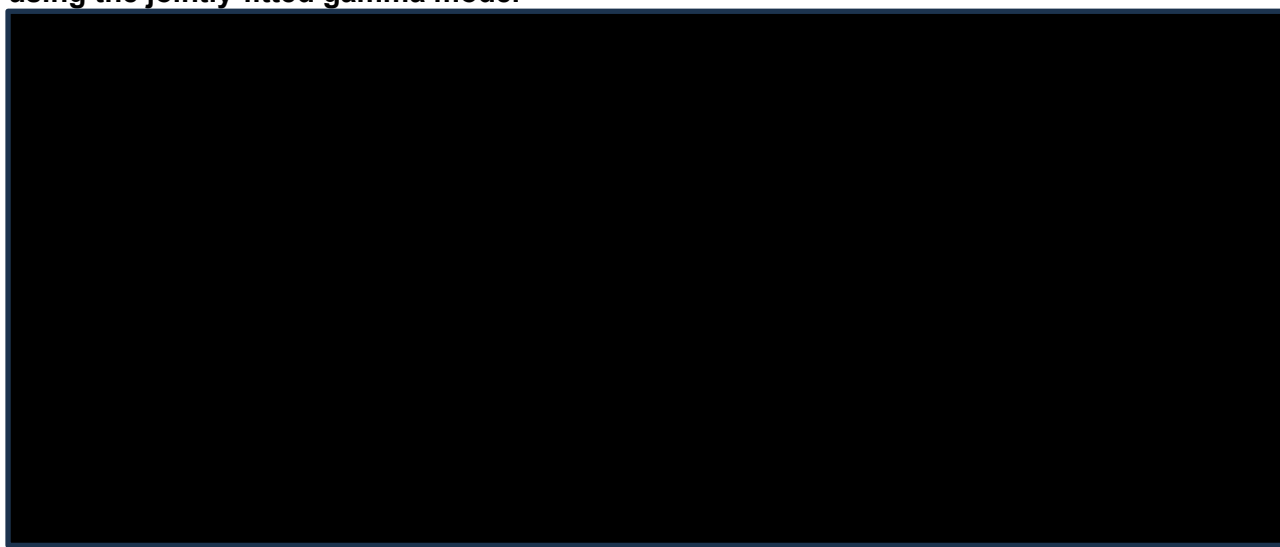
Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real-world evidence; TTNTD, time to next treatment or death.

Figure 40: Observed and estimated TTNTD (proxy for PFS) from the CAS RWE study using the jointly-fitted Weibull model



Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real-world evidence; TTNTD, time to next treatment or death.

Figure 41: Observed and estimated TTNTD (proxy for PFS) from the CAS RWE study using the jointly-fitted gamma model



Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real-world evidence; TTNTD, time to next treatment or death.

3.3.5.3 *Base case distribution selection for TTNTD*

Based on a combination of statistical goodness-of-fit and visual fit, the generalised gamma distribution was selected as the base case parametric model for TTNTD, as for OS.

3.3.6 **Modelling of time to treatment discontinuation or death (TTDD) from CAS RWE**

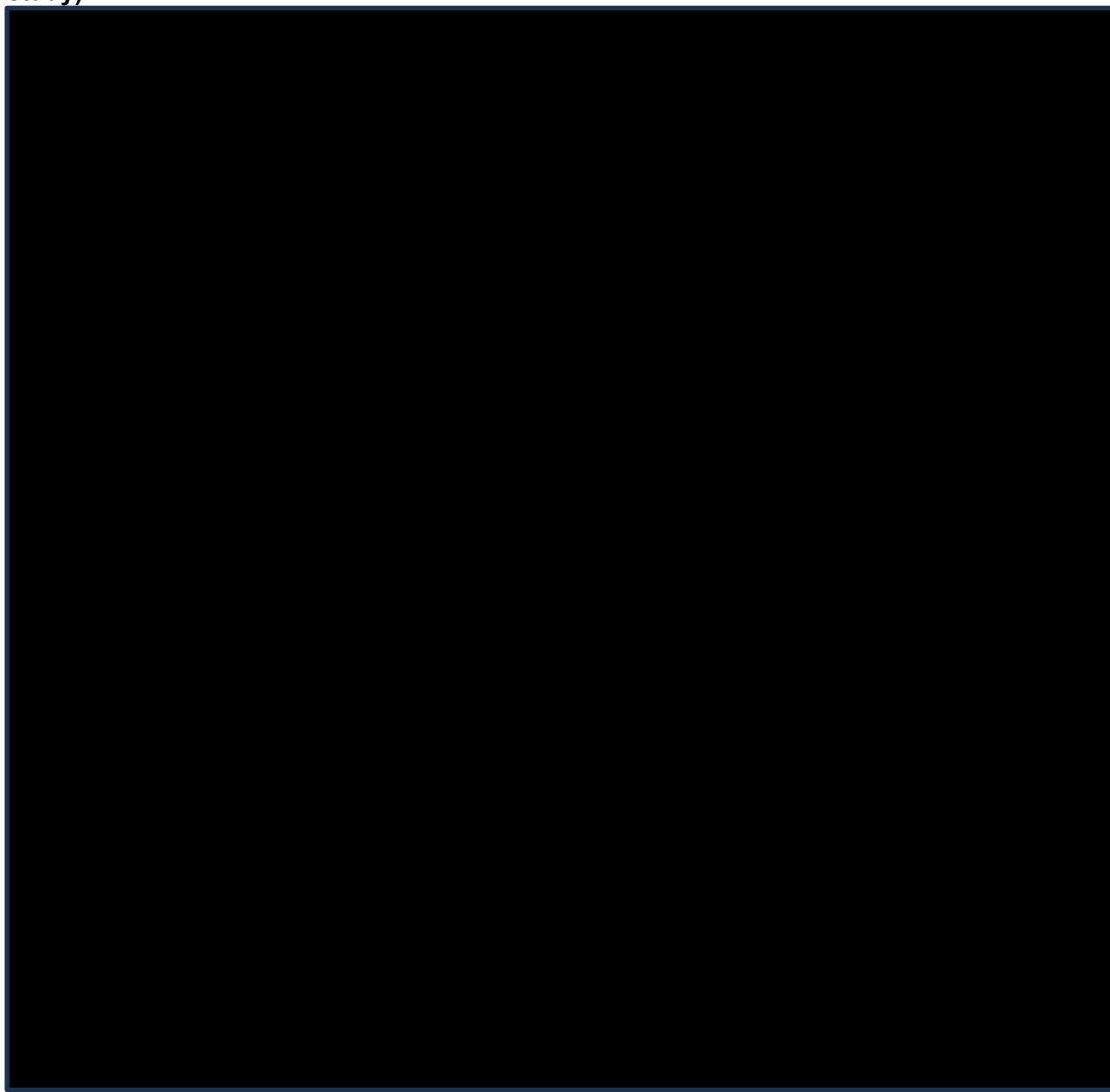
As for OS and TTNTD, TTDD for sotorasib and docetaxel was modelled based on parametric curves fitted to the pseudo patient-level data from the CAS RWE study. A summary of the observed trial data and corresponding KM curves are presented in Table 46 and Figure 42.

Table 46: Summary of weighted TTDD data from the CAS study

	Sotorasib (N=394)	Docetaxel (N=363)
Total events, n (%)	██████	██████
Censored, n (%)	██████	██████
Median TTDD (95% CI) (months)	5.06 (4.34, 6.11)	2.30 (2.07, 2.76)

Abbreviations: CAS, cancer analysis system; CI, confidence interval; TTDD, time to discontinuation or death.

Figure 42: Original KM TTDD plot for sotorasib and docetaxel after SMRW (CAS RWE study)



Abbreviations: CAS, Cancer Analysis System; KM, Kaplan-Meier; RWE, real-world evidence; SMRW, standardised mortality ratio weighting; TTDD, time to treatment discontinuation or death.

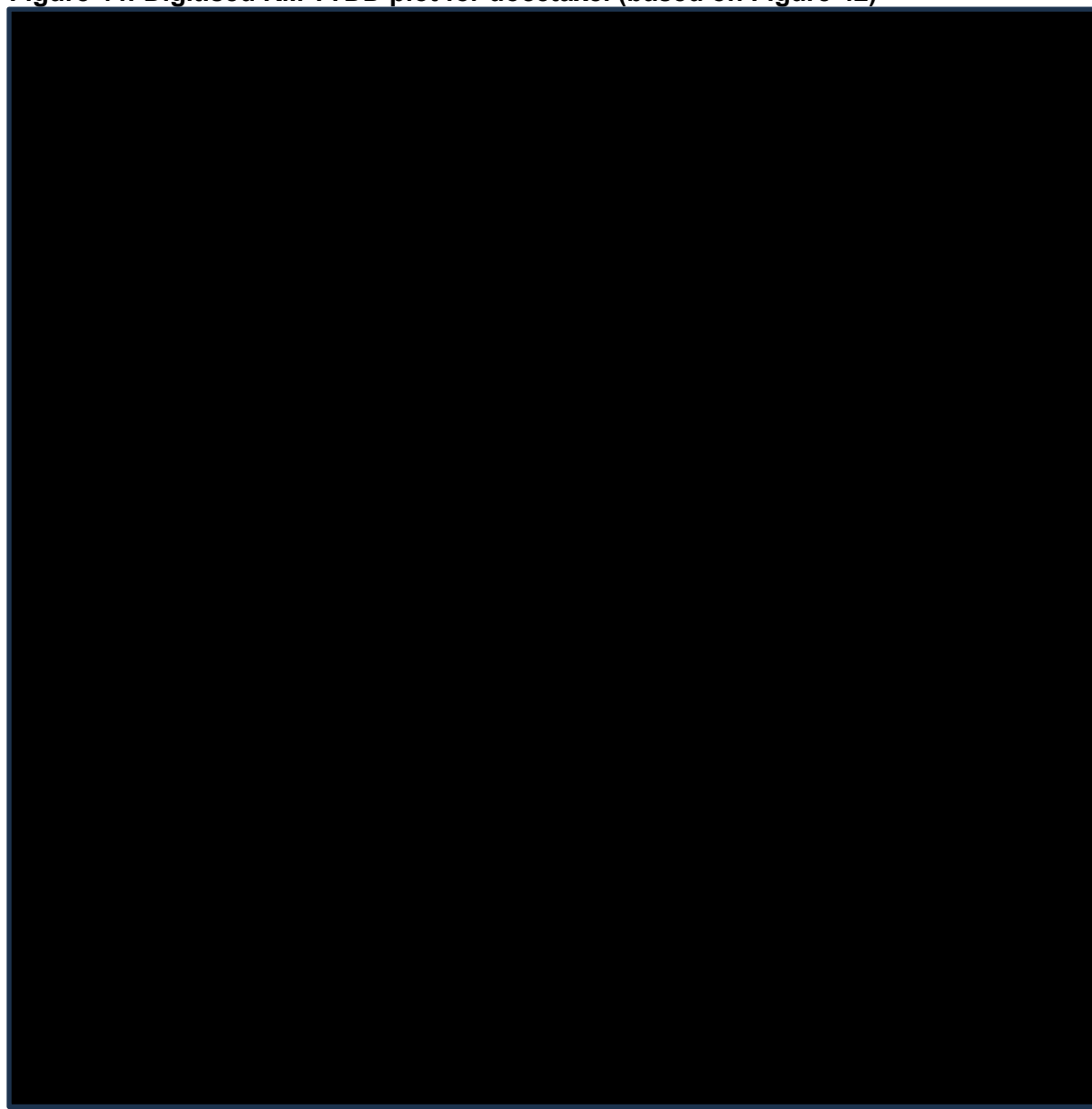
The digitised KM TTDD curves for sotorasib and docetaxel with their accompanying confidence intervals are shown below in Figure 43 and Figure 44.

Figure 43: Digitised KM TTDD plot for sotorasib (based on Figure 42)



Abbreviations: KM, Kaplan-Meier; TTDD, time to treatment discontinuation or death.
Note: X axis time units in months.

Figure 44: Digitised KM TTDD plot for docetaxel (based on Figure 42)



Abbreviations: KM, Kaplan-Meier; TTDD, time to treatment discontinuation or death.
Note: X axis time units in months.

Standard parametric distributions were fitted to the adjusted time-to-event data with joint fitting and independent fitting conducted using R (ver. 4.4.2) and the *flexsurv* package.

3.3.6.1 Diagnostic assessment

3.3.6.1.1 Statistical goodness-of-fit

Goodness-of-fit statistics using AIC and BIC are presented for jointly fitted and independent models (Table 47). For individually fitted curves, several models could

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be deemed the best-fitting; for sotorasib, the log-logistic, log-normal and generalised gamma models all had similar AIC and BIC statistics, whereas for docetaxel, the gamma, generalised gamma, and Weibull distributions were the best-fitting, with little (<3) differentiation in the AIC and BIC values for each of these curves.

For the jointly fitted curves, AIC and BIC indicate that the generalised gamma, gamma, and log-logistic models generated the best-fitting curves, again with little to differentiate the curves depending on whether AIC or BIC was used to distinguish models from one another.

Table 47: Goodness-of-fit statistics for independent and jointly fitted models for TTDD

Model	Independent fit – sotorasib		Independent fit – docetaxel		Jointly-fitted	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	2042.76	2046.74	1299.80	1303.69	3342.56	3351.82
Gamma	2041.73	2049.69	1169.24	1177.03	3273.47	3287.36
Generalised gamma	2018.66	2030.59	1170.30	1181.98	3267.20	3285.72
Gompertz	2040.61	2048.56	1237.49	1245.28	3344.47	3358.36
Log-normal	2018.01	2025.96	1195.73	1203.51	3284.19	3298.08
Log-logistic	2016.22	2024.18	1206.45	1214.24	3273.60	3287.49
Weibull	2044.27	2052.22	1171.85	1179.64	3285.06	3298.95

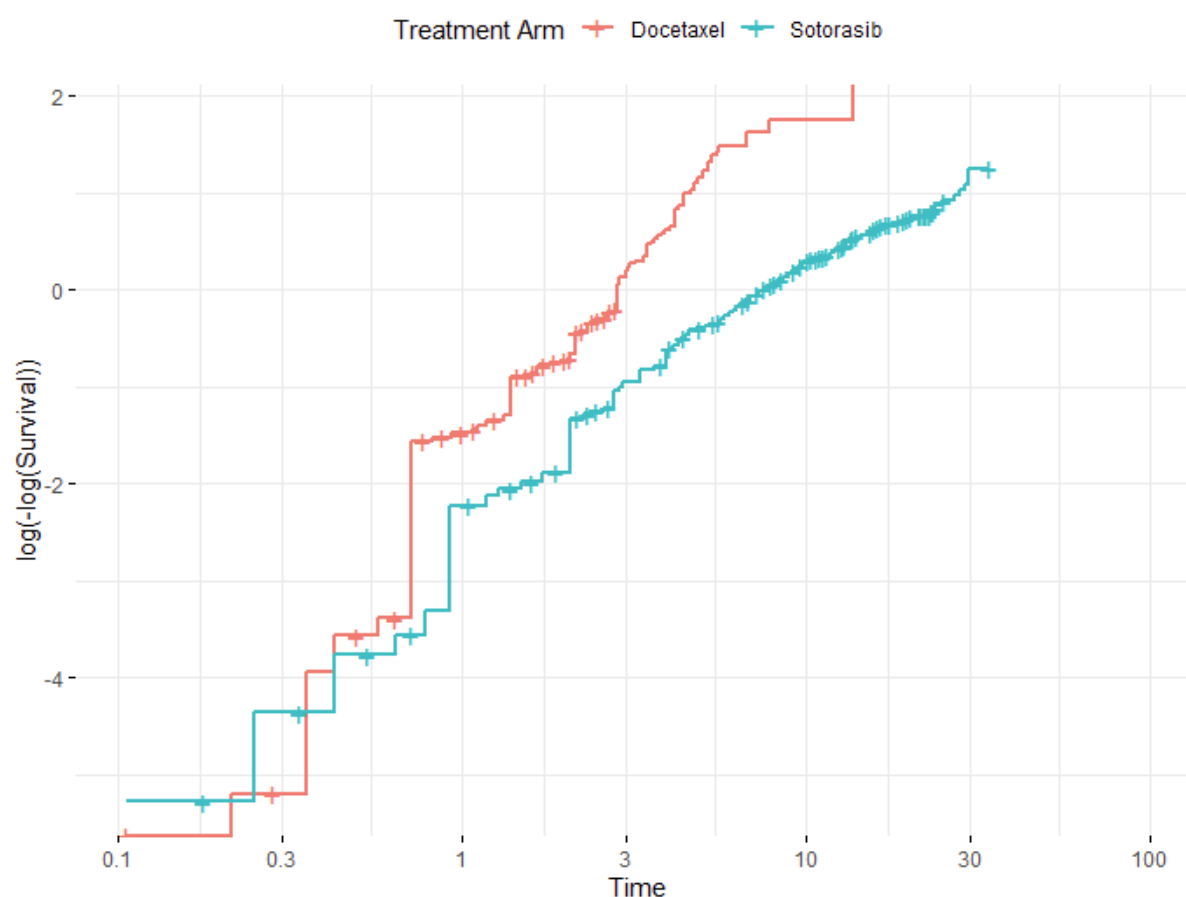
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTDD, time to treatment discontinuation or death.

Bold text indicates the best-fitting models.

3.3.6.1.2 Assessment of PH

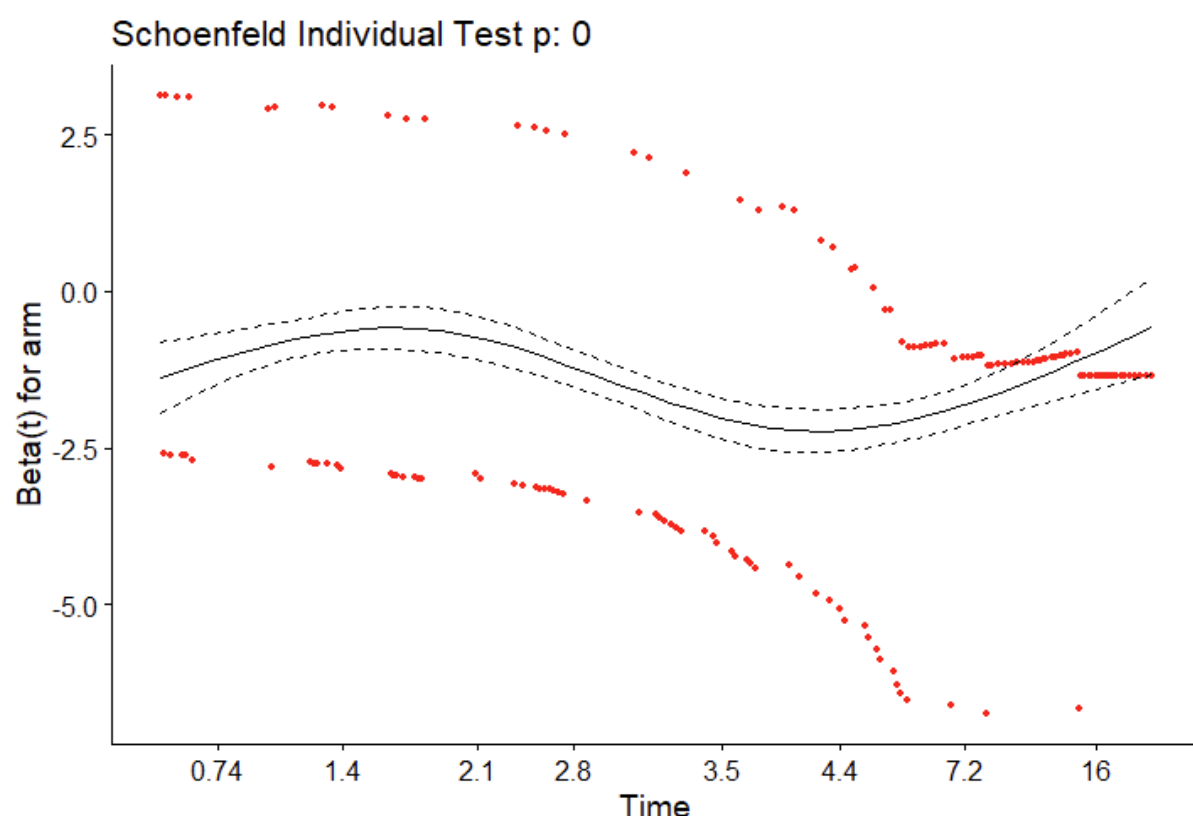
As for OS and TTNTD, the PH assumption and its appropriateness for the modelling of TTDD was assessed using a log-cumulative hazard plot (Figure 45) and a Schoenfeld residuals plot (Figure 46). The plots did not support the existence of PH as evidenced by the non-parallel log-cumulative hazard plots and the curved Schoenfeld residual plot, indicating that the relative hazard between sotorasib and docetaxel changes over time. The Schoenfeld residual test result also demonstrated the absence of PH ($p \leq 0.01$).

Figure 45: Log-cumulative hazards plot for TTDD



Abbreviations: TTDD, time to treatment discontinuation or death.
Note: X axis time units in months.

Figure 46: Schoenfeld residuals plot for TTDD

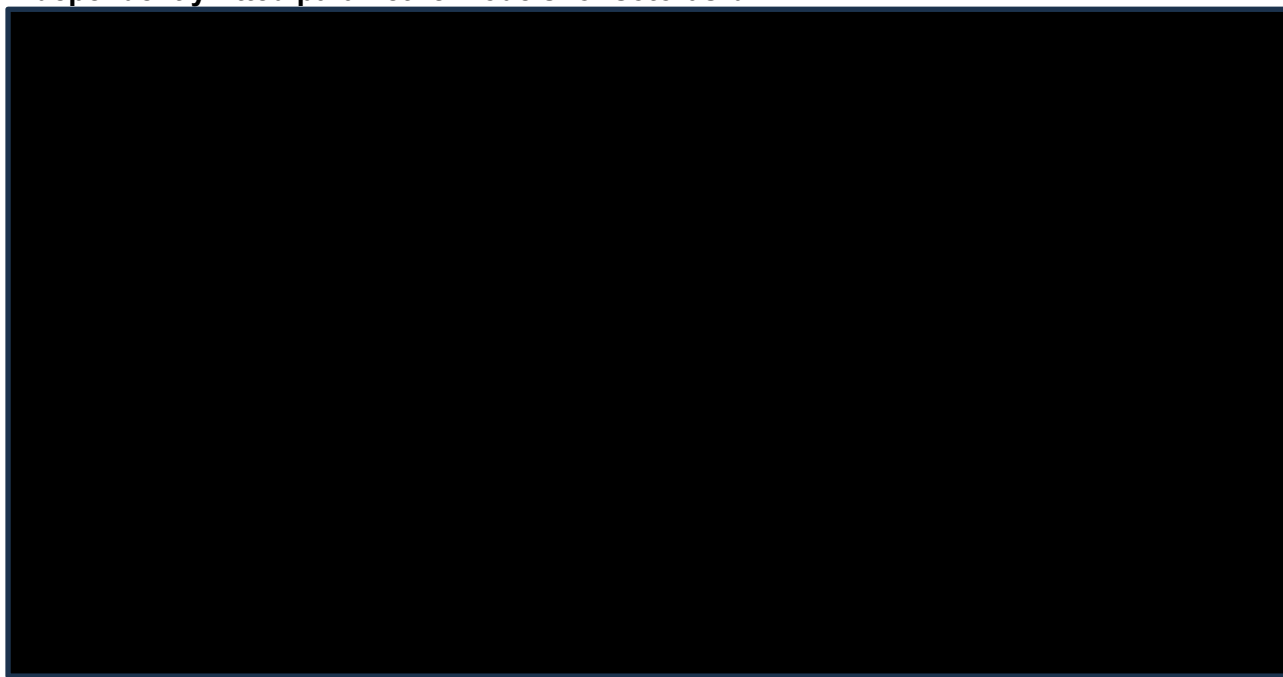


Abbreviations: TTDD, time to treatment discontinuation or death.
Note: X axis time units in months.

3.3.6.2 *Visual inspection*

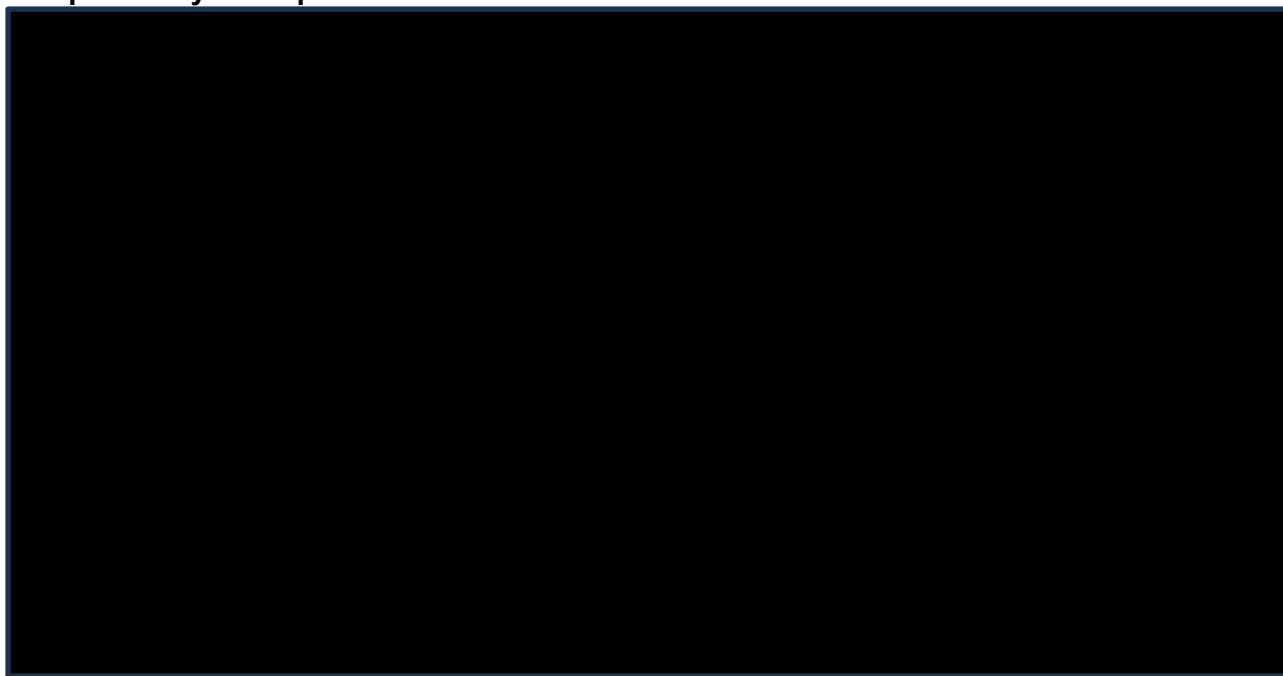
As the PH assumption was violated, the visual fit of the independently-fitted TTDD models was assessed. Due to the completeness and maturity of the TTDD KM data, there was little visual difference between the different parametric models (Figure 47 and Figure 48).

Figure 47: Observed and estimated TTDD from the CAS RWE study using independently-fitted parametric models for sotorasib



Abbreviations: CAS, Cancer Analysis System; RWE, real-world evidence; TTDD, time to treatment discontinuation or death.

Figure 48: Observed and estimated TTDD from the CAS RWE study using independently-fitted parametric models for docetaxel



Abbreviations: CAS, Cancer Analysis System; RWE, real-world evidence; TTDD, time to treatment discontinuation or death.

3.3.6.3 Base case distribution selection for TTDD

The generalised gamma distribution was the best-fitting (per AIC) for sotorasib and the second-best fitting for docetaxel, although there was little distinguishing the three best-fitting models (log-logistic, log-normal and generalised gamma for sotorasib; gamma, generalised gamma, and Weibull for docetaxel) in a statistical sense. The generalised gamma model was selected for both sotorasib and docetaxel (in line with the guidance in NICE DSU TSD 14, which states that the same model form should be used across treatment arms per outcome) based on its visual fit to the sotorasib TTDD KM curve.

3.3.7 Alternative comparative efficacy data source

3.3.7.1 CodeBreak 200

3.3.7.1.1 Overall survival

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 receiving commercial KRAS^{G12C} inhibitor. Crossover accounted for 60% 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 DSU TSD16 guidance (86), crossover adjustments were performed. The TSE crossover adjustment analysis was considered the most suitable method performed for docetaxel OS data, with the CodeBreak 200 trial design meeting the assumptions required for the TSE (86). Crossover in the trial was limited until after patients progressed, allowing progression to serve as the secondary baseline required for the analysis.

The HRs for sotorasib versus unadjusted docetaxel and sotorasib versus TSE crossover adjusted docetaxel are presented in Table 48. The OS HR for the TSE crossover adjusted analysis is estimated as 0.82 (considering for both per-protocol crossover, and crossover due to the participation in an early access program). However the uncertainty is substantial, with 95% CIs ranging from 0.32 to 1.31.

Table 48: HRs for sotorasib versus docetaxel ITT unadjusted for crossover and TSE crossover adjusted treatment effect estimates

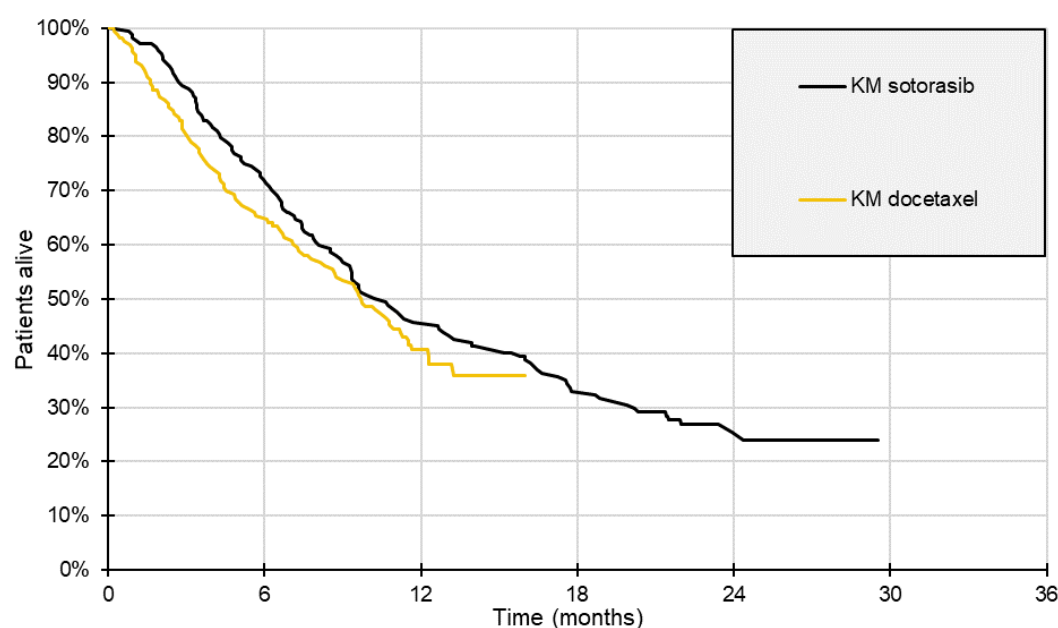
Analyses	Treatment effect for OS (95% CI)
Unadjusted for crossover: ITT	1.01 (0.77-1.33)
Adjusted for crossover†: TSE	0.820 (0.315-1.309)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; TSE, two-stage estimation.

† Considering both per-protocol crossover, and crossover due to the participation in an early access program.

The plot comparing the KM OS curve for sotorasib (in black) to the TSE adjusted OS curve for docetaxel (in yellow) is shown in Figure 49. OS was restricted so as to not exceed the survival expected in the general population – age based mortality was calculated using the National life tables for the UK (121).

Figure 49: KM OS plot for sotorasib and docetaxel with crossover TSE adjustment



Abbreviations: KM, Kaplan-Meier; OS, overall survival; TSE, two-stage estimation.

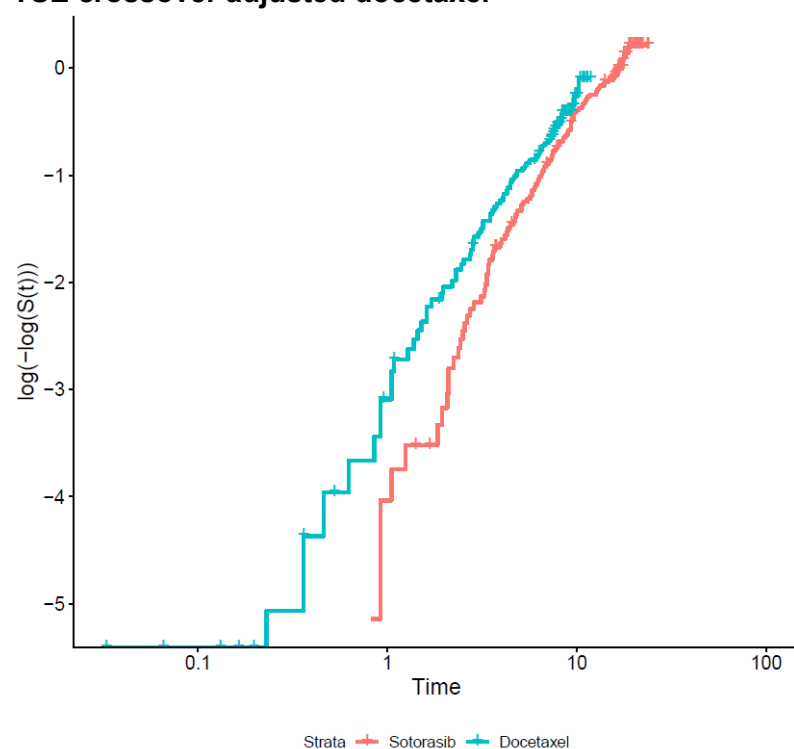
To determine a suitable approach of modeling OS, the PH and the accelerated failure time (AFT) assumptions were tested. The basis for this analysis was the TSE crossover adjusted OS data. The assumption of PH between the two treatments for individual fits was assessed using the log-cumulative hazards plot (Figure 50) and the Schoenfeld residuals plot (Figure 51). The AFT assumption was assessed using the Q-Q plot (Figure 52).

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The log-cumulative hazards and the Schoenfeld residual plot for sotorasib and docetaxel indicated that the validity of the PH assumption had some limitations but was sufficiently valid. The log-cumulative hazards plots show a slight convergence over the time horizon but remain largely parallel (Figure 50). The Schoenfeld residuals plot supported the validity of the PH assumption, with the point-wise CIs of the plot including zero for the whole time horizon (Figure 51). The global test score supported the graphical interpretation of the validity of the PH assumption by reporting a non-significant relationship between residuals and time ($p=0.1634$).

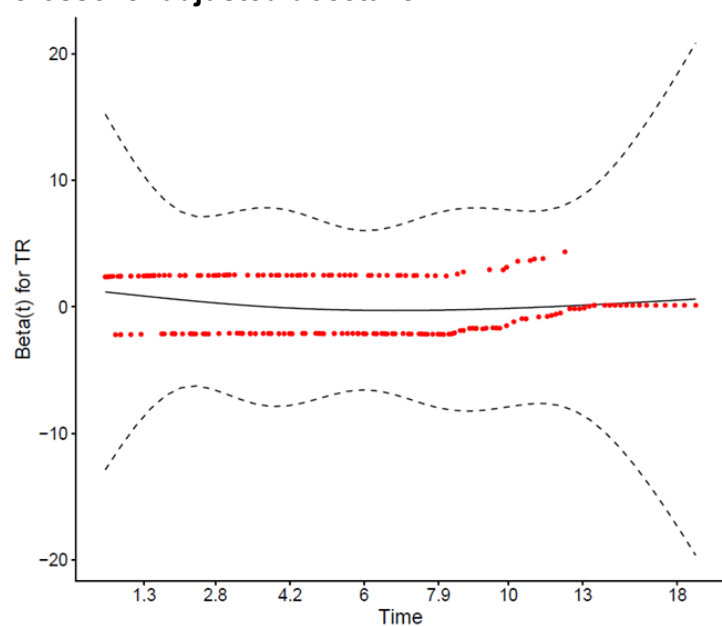
The Q-Q plot gave a roughly straight line, indicating the use of AFT was appropriate, supporting the selection of a restricted model (Figure 52).

Figure 50: Log-cumulative hazards plot for OS using the base case for sotorasib and TSE crossover adjusted docetaxel



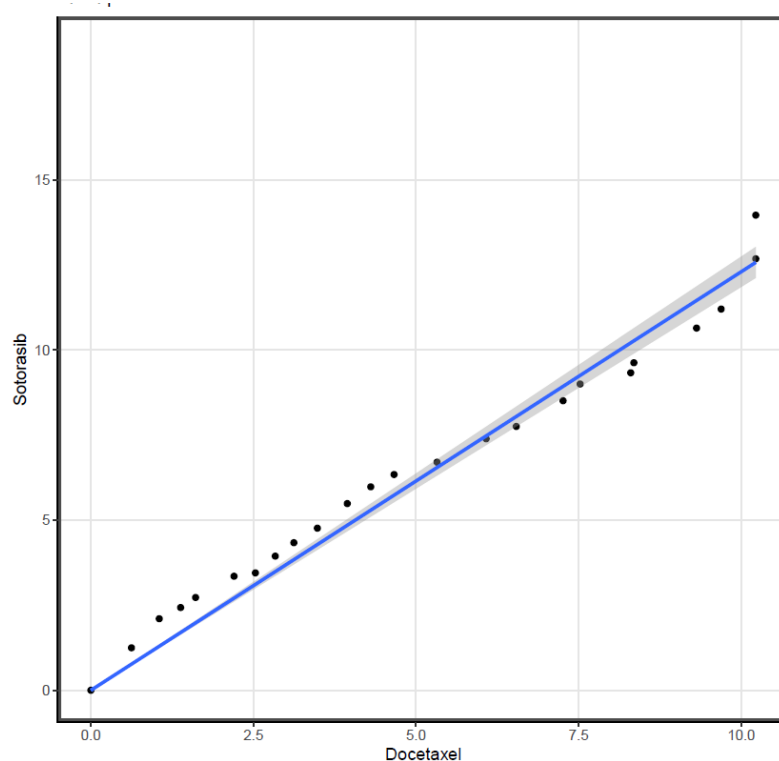
Abbreviations: OS, overall survival.

Figure 51: Schoenfeld residuals plot for OS using the base case for sotorasib and TSE crossover adjusted docetaxel



Abbreviations: OS, overall survival.

Figure 52: Q-Q plot for OS using the base case for sotorasib and TSE crossover adjusted docetaxel



Abbreviations: Q-Q, quantiles-quantiles; OS, overall survival.

In conclusion, the PH assumptions was assessed to be sufficiently reasonable. Furthermore, the AFT assumption was strongly supported. Therefore, the use of a jointly fitted model or the application of a relative treatment effect was considered appropriate.

The jointly fitted models were assessed for best fit using AIC and BIC values (Table 49). The AIC and BIC values were inconclusive for supporting either the unrestricted or restricted models, with the best fit according to AIC being the log-normal unrestricted distribution and according to BIC being the log-normal restricted distribution. Therefore, due to the lack of inconsistency in best fit, there was instability in the selection of a best fit parametric distribution.

Table 49: Goodness-of-fit statistics for jointly fitted OS models

Model	Joint unrestricted fit: Combined ITT (sotorasib) and TSE adjusted (docetaxel)		Joint restricted fit: Combined ITT (sotorasib) and TSE adjusted (docetaxel)	
	AIC	BIC	AIC	BIC
Exponential	1366	1373	1366	1373
Gompertz	1369	1384	1367	1378
Weibull	1362	1378	1360	1372
Gamma	1360	1375	1358	1370
Generalised gamma	1351	1371	1352	1368
Log-logistic	1354	1369	1353	1364
Log-normal	1350	1365	1351	1362

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention-to-treat; OS, overall survival; TSE, two-stage estimation.

Note: Emboldened values indicate the best statistically fitting parametric distribution.

Due to the instability of the jointly fitted models, for the scenario analysis to model the OS efficacy based on CodeBreakK 200, the constant HR approach was selected for simplicity. As crossover only affects the docetaxel arm, the survival in the docetaxel arm was derived via a comparative effectiveness measure. In contrast, OS was not biased in the sotorasib arm. Therefore, as a reference, a parametric curve was fitted to the sotorasib arm.

The best fit individually fitted distribution for sotorasib was selected based on goodness-of-fit statistics using the AIC and BIC. The AIC and BIC values for each distribution are presented for the individually fitted model (Table 50). The AIC and Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

BIC scores showed the log-normal distribution was the best fit. Therefore, the individually fitted log-normal distribution was chosen as the base-case parametric distribution for sotorasib used for the extrapolation in the cost-effectiveness model (CEM).

The goodness-of-fit can be considered comparable to a difference in AIC of less than four with respect to the lowest AIC (122) and a difference in BIC of less than 10 with respect to the lowest BIC (123). The log-normal and generalised gamma distributions met these criteria. The individually fitted generalised gamma was tested in scenario analysis, along with the best fit jointly fitted distribution (log-normal).

Table 50: Goodness-of-fit statistics for individually fitted OS models for sotorasib

Model	Individual fit – sotorasib (ITT)	
	AIC	BIC
Exponential	837	840
Gompertz	839	845
Weibull	834	840
Gamma	832	838
Generalised gamma	824	834
Log-logistic	826	832
Log-normal	823	829

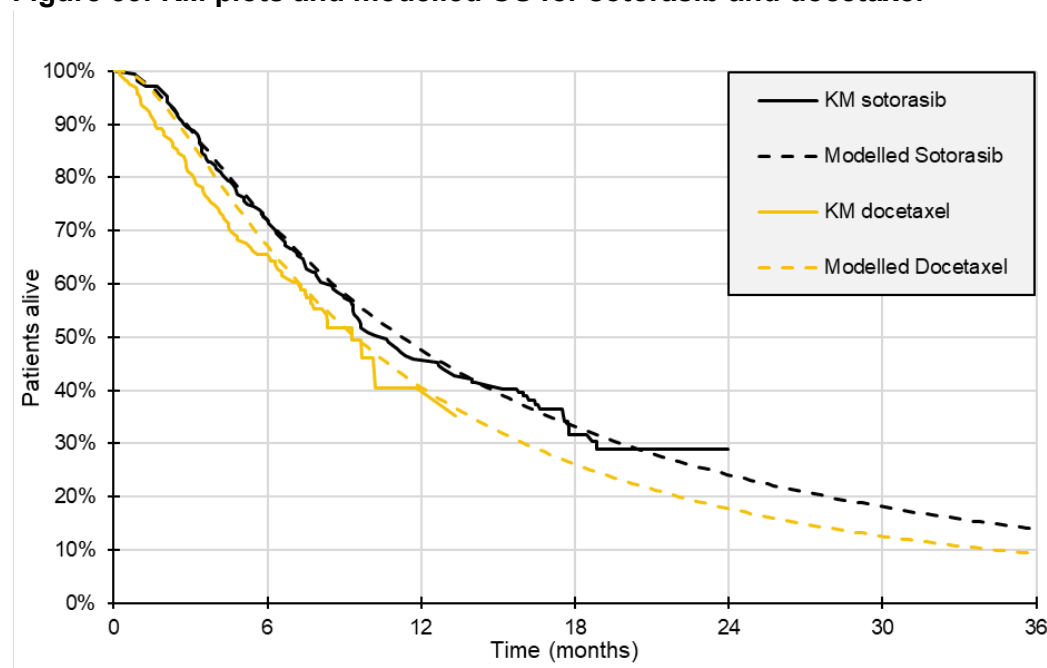
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention-to-treat; OS, overall survival; TSE, two-stage method.

Note: Emboldened values indicate the best statistically fitting parametric distribution.

A plot of the modelled OS using the individually fit log-normal distribution for sotorasib and TSE crossover adjusted HR for docetaxel is shown in Figure 53.

Visual inspection of the curves shows the modelled curves fit the KM curves well for the length of the trial. Table 51 shows in trial predictions for the proportion of patients remaining alive, which also shows sotorasib having a survival benefit when compared to docetaxel. The survival benefit continued for the long-term out of trial OS predictions presented in Table 52.

Figure 53: KM plots and modelled OS for sotorasib and docetaxel



Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 51: OS predictions for models using individually fitted log-normal model for sotorasib and HR versus TSE crossover adjusted docetaxel

	Sotorasib	Docetaxel
2 months	95.3%	94.4%
6 months	72.1%	67.2%
12 months	47.7%	40.7%
24 months	24.2%	17.8%

Abbreviations: HR, hazard ratio; OS, overall survival; TSE, two-stage estimation.

Table 52: Long-term OS predictions for models using individually fitted restricted log-normal model for sotorasib and HR versus TSE crossover adjusted docetaxel

	Sotorasib	Docetaxel
3 years	14.1%	9.3%
5 years	6.1%	3.3%
10 years	1.4%	0.6%

Abbreviations: HR, hazard ratio; OS, overall survival; TSE, two-stage estimation.

3.3.7.1.2 Progression-free survival

PFS was the primary endpoint of the trial and was measured using two separate methods; investigator assessed (IA) and by BICR. The IA method refers to the assessment of the patient's condition by the local investigator to determine

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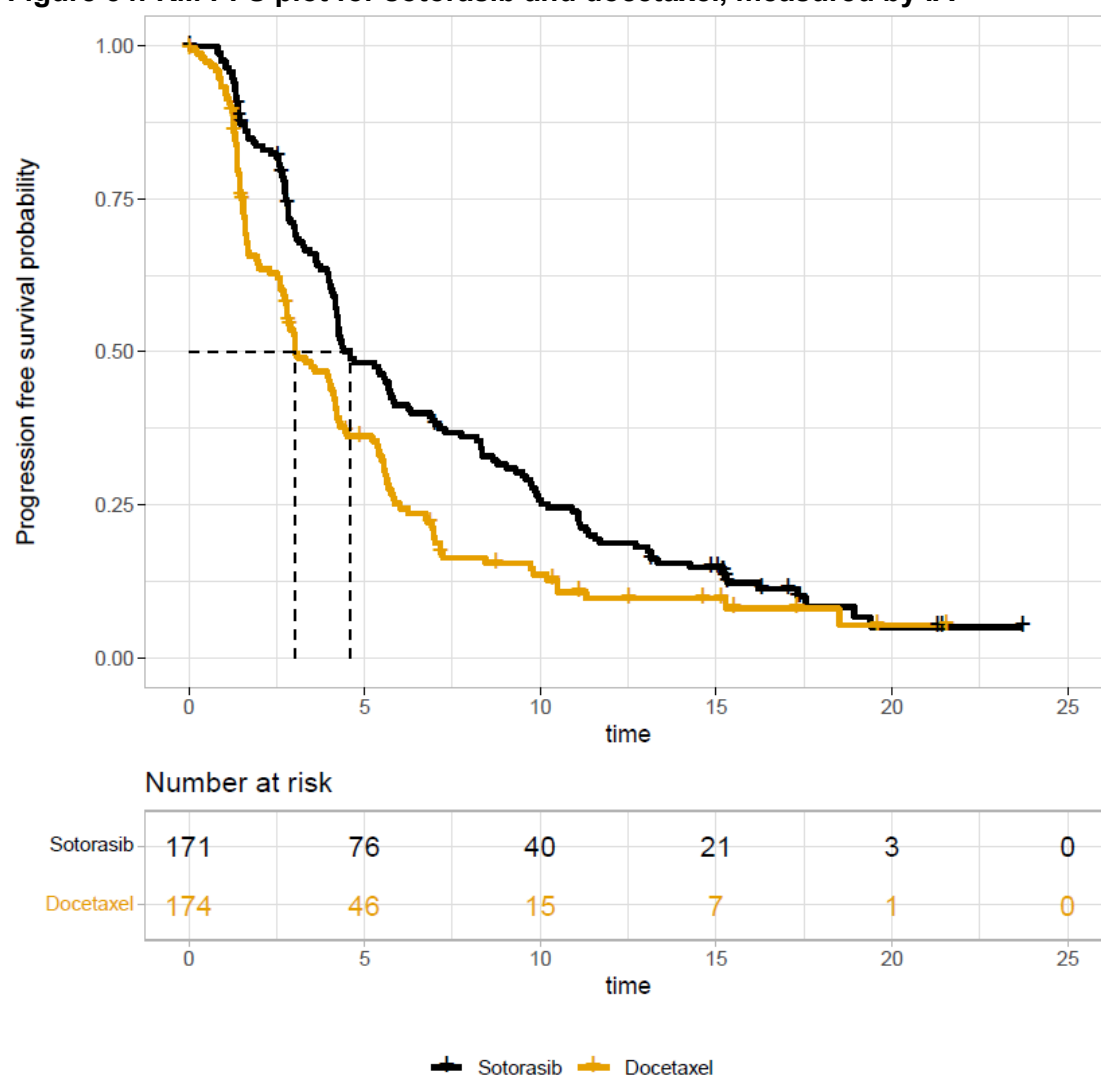
progression status. BICR refers to the method where radiologists, blinded to the treatment arm of the patient and the assessment of the local investigator, assess scans of the patient to determine the progression status.

The trial used PFS measured by BICR as the primary endpoint as this approach provided the most validity when establishing a treatment effect, reducing any potential systematic imaging reader bias (124). However, using BICR may introduce significant bias into the model through informative censoring (124). In the trial, a large proportion of patients in the docetaxel arm crossed over onto sotorasib treatment (26.4%) with a further portion (7.5%) receiving subsequent other KRAS inhibitor treatments outside of the trial protocol. The start of subsequent treatment use, and therefore treatment crossover, was driven by progression measured by IA. Progression status measured by BICR was not known to the participants or local investigators and therefore did not affect decision-making. As progression could have been defined differently between IA and BICR, patients who progressed according to IA and moved onto subsequent therapy before progression occurred according to BICR were censored in the BICR dataset. Overall, 23 of the 143 (18.6%) PFS IA events for docetaxel were censored in the BICR dataset. Therefore, the PFS BICR dataset contained significant bias, and was therefore less reliable.

The IA dataset therefore provided a more accurate representation of progression as per the trial and was considered the most appropriate for informing the model. IA is also the standard approach in clinical practice, and therefore may provide a more accurate representation of the real-world scenario (125). The use of the BICR dataset was tested in the scenario analysis.

Figure 54 shows the base-case KM PFS curve measured by IA for sotorasib (in black) versus docetaxel (in yellow). Sotorasib showed a significant PFS benefit during the trial period.

Figure 54: KM PFS plot for sotorasib and docetaxel, measured by IA



Abbreviations: IA, investigator assessment; KM, Kaplan-Meier; PFS, progression-free survival.

PFS for sotorasib and docetaxel was modelled using the best fit parametric distribution, in line with the methods detailed in NICE DSU TSD 14 (119). To determine the most appropriate modelling approach, the PH and AFT assumptions were tested for PFS measured by IA. The assumption of PH between the two treatments for individual fits was assessed using the log-cumulative hazards plot (Figure 55) and the Schoenfeld residuals plot (Figure 56). The AFT assumption was assessed using the quantile-quantile (Q-Q) plot (Figure 57).

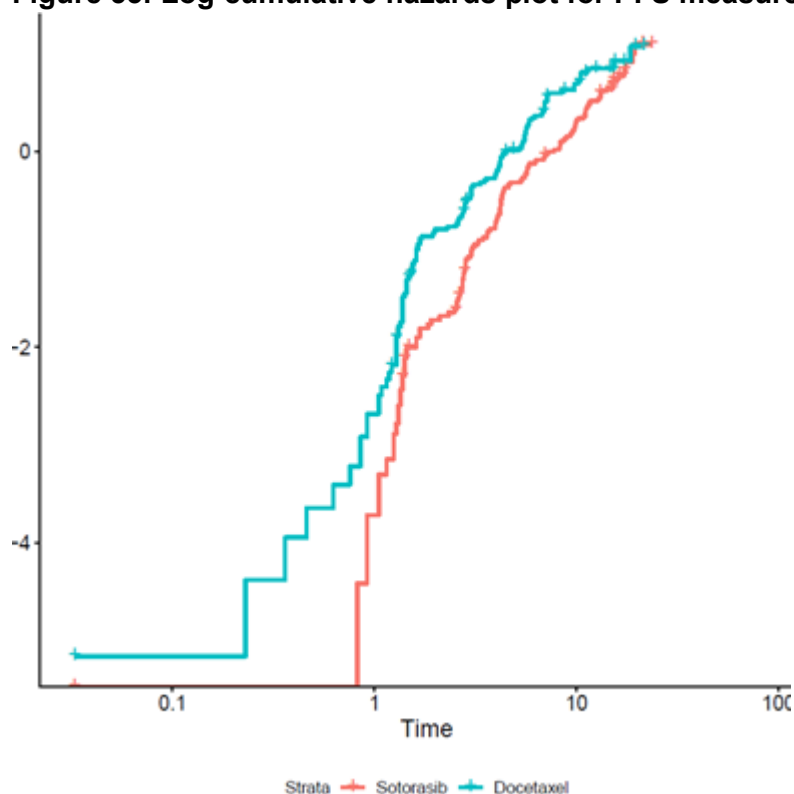
The validity of the PH assumption holding was uncertain. The log-cumulative hazards plot demonstrated a repeated convergence and divergence of the sotorasib and docetaxel curves, suggesting the PH assumption did not hold (Figure 55).

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However, the Schoenfeld residuals plot suggested the PH assumption did hold ($P = 0.0289$) with the point-wise confidence intervals (CIs), shown in red (Figure 56), containing zero for the time horizon.

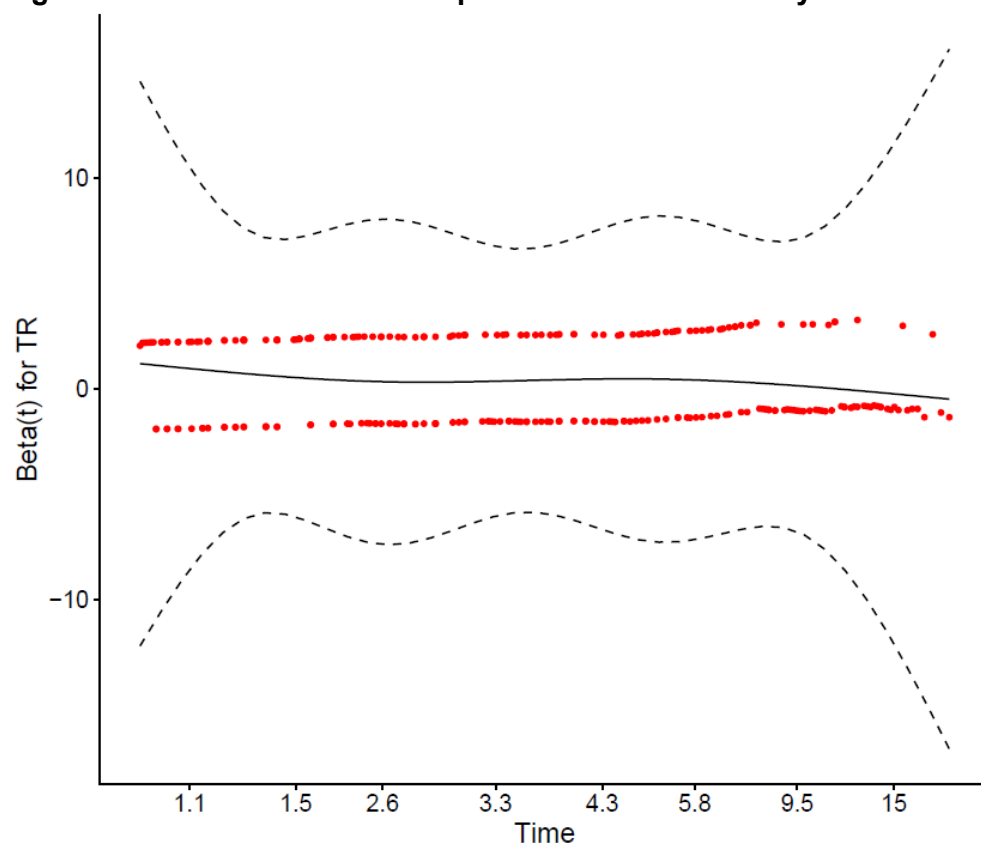
The Q-Q plot indicated that the AFT assumption was sufficiently valid. Despite some deviations that may have been sample size driven, overall the Q-Q plot indicated a straight line (Figure 57).

Figure 55: Log-cumulative hazards plot for PFS measured by IA



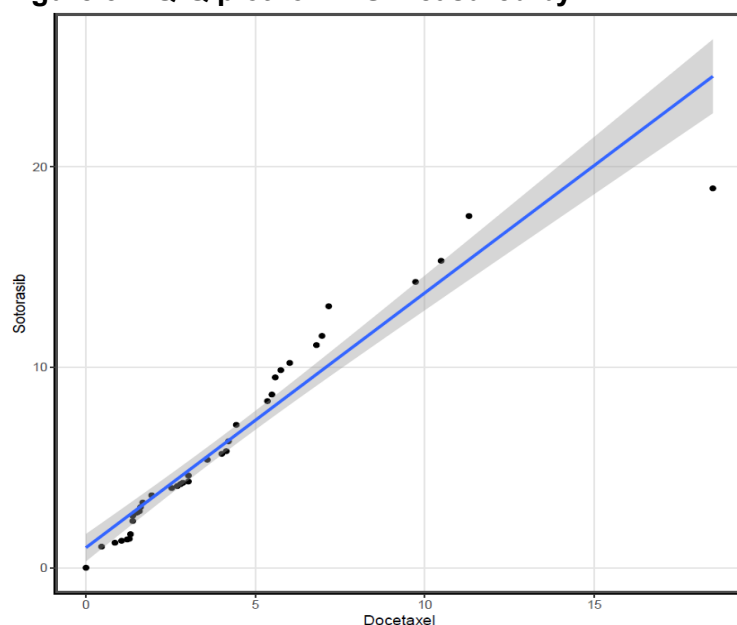
Abbreviations: IA, investigator assessed; PFS, progression-free survival.

Figure 56: Schoenfeld residuals plot for PFS measured by IA



Abbreviations: IA, investigator assessed; PFS, progression-free survival; TR, treatment variable.

Figure 57: Q-Q plot for PFS measured by IA



Abbreviations: IA, investigator assessed; PFS, progression-free survival; Q-Q, quantiles-quantiles.

In summary, there were smaller deviations from the PH assumptions, but the AFT assumption appeared to sufficiently hold. This supports the selection of jointly fitted restricted parametric models. The best fit distribution was selected based on goodness-of-fit statistics using the AIC and BIC (126). The lower values for AIC and BIC represent a better fit distribution. The AIC and BIC values for each approach and distribution are presented for the jointly fitted (unrestricted and restricted) models (Table 53). The AIC and BIC scores showed the log-logistic distribution was the best fit for both the unrestricted and restricted models. The restricted distribution was preferred by both AIC and BIC; therefore the base-case distribution for PFS was the jointly fitted restricted log-logistic distribution.

The goodness-of-fit can be considered comparable to a difference in AIC of less than 4 with respect to the lowest AIC (122) and a difference in BIC of less than 10 with respect to the lowest BIC (123). The log-normal and generalised gamma-restricted distributions met these criteria. The log-normal distribution was tested in scenario analysis, along with the best fit individually fitted distribution (log-normal).

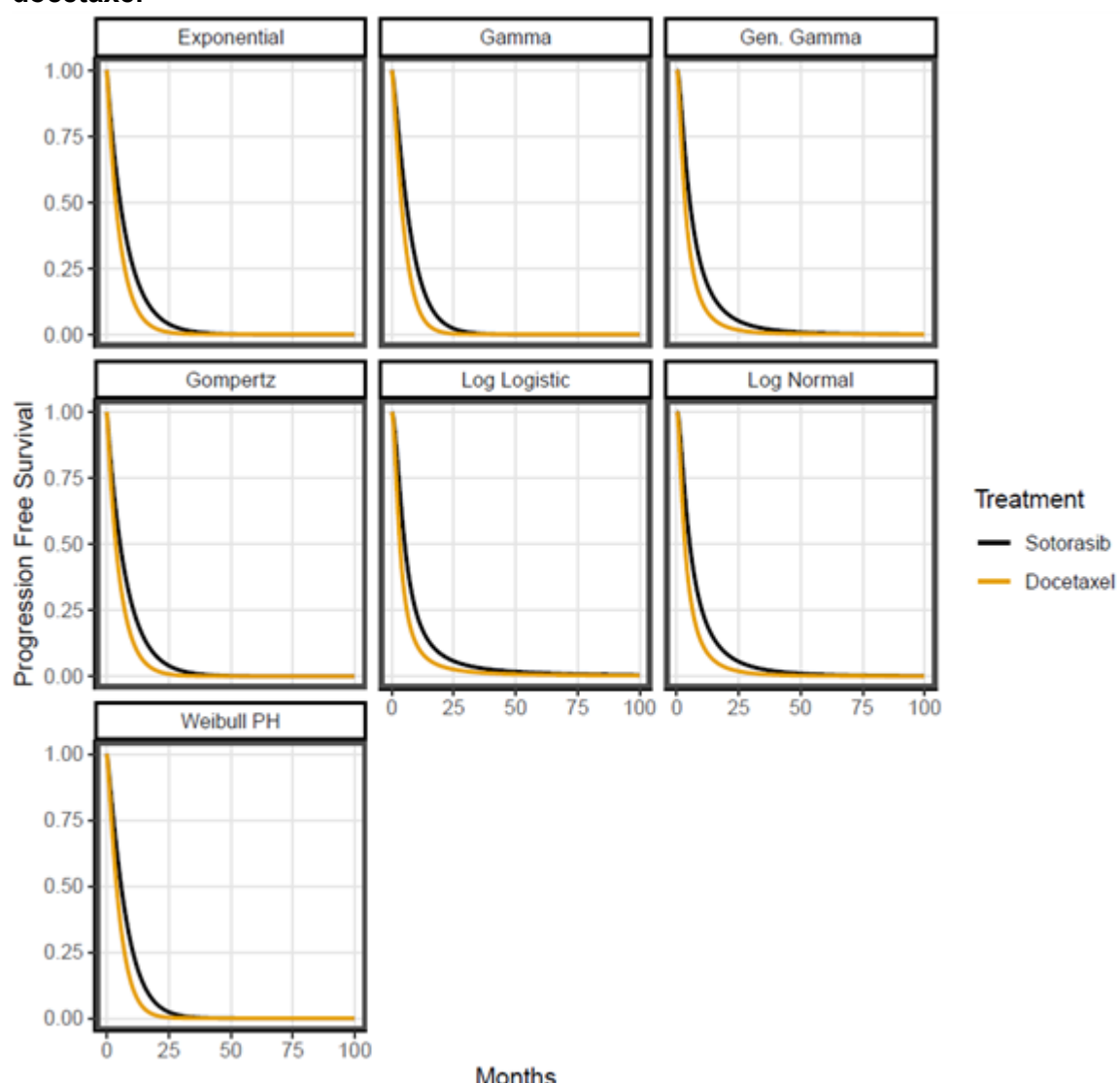
Table 53: Goodness-of-fit statistics jointly fitted PFS models for IA dataset

Model	Joint fit (unrestricted)		Joint fit (restricted)	
	AIC	BIC	AIC	BIC
Exponential	1531	1539	1531	1539
Gompertz	1533	1548	1533	1545
Weibull	1525	1541	1525	1536
Gamma	1518	1533	1517	1528
Generalised gamma	1494	1514	1494	1509
Log-logistic	1492	1507	1490	1502
Log-normal	1493	1508	1492	1504

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; IA, investigator assessed.
Note: Emboldened values indicate the best statistically fitting parametric distribution.

Plots showing jointly fitted restricted curves for sotorasib and docetaxel and for each of the seven distributions is presented in Figure 58. Sotorasib is shown to have a PFS benefit in all distributions.

Figure 58: PFS measured by IA jointly restricted fitted curves for sotorasib and docetaxel

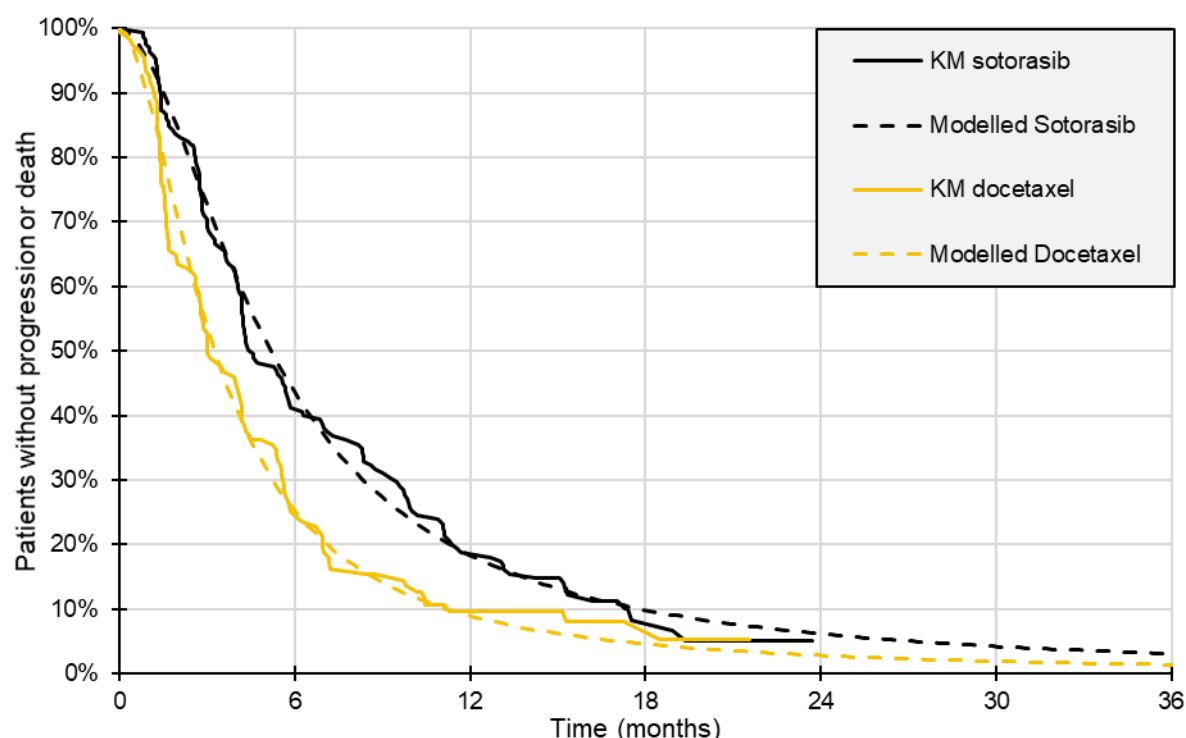


Abbreviations: IA, investigator assessed; PFS, progression-free survival; Q-Q, quantiles-quantiles.

A plot of the base-case PFS measured by IA modelled in the CEM versus the KM curve for sotorasib and docetaxel is shown in Figure 59. Visual inspection of the curves shows the modelled curves fit the KM curves well for the length of the trial – the area under the curve between the KM curve and the fitted curve is greater for sotorasib in the period 0 to 12 months and greater for docetaxel in the period 12 to 24 months. The Table 54 shows trial predictions for the proportion of patients remaining in the PF state, with sotorasib showing a large PFS benefit for all landmark timepoints. The long-term trial predictions for PFS shown in Table 55 predict sotorasib maintaining a small PFS benefit.

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Figure 59: KM plots and jointly fitted restricted log-logistic PFS measured by IA for sotorasib and docetaxel



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; IA, investigator assessment.

Table 54: PFS predictions for models using joint fitted restricted model

	Sotorasib	Docetaxel
2 months	86.4%	73.5%
6 months	43.7%	25.4%
12 months	18.5%	9.0%
24 months	6.2%	2.8%

Abbreviations: PFS, progression-free survival.

Table 55: Long-term PFS predictions for models using joint fitted restricted model

	Sotorasib	Docetaxel
3 years	3.1%	1.4%
4 years	1.9%	0.8%
5 years	1.3%	0.6%

Abbreviations: PFS, progression-free survival.

3.3.7.1.3 Time to treatment discontinuation

Patients are targeted to receive treatment with sotorasib or docetaxel until

progression, however patients may discontinue prior to progression. Therefore, it is Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

important to model the true time on treatment so that drug and administration costs were not overestimated. The model estimated time on treatment by taking a probability of patients remaining on treatment (while in the PF health state) and applying it to the proportion of patients remaining in the PF state. The probabilities of patients on treatment were calculated over three time periods to capture the different time on treatment (less than one month, between one month and one year and after one year), to reflect the changes in treatment continuation over time observed in CodeBreak 200 trial. The time periods were chosen to best represent the trends seen between PFS and time on treatment. Table 56 shows the proportions by treatment arm for each time period used within the model.

Table 56: Proportion of patients (in the PF state measured by IA) on treatment from CodeBreak 200

	Proportion of patients, % (95% CI)	
	Sotorasib	Docetaxel
Month 0-1		
Month 1-12		
Month 12+		

Abbreviations: IA, investigator assessment; PF, progression-free.

3.3.7.2 *Flatiron US real-world evidence*

Please refer to Appendix L.

3.4 *Measurement and valuation of health effects*

As described in Section 3.1, an SLR was conducted to identify published studies for evaluating cost-effectiveness, costs and resource use and HRQoL for treatments in NSCLC relevant to the decision problem. Full details on the methodology and findings of the SLR, including search terms, PRISMA diagram and outcomes are detailed in Appendix E and Appendix F.

The SLR and the SLR update identified five studies relevant for the current submission reporting on HRQoL of patients with NSCLC with *KRAS G12C* mutation or more broadly with any *KRAS* mutation. The results are described in Section 3.4.3. One study highlighted new source of disutilities for the current submission.

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The original submission for sotorasib (TA781) used utility data from the CodeBreak 100 study, which was primary source of clinical efficacy, safety and HRQoL (EQ-5D-5L) data. The analytical approaches for utility estimation included both estimation by time to death and by health state and the methods used in the following sections. In the base case analysis, the time to death utility approach was used to better reflect the deterioration of patient QoL at the end of life based on clinical expert feedback. Utilities based on health state (progression-free or progressed) were explored in a scenario analysis. A similar approach to estimation of health state utility values (HSUVs) was applied to the EQ-5D-5L data from CodeBreak 200 which was utilised in this submission.

3.4.1 Health-related quality-of-life data from CodeBreak 200

In CodeBreak 200, the EQ-5D-5L questionnaire was administered prior to any clinical assessments and after receiving study medication at the beginning of each 3week treatment cycle for the first seven cycles, and every 6 weeks subsequently for as long as the patient remained on treatment. The EQ-5D-5L was also administered at end of treatment visit as well as at the safety follow-up visit (~30 days after the last dose of sotorasib).

The analysis uses the EQ-5D-5L analysis set, consisting of all subjects in the Phase 3 FAS (all randomised subjects from the ITT population) with a non-missing utility index (i.e. all five dimensions complete) for at least one timepoint across the whole study period.

Descriptive statistics for the EQ-5D-5L scores by visit were produced for each utility index (e.g. number of observations, mean, SD, lower and upper CI). Data analyses included an initial descriptive analysis of the index score for (a) time-to-death categories (>6 months, 3 to 6 months, 1 to 3 months and <1 month before death) and (b) by health state based on disease progression (progression-free and post-progression).

The descriptive statistics use each observation as an independent variable, however a plot of mean EQ-5D for each visit by treatment arm can be presented to understand change over time and differences between the treatment arms.

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Data on completion rates are presented in Appendix J.

3.4.2 Mapping

The NICE reference case stipulates the EQ-5D-3L instrument. It was therefore necessary to map the trial outcomes from the 5-level instrument to the 3-level instrument to align with the NICE reference case. This was done using the NICE recommended crosswalk algorithm using the UK tariff (127).

3.4.3 Health-related quality-of-life studies

A search for studies reporting HRQoL in patients with the *KRAS G12C* mutation or more broadly with any *KRAS* mutation were conducted as part of the original economic SLR and SLR update. Five studies were relevant for the current submission (see Appendix F).

Out of five identified HRQoL studies, two were published as an abstract (128, 129) and three as a full publication (69, 113, 130). The study by Yang et al, 2016 was identified via the original SLR.

Yang et al, 2016 (128) reported HRQoL in patients with advanced NSCLC which investigated the effect of including biomarker testing to guide individual therapy. However, the scale used in the HRQoL score was not reported. Chouaid et al, 2025 (130) reported real world evidence on HRQoL outcomes based on *KRAS* mutation status in patients with NSCLC receiving second line or later treatment, however, the results were reported for patients in France and Germany. Felip et al, 2024 (129) reported on the initial HRQoL results from the KRYSTAL-12 RCT, which compares adagrasib and docetaxel in patients with *KRAS G12C*-mutated NSCLC, who had previously received both platinum-based chemotherapy and anti-PD-L1 immunotherapy. The value set used in the study to develop utilities was not reported.

Zhu et al, 2024 (113) utilised the health state utility values from an international study in NSCLC. The values were for China and the US, however, the source (Nafees et al, 2017 (131)) reported disutilities for the UK population for AEs included in the current submission. Please see Table 59 for updated disutilities.

The study by Waterhouse et al, 2024 (69) reported PROs, including HRQoL, from CodeBreak 200 for sotorasib and docetaxel. The study utilised a range of validated questionnaires to capture patient HRQoL and symptom burden. Overall, patients receiving sotorasib reported lower burden of side effects and symptom severity than patients receiving docetaxel. The publication did not report utility values for specific populations. Thus, the EQ-5D-5L data from CodeBreak 200 for the UK patients utilised in this submission was sourced from a de novo utility analysis (see Section 3.4.4 (69, 129, 130)).

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

Descriptive statistics for the EQ-5D scores by visit were produced for each utility index (e.g. number of observations, mean, SD, lower and upper CI) as described in Section 3.4.1. The descriptive statistics were analysed by progression status and time-to-death for both treatment arms.

A study by Hatswell et al, 2014 (132) suggested that time left alive is a better determinant of patient QoL compared to disease progression in patients with advanced melanoma. Time-to-death utilities have also been used solely, or in combination with progression-based utilities, in recently published cost-effectiveness analyses of NSCLC treatments and accepted in health technology appraisal (HTA) submissions in Canada, the US and by NICE in the UK (133-135).

For CodeBreak 200 it could be shown that time-to-death utilities better explain the variability of reported QoL estimates, whereas the health-state utility approach explained solely 2.3% of the uncertainty (i.e. the total sum-of-squares of error), the time-to-death approach explained 10.2% – more than four times as much uncertainty (assessment based on UK tariffs, may vary slightly by utility set applied).

In contrast, based on methodological restrictions it was not possible to combine the progression status and time-to-death utilities approach. This is due to the model structure of PSM models: they do not follow individual patients but solely report patient shares over time. Whereas the health-state approach corresponds to a cross-sectional analysis for a given point in time (vertical line in of the OS curve) the time-

to-death approach corresponds to a cross-sectional analysis for a given share of subjects being alive (horizontal line in the OS curve).

Based on the above, the model base case assumes time-to-death utilities separated by treatment arm (Table 57). The table shows an improvement in the QoL for all health states for sotorasib compared with docetaxel. An alternative approach, with utilities per progression status, is presented in Table 58 and was explored in scenario analysis.

Table 57: Time-to-death utility inputs included in the model

Health state / event	Mean	SE	95% CI	Reference
Sotorasib				
Utility more than 6 months to death	■	■	■	CodeBreak 200 EQ-5D-5L analyses using UK crosswalk tariffs (the primary data cut)
Utility between 3 and 6 months to death (vs more than 6 months)	■	■	■	
Utility between 1 and 3 months to death (vs more than 6 months)	■	■	■	
Utility in last month of life (vs more than 6 months)	■	■	■	
Docetaxel				
Utility more than 6 months to death	■	■	■	CodeBreak 200 EQ-5D-5L analyses using UK crosswalk tariffs (the primary data cut)
Utility between 3 and 6 months to death (vs more than 6 months)	■	■	■	
Utility between 1 and 3 months to death (vs more than 6 months)	■	■	■	
Utility in last month of life (vs more than 6 months)	■	■	■	

Abbreviations: CI, confidence interval; SE, standard error

Analysis based on CodeBreak 200 reported EQ-5D-5L from 02 August 2022 data cut.

Table 58: Utility inputs per progression status included in the model

Health state / event	Mean	SE	95% CI	Reference
Sotorasib				
PF	■	■	■	CodeBreaK 200 EQ-5D-5L analyses using UK crosswalk tariffs (the primary data cut)
Progressed disease	■	■	■	
Docetaxel				
PF	■	■	■	CodeBreaK 200 EQ-5D-5L analyses using UK crosswalk tariffs (the primary data cut)
Progressed disease	■	■	■	

Abbreviations: CI, confidence interval; PF, progression-free; SE, standard error.

3.4.5 Adverse reactions

Disutilities associated with grade 3/4 AEs were included in a scenario analysis and not included in the base case of the model to avoid double counting of AE impact on utilities when utilising time-to-death utility values. The AE disutilities were estimated using the incidence of grade 3 and 4 AEs by treatment, multiplied by the associated AE disutilities. AE disutilities were sourced from the literature when available or from NICE technology appraisals (Table 59). Disutilities associated with AEs were assumed to last for four weeks.

For diarrhoea, fatigue, febrile neutropenia and neutropenia, the AE disutilities were sourced from the updated study by Nafees et al, 2017 (131). SE were assumed equal to 5% of the input value due to a lack of reporting in the study. The disutilities are higher than reported in the previous study (Nafees et al 2008 (136)), however, Nafees et al, 2017 (131) utilised the time trade-off method, rather than standard gamble as in Nafees et al, 2008 (136), which is a preferred method as reported in NICE TSD 11 (137).

Table 59: Utility decrements per AE

AE	Mean disutility (95%CI)	Source
Anaemia	0.073 (0.058; 0.088)	Westwood 2014 (138)
Decreased neutrophils	0.000 (0.000; 0.000)	Assumption, value used in NICE TA484 (139)

AE	Mean disutility (95%CI)	Source
Decreased white blood cell count	0.050 (0.040; 0.060)	Assumption, value used in NICE TA347 (67), TA520 (140) and TA484 (139)
Diarrhoea	0.320 (0.289; 0.351)	Nafees et al. 2017 (131)
Dyspnoea	0.050 (0.026; 0.074)	Doyle et al. 2008 (141)
Fatigue	0.410 (0.370; 0.450)	Nafees et al. 2017 (131)
Febrile neutropenia	0.500 (0.451; 0.549)	Nafees et al. 2017 (131)
Increased ALT	0.050 (0.040; 0.060)	Assumption, value used in NICE TA484 (139)
Increased AST	0.000 (0.000; 0.000)	Assumption due to AST elevation being asymptomatic
Neutropenia	0.460 (0.415; 0.505)	Nafees et al. 2017 (131)
Pneumonia	0.008 (0.006; 0.010)	Marti et al. 2013 (142)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

3.5 ***Cost and healthcare resource use identification, measurement and valuation***

As described in Section 3.1, an SLR was conducted to identify published studies for evaluating cost-effectiveness, costs and resource use and HRQoL for treatments in NSCLC relevant to the decision problem. Full details on the methodology and findings of the SLR, including search terms, PRISMA diagram and outcomes are detailed in Appendix E and Appendix G.

A total of 23 studies were identified in the original and updated SLR. Of these, seven studies (five abstracts (109, 112, 114, 143, 144) and two full publications (113, 145)) examined resource use or costs associated with *KRAS G12C* mutation or any other *KRAS* mutation. However, no studies were considered relevant for this appraisal. One study investigated the costs associated with genetic testing (145) and one study costs related to hepatotoxicity management (112). Insufficient details were reported in four studies reporting on various type of costs, including healthcare related or

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treatment costs, for patients with NSCLC and *KRAS* G12C mutation (109, 114, 143, 144). Finally, one study reported the costs associated with treatment with sotorasib and docetaxel. However, the values were reported from the US and Chinese perspective, thus, considered not relevant (113).

3.5.1 Intervention and comparators' costs and resource use

The drug acquisition costs per treatment are presented in Table 60 below. The unit cost for sotorasib (list price) was sourced from the technology appraisal guidance for sotorasib (TA781) (9), whereas the docetaxel unit cost was sourced from the electronic market information tool (eMIT) (146). The sotorasib dose of 960 mg per day is consistent with the license and the dosing regimen in CAS RWE study and CodeBreak 200.

To account for temporary treatment interruptions, dose reductions, and/or missed doses, the model applies for all treatments the relative dose intensity (RDI). The RDI for both sotorasib and docetaxel was obtained from the CodeBreak 200 CSR using the SAS (68).

Table 60: Unit costs associated with the technology in the economic model

Drug	Unit	Unit cost (£)	Reference	Dose	RDI	Cost per month (£) [‡]
Sotorasib	240 x 120 mg (or 120 x 240 mg) tablets	6,907.35	TA781 (9)	960 mg per day	86.42% [†]	2,129.76
Docetaxel	160 mg per vial	19.70	eMIT (146)	75 mg/m ² on day of treatment	90.40% [†]	21.90 [§]

Abbreviations: BNF, British National Formulary; eMIT, electronic market access tool; RDI, relative dose intensity.

[†] CodeBreak 200 phase 3 NSCLC cohort, safety analysis set Table 14-5.1.1 (68)

[‡] Calculated from CEM.

[§] Docetaxel cycle cost is based on cost per mg x dose per administration (75 mg/m²) x body surface area (1.81 m²).

The model includes the administration costs associated with the IV delivery of the comparator treatments. The cost was obtained from standard NHS England reference cost sources (Table 61) and were applied per IV administration. It was assumed there were no costs associated with oral administration of sotorasib.

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Table 61: Administration costs

Drug	Cost (£)	Source
Sotorasib	0.00	Assumption
Docetaxel (per administration)	394.17	NHS Reference Costs 2023/2024 [SB12Z] (147)

Abbreviations: NHS, National Health Service.

3.5.2 Health-state unit costs and resource use

Disease monitoring and management costs were based on previously accepted values from TA781 for sotorasib (9). The costs align with the model structure and reflect healthcare resource utilisation (HCRU) in both progression-free and post-progression health states, as well as one-off costs associated with treatment initiation and at the point of progression. All costs were sourced from the latest available NHS Reference costs 2023/24 (147) or PSSRU 2024 (148).

A summary of the costs used in the economic model are presented in Table 62. Full details of the resource assumptions and unit costs are provided in Appendix M.

Table 62: Health state and one-off disease management costs per model cycle

	Cost per model cycle (£)	Source
Health state		
Progression-free	77.53	NHS Reference Costs 2023/2024 (147); NICE TA347 (67)
Post progression	41.89	
Event		
At treatment initiation	881.58	NHS Reference Costs 2023/2024 (147); NICE TA347 (67)
At progression	157.62	

Abbreviations: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

3.5.3 Biomarker testing

KRAS testing is routinely commissioned by NHS in NSCLC (64) and no additional tests beyond those used in the routine diagnostic work up and management of patients with NSCLC are required. Testing costs were also not included in the currently ongoing appraisal of adagrasib (115). Therefore, the genetic costs associated with *KRAS* testing were not included in the base case, but were

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considered in a scenario analysis; the input costs of genetic testing are reported in Appendix M.

3.5.4 Adverse reaction unit costs and resource use

The AEs included in the economic model are previously described in Section 3.4.5. The unit costs were sourced from the NHS Reference Costs 2023/2024 (147). The HRG codes for most of the AEs were based on the ERG codes reported in the committee papers for NICE GID-TA11423 (in development) (149). For dyspnoea and pneumonia, the HRG4+ Payment Grouper was used to find Healthcare Resource Group (HRG) codes based on the ICD-10 codes. The costs for all complications and comorbidities (CC) codes were included. AEs and associated costs are outlined in Table 63.

Table 63: AEs and associated costs

Event	Unit cost (£)	Source [†]
Anaemia	2,292.02	HRG codes SA01G-SA01K (Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, CC score 0-8+) from Table 29 of the ERG report (Anaemia; NICE GID-TA11423) (147, 149)
Decreased neutrophils	159.94	Code 800 (Clinical Oncology Service) from Table 29 of the ERG report (Neutrophil count decreased; NICE GID-TA11423) (147, 149)
Decreased white blood cell count	159.94	Assumed the same approach as for 'Decreased neutrophils' based on NICE GID-TA11423
Diarrhoea	4,787.87	HRG codes FD10E-FD10H (Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, CC score 0-9+) from Table 29 of the ERG report (Diarrhoea; NICE GID-TA11423) (147, 149)
Dyspnoea	3,531.54	HRG codes DZ19J-DZ19K (Other Respiratory Disorders with Single Intervention, with CC score 0-5+) based on the results from HRG4+ Payment Grouper utilising R060 ICD-10 code (Dyspnoea). Assumed a single intervention codes as for febrile neutropenia and diarrhoea. (147, 150)
Fatigue	2,292.02	HRG codes SA01G-SA01K (Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, CC score 0-8+) from Table 29 of the ERG report (Fatigue; NICE GID-TA11423) (147, 149)
Febrile neutropenia	5,343.40	HRG codes WH07C-WH07D (Infections or Other Complications of Procedures, with Single Intervention, CC score 0-2+) from Table 29 of the ERG report (Febrile neutropenia; NICE GID-TA11423) (147, 149)
Increased ALT	159.94	Assumed the same approach as for 'Decreased neutrophils' based on NICE GID-TA11423
Increased AST	159.94	Assumed the same approach as for 'Decreased neutrophils' based on NICE GID-TA11423

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Event	Unit cost (£)	Source [†]
Neutropenia	1,534.73	HRG codes SA08G-SA08J (Other Haematological or Splenic Disorders, CC score 0-6+) from Table 29 of the ERG report (Neutropenia; NICE GID-TA11423) (147, 149)
Pneumonia	4,983.35	HRG codes DZ11N-DZ11Q (Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 0-13+) based on the results from HRG4+ Payment Grouper utilising J189 ICD-10 code (Pneumonia). Assumed a single intervention codes as for febrile neutropenia and diarrhoea. (147, 150)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CC, complications and comorbidities; ERG, Evidence Review Group; HRG, Healthcare Resource Group.

† Please note that NICE GID-TA11423 is currently in development with expected publication date of 6th of August 2025.

3.5.5 Subsequent treatment costs

The costs of subsequent treatment were included in the economic model as a one-off cost at disease progression (Table 64).

The distribution of subsequent treatments for patients who progress on sotorasib were informed by UK clinical experts during the original submission for sotorasib in this indication (TA781) who advised that a greater proportion of patients are likely to be able to tolerate active treatment and that subsequent docetaxel would be preferred over rechallenge with platinum-based chemotherapy regimens.

The duration of subsequent treatments used in the economic model was 3.3 months and is consistent with previous assumptions used in NICE TA347 and TA428 (67, 151). Detailed costs used to derive subsequent treatments were sourced from eMIT and are presented in Appendix I. Best supportive care was assumed to have no cost in the model.

Table 64: Subsequent treatment costs

Subsequent treatment	BSC	Platinum-based	Docetaxel	Source
Sotorasib (%)	50%	10%	40%	Assumption based on clinical expert feedback
Docetaxel (%)	70%	30%	0%	NICE TA347 – assumption (67)
Cost of subsequent treatment (£)	0	3,641.21	1,957.58	Calculation (Appendix I)

Abbreviations: BSC, best supportive care; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

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3.5.6 Terminal care costs

A one-off cost is applied to those patients at the time of dying to reflect the cost of terminal care. The resource consumption reflects treatment received in various care settings as reported in the original submission for sotorasib (TA781) (9) and based on the values used in the NICE TA374 and TA428 (151, 152). These costs are assumed to be the same for all treatments. The terminal care cost used in the model is summarised in Table 65 and detailed calculations are presented in Appendix M.

Alternative terminal costs from literature (Round et al, 2015 (153)) were tested in a scenario analysis. The uplifted costs reported in GID-TA11432 (115) were further adjusted to the current year (2023/2023) utilising the inflation indices reported in the PSSRU Unit Costs of Health and Social Care 2024 (148) (Appendix M).

Table 65: Terminal care costs

Cost type	Unit cost (£)	Source
Terminal care	4,489.57	PSSRU 2024 (148), aligned with TA347 and TA428 (151, 152)

3.6 Severity

NSCLC accounts for approximately 80–85% of lung cancers in the UK (2). There are several key drivers of tumour proliferation and growth in patients with NSCLC for which targeted therapies have been developed. However, there are other oncogenic mutations, with the *KRAS G12C* mutation being the most common mutation in the *KRAS* gene in NSCLC (4).

For those patients, outcomes with non-targeted treatments are associated with poor prognosis, as described in Section 1.3.1.2.2. Targeted treatment options in the UK are very limited (4, 26, 27); sotorasib is recommended for use within the Cancer Drugs Fund (9) and adagrasib is undergoing evaluation by NICE (115). There is a significant need for a highly targeted, effective, tolerable, and convenient treatment that improves clinical outcomes and QoL for patients with *KRAS G12C*-mutated NSCLC. Thus, the current evaluation applies a severity modifier as described in the NICE manual (116) and DSU TSD 23 (154).

Summary features of the quality-adjusted life year (QALY) shortfall analysis are presented in Table 66. The QALY weighting used in the only other appraisal in this indication are presented in Table 67.

Table 66: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Age at baseline (years)	63.50	Section 3.3.1
Gender (female; %)	40.9%	

Abbreviations: QALY, quality-adjusted life year.

Table 67: Summary list of QALY shortfall from previous evaluations

TA	Absolute shortfall	Proportion shortfall	QALY weighting
GID-TA11432 (115)	10.76	95.37%	1.7

Abbreviations: QALY, quality-adjusted life year.

Table 68 presents the base case analysis undiscounted life years for patients receiving docetaxel. Please note that the utility values per health state were not used in the base case. Instead, this submission utilised time-to-death utilities reported in Section 3.4.4.

Table 68: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value	Undiscounted life years (docetaxel)
Progression-free	N/A	0.66
Post-progression	N/A	0.29

Abbreviations: QALY, quality-adjusted life year.

The QALY Shortfall Calculator (155) was used to estimate absolute and proportional shortfall and the QALY weight. QALY shortfall calculations were estimated using a reference case of the calculator, including ONS-reported general population mortality rates and general population utility values.

A summary of the results is presented in Table 69 with the estimated QALY weight at 1.7 based on proportional shortfall calculations. In addition, during the original submission for sotorasib, the committee agreed that sotorasib meets the short life expectancy criterion for end of life. Considering all above and a positive

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recommendation from the External Assessment Group (EAG) to apply the QALY weight of x1.7 for adagrasib in the same indication (115), the current submission applies a QALY weight of 1.7 to the base case results.

Table 69: Summary of QALY shortfall analysis[†]

Treatment	Absolute shortfall	Proportional shortfall	QALY weighting
Docetaxel	10.89	95.03%	1.7

Abbreviations: QALY, quality-adjusted life year.

[†] Please note that the average for absolute and proportional shortfall was calculated based on population aged 63 and 64 years old to align with the population in the model (average age of 63.5 years).

3.7 Summary of base-case analysis inputs and assumptions

3.7.1 Summary of base-case analysis inputs

A summary of the variables applied in the economic model is presented in Appendix N.

3.7.2 Assumptions

Key assumptions in the base case are outlined in Table 70.

Table 70: The base case assumptions

Assumption	Assumption description	Rationale
Time horizon	20-year (lifetime) time horizon	The time horizon was considered sufficient to capture all costs and benefits over the lifetime of the modelled population
Comparator	Primary comparator was docetaxel	Docetaxel is the standard of care for previously treated (i.e. 2L) NSCLC Nintedanib plus docetaxel was not explored in this submission as only a small proportion of patients might receive it in clinical practice (as described in Section 3.2.3).
Treatment position	Positioned in 2L+	Modelled patients have received previous treatment for advanced Stage IIIb/IV NSCLC
Population	Adults with advanced NSCLC with <i>KRAS G12C</i> mutation who have been previously treated for advanced disease	The population is generalisable to the UK clinical practice and reflects a population with minimal treatment options
OS	OS is modelled using a jointly-fitted generalised gamma distribution for docetaxel and sotorasib based on the results of the CAS RWE study	The PH assumption was not found to be violated, and generalised gamma provided a combination of good statistical and visual fit
PFS (TTNTD)	TTNTD from CAS RWE study is used as a proxy for PFS and modelled using a jointly-fitted	Time to next treatment or death is a suitable proxy for disease progression status as it is reflective of clinical practice, i.e. treatment to

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Assumption	Assumption description	Rationale
	generalised gamma distribution for docetaxel and sotorasib	progression. The PH assumption was not found to be violated, and generalised gamma provided a combination of good statistical and visual fit
TTDD	TTDD from CAS RWE study is modelled using independently-fitted generalised gamma models for docetaxel and sotorasib	The PH assumption appeared to be violated, and so curve selection was performed based on a combination of statistical and visual goodness-of-fit
HRQoL	QoL is appropriately captured using time-to-death approach	Time-to-death utility approach used in the base case, supported by literature demonstrating better quality of life discrimination in advanced tumours
HRQoL	Utility decrement for IV administration	Any utility decrement for IV therapy is assumed to be captured in the separated utility values from CodeBreak 200. A disutility applied for IV administration for docetaxel is tested in the scenario analysis.
HRQoL	HRQoL impact of adverse events is captured directly	Proximity to death provides a better estimate of utility than the traditional health state-based approach, although health state-based utilities are explored in a scenario analysis.
AEs	Grade 3/4 treatment-related AEs with an incidence of $\geq 5\%$ in any study were included	Sensitivity analysis for treatment-emergent AEs
Costs	Disease management costs are generalisable	Disease management costs are consistent with previous NICE appraisals in NSCLC (67, 151) and reflect the model structure and resource utilisation
Costs	No costs are assumed for <i>KRAS</i> mutation testing	<i>KRAS</i> testing is routinely commissioned by NHS in NSCLC (64) and no additional tests beyond those used in the routine diagnostic work up and management of patients with NSCLC are required. Inclusion of genetic testing is explored in scenario analysis
Costs	Treatment duration approach is appropriate	Disease progression is the major driver for discontinuation. On average patients may discontinue prior to progression

Abbreviations: AE, adverse event; CAS, cancer analysis system; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intention to treat; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PH; proportional hazards; QoL, quality of life; RWE, real-world evidence; SAS, safety analysis set; TTDD, time to treatment discontinuation or death.

3.8 *Base-case results*

3.8.1 **Base-case incremental cost-effectiveness analysis results**

The deterministic model base case investigated the comparison between sotorasib and docetaxel with the deterministic results presented in Table 71 and Table 72.

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Using a 20-year time horizon, the incremental total life-year gain of sotorasib versus docetaxel was [REDACTED] years. The discounted incremental costs of £[REDACTED] and incremental QALYs of [REDACTED] resulted in an incremental cost-effectiveness ratio (ICER) of £26,276 versus docetaxel. This is below the willingness-to-pay threshold of £30,000 per QALY considering severity modifier of 1.7. Please see Appendix H for the clinical outcomes and disaggregated results.

Table 71: Base-case results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	11,731	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	26,276

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 72: Net health benefit (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7)	NMB at £20,000	NMB at £30,000
Docetaxel	11,731	■	-	-	-	-
Sotorasib	■	■	■	■	-4,610	2,735

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NMB, net monetary benefit.

3.9 Exploring uncertainty

3.9.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken to explore the uncertainty of all model parameters and their associated impact on cost-effectiveness results. To ensure convergence, 3,000 iterations were used. The total costs and QALYs were recorded for each iteration and averaged. PSA results for the comparison to docetaxel are presented in Table 73. The deterministic ICER for sotorasib compared to docetaxel (£26,276) is in line with the PSA results of £27,002 confirming that the results are robust to parameter uncertainty.

Table 73: Probabilistic base-case results: sotorasib versus docetaxel

Technologies	Total costs (£) (95% CI)	Total LYGs (95% CI)	Total QALYs (95% CI)	Incremental costs (£)	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	11,611 (10,659; 12,648)	■ (0.81; 1.05)	■ (0.50; 0.66)	-	-	-
Sotorasib	■ (17,365; 40,025)	■ (1.21; 1.59)	■ (0.87; 1.15)	■	■	27,002

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

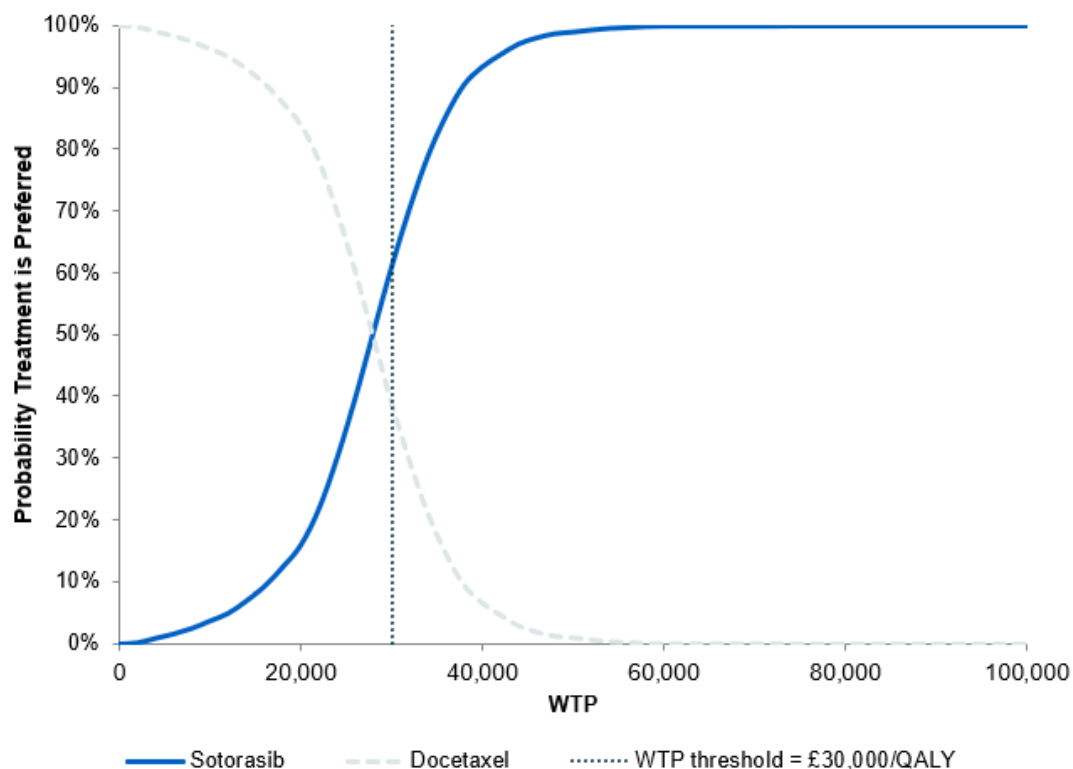
Figure 60 represents the scatter plot of the incremental costs and QALYs from the PSA results based on 3,000 iterations. As shown in the cost-effectiveness acceptability curve (Figure 61) sotorasib has a 61.0% probability of being cost-effective versus docetaxel considering the £30,000 WTP threshold.

Figure 60: Cost-effectiveness plot for sotorasib versus docetaxel



Abbreviations: QALY, quality-adjusted life year

Figure 61: Cost-effectiveness acceptability plot for sotorasib versus docetaxel



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

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3.9.2 Deterministic sensitivity analysis (DSA)

A series of one-way sensitivity analyses (OWSA) were performed to evaluate the sensitivity of the model ICER to individual inputs, holding all else constant. In the DSA, the upper and lower bounds of a parameter were taken from their 95% CIs if these were available from the data source. When such information was not available, the upper and lower bounds were assumed to be within $\pm 20\%$ for all base case values. Some parameters are not appropriate to vary independently, for example, parameters for parametric survival models; these values were not included in the DSA.

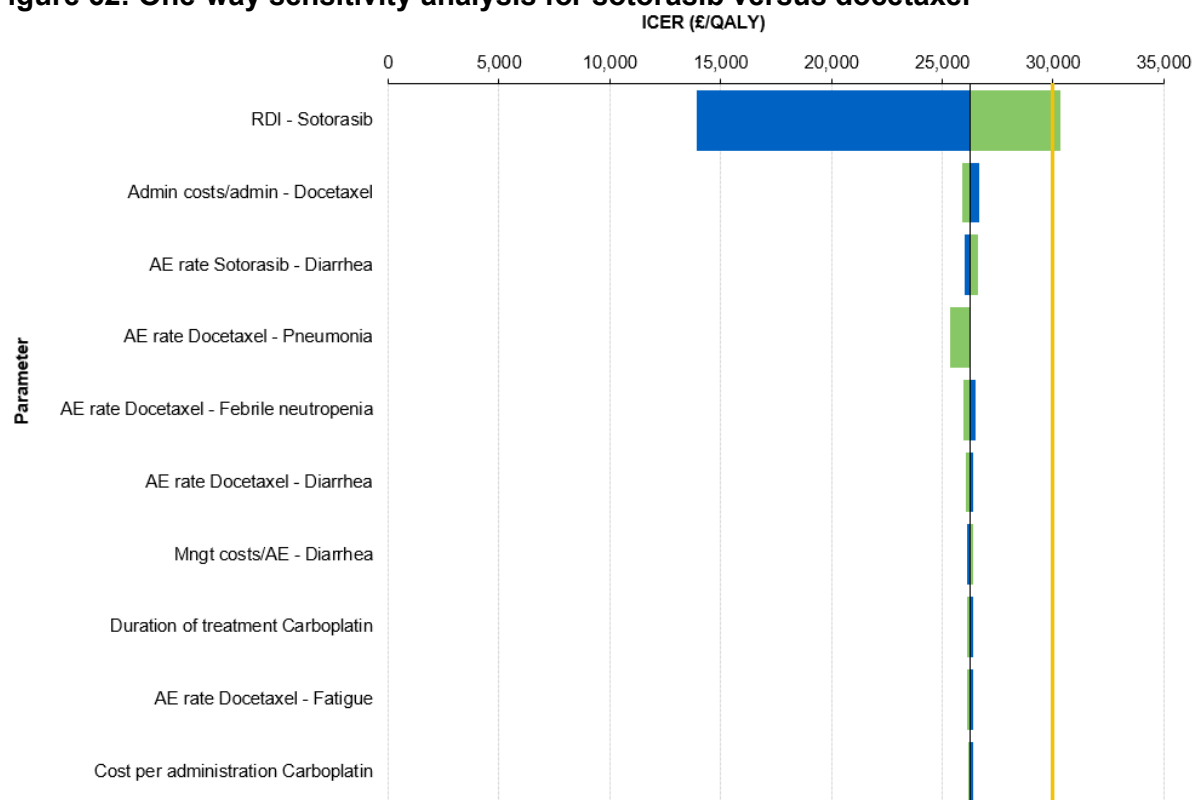
A summary of the variables and distributions applied in the economic model is presented in Appendix M, including references to the corresponding sections in the submission where each is explained in more detail.

Each value was varied based on its uncertainty parameters.

Figure 62 presents the tornado diagram for the top ten parameters in terms of ICER impact which were varied in the OWSA. Parameters are shown in descending order of ICER sensitivity.

These results demonstrate that the ICER is most sensitive to RDI of sotorasib. All other analyses had little impact on the results.

Figure 62: One-way sensitivity analysis for sotorasib versus docetaxel



Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; RDI, relative dose intensity; QALY, quality-adjusted life year

3.9.3 Scenario analysis

The list of scenario analyses performed is included in Table 74 with the deterministic results presented in Table 75.

Table 74: List of scenario analyses

Scenario #	Parameter / setting	Base case	Scenario
1	Source of clinical data: CAS RWE study with Flatiron analysis OS for docetaxel	CAS RWE study (jointly fitted generalised gamma for OS, PFS and TTDD)	PFS and TTDD as per CAS RWE study (jointly fitted generalised gamma) For OS, generalised gamma for sotorasib and docetaxel estimated with a constant HR from the Flatiron 2L+ RWE
2	Source of clinical data: CAS RWE study with PFS from CodeBreak 200		OS and TTDD as per CAS RWE study (jointly fitted generalised gamma) PFS: jointly fitted log-logistic distributions from CodeBreak 200 IA

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Scenario #	Parameter / setting	Base case	Scenario
3	Source of clinical data: CodeBreak 200 with Flatiron analysis OS for docetaxel		OS for sotorasib: individually fitted log-normal distribution from CodeBreak 200 OS for docetaxel: estimated with a constant HR from the Flatiron 2L+ RWE PFS: jointly fitted log-logistic distributions from CodeBreak 200 IA TTDD: CodeBreak 200 PFS ToT event rate
4	Source of clinical data: CodeBreak 200 primary analysis		OS for sotorasib: individually fitted log-normal distribution from CodeBreak 200 OS for docetaxel: estimated with a constant HR from the CodeBreak 200 adjustment for crossover (primary analysis) PFS: jointly fitted log-logistic distributions from CodeBreak 200 IA TTDD: CodeBreak 200 PFS ToT event rate
5	Distributions used for the CAS RWE study	Jointly fitted generalised gamma for OS, PFS and TTDD	Jointly fitted log-logistic for OS, PFS and TTDD
6	Inclusion of per progression utilities	Time-to-death utility approach	Per progression utilities
7	Inclusion of genetic testing costs (Hamblin 2017 (156))	Genetic costs not included (£0)	Genetic costs included (£401.82)
8	Alternative source of terminal costs	Terminal costs aligning with TA781	Terminal costs sourced from Round 2015 (153)

Abbreviations: CAS, Cancer Analysis System; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence; TTDD, time to discontinuation or death; ToT, time on treatment

Table 75: Deterministic scenario analysis results

Scenario #	Incremental versus docetaxel				Severity modifier
	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALYs)	
Deterministic base case	■	■	■	26,276	1.7
1	■	■	■	25,735	
2	■	■	■	25,884	
3	■	■	■	16,888	
4	■	■	■	25,352	

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Scenario #	Incremental versus docetaxel				Severity modifier
	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALYs)	
5	■	■	■	26,790	
6	■	■	■	27,732	
7	■	■	■	28,444	
8	■	■	■	26,250	

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

A comparison of sotorasib to docetaxel was performed utilising other clinical data (scenarios #1 to #4). Scenario #1 utilised the base case with OS for docetaxel estimated utilising a constant HR from the Flatiron 2L+ RWE. Scenario #2 utilised the base case with PFS estimated utilising jointly fitted log-logistic distributions from CodeBreak 200 IA to check the validity of using proxy for PFS in the CAS RWE study. In scenario #3 and #4, the data from CodeBreak 200 clinical trial was used for OS, PFS and TTDD. The scenarios differed in approach to estimate OS for docetaxel i.e., utilising Flatiron 2L+ or CodeBreak 200 HRs.

For scenarios #1 and #2, incremental total life-year gain of sotorasib versus docetaxel was ■ and ■ years, respectively. The discounted incremental costs of ■ and ■ and incremental QALYs of ■ and ■ resulted in an ICER of £25,735 and £25,884 versus docetaxel, respectively. Thus, changing the method of estimating OS for docetaxel or using proxy for PFS in the CAS RWE study had small impact on ICER.

For scenario #3, incremental total life-year gain of sotorasib versus docetaxel was ■ years, discounted incremental costs of ■ and incremental QALYs of ■ resulting in an ICER of £16,888 versus docetaxel. In this scenario, OS for patients on docetaxel is substantially reduced impacting the LYG and QALY results.

For scenario #4, incremental total life-year gain of sotorasib versus docetaxel was ■ years, discounted incremental costs of ■ and incremental QALYs of ■ resulting in an ICER of £25,352 versus docetaxel aligning well with the base case. The CAS RWE analysis, however, includes the data from patients treated with

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sotorasib and docetaxel in clinical practice in the UK which better resembles patient outcomes than trial data.

In addition to alternative clinical data sources, alternative distribution from the CAS RWE study was tested in scenario analysis (#5). The best fitting distribution for the OS, PFS and TTDD of jointly fitted log-logistic based on the AIC and BIC criteria was used instead of generalised gamma. The results were comparable to the base case analysis with the incremental total life-year gain of sotorasib versus docetaxel of [REDACTED] years, discounted incremental costs of [REDACTED] and incremental QALYs of [REDACTED] resulting in an ICER of £26,790 versus docetaxel.

Inclusion of utility values based on the progression status (scenario #6), inclusion of genetic costs (scenario #7) or using alternative source of terminal costs (scenario #8) were also tested in scenario analysis. The results were comparable to the base case analysis with no substantial deviations in incremental LYG, QALY or cost results (Table 75).

3.9.4 Subgroup analysis

As mentioned in Section 3.2.1, subgroup analyses were not included in this submission.

3.10 Benefits not captured in the QALY calculation

All benefits are captured in the QALY calculations.

3.11 Validation

3.11.1 Validation of cost-effectiveness analysis

The current model was validated using the model inputs from the original TA781 submission and generated consistent results.

Additionally, as summarised in Section 3.3.4 and 3.3.5, modelled OS and TTNTD are similar to the reported values from the CAS RWE study. The scenario analysis (Section 3.9.3) using the clinical results from the CodeBreak 200 provided comparable results to the base case further supporting the robustness of the results generated utilising the CAS RWE study.

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Finally, the selection of the parametric models used in the economic analysis was performed according to the guidance published in NICE DSU TSD 14 (119).

3.11.2 Quality control

The model was subjected to systematic examination of calculations and Visual Basic for Applications coding accuracy by modelling experts in and outside of Amgen who did not build the model. A cost-effectiveness model verification checklist guided the quality control process, which, among others checks, included extreme value analysis and tracing of calculations.

3.12 Interpretation and conclusions of economic evidence

- Based on the results from the CAS RWE study, sotorasib is a clinically effective treatment option for *KRAS G12C*-mutated NSCLC which substantially improves life-years and QALYs compared with docetaxel in the UK clinical setting.
- The efficacy and safety of sotorasib observed in the CAS RWE study was based on patients treated within the NHS setting, therefore, is generalisable to UK clinical practice. The primary analysis is well-aligned to the decision problem and reflective of UK clinical practice. Furthermore, the model was developed using cost sources most relevant to the NHS in England.
- The most clinically plausible extrapolations of TTNTD, as a proxy for PFS, and OS data were selected for the base case analyses and extensive scenario analyses were presented with only a small impact to the results of the analyses.
- The base case modelling approach, including structure, costs included, and utility values applied, is consistent with previous submission for sotorasib (TA781) (9) and ongoing evaluation of adagrasib (115).
- In the primary comparison base case analysis the ICER for sotorasib versus docetaxel was £26,276 per QALY gained; results of the alternative analysis using the CodeBreak 200 clinical trial results reported the ICER of £25,352 per QALY gained, suggesting the base case ICER may be conservative.
- Sotorasib qualifies for the severity modifier of 1.7 and was demonstrated to be cost-effective use of NHS resources.

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5 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis

Appendix D: Adverse reactions

Appendix E: Published cost-effectiveness studies

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Appendix L: Flatiron scenario analysis efficacy inputs

Appendix M: Detailed resource use and unit costs calculations

Appendix N: Summary of variables applied in the economic model

Company evidence submission template for sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]

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]

Summary of Information for Patients (SIP)

June 2025

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6287 sotorasib NICE SIP vFINAL [noCON]	V1.0	No	25 th June 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Sotorasib (Brand name: LUMYKRAS™)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Sotorasib is an oral medicine used to treat adults with a type of lung cancer called non-small cell lung cancer (NSCLC). It's used when the cancer is advanced (described as locally advanced or metastatic), and its cells have a specific genetic change or mutation. This mutation is in the *KRAS* gene and is called *KRAS G12C*. The *KRAS* gene controls the production of KRAS proteins that are involved in normal bodily processes of cell growth and cell survival (1). Mutations in *KRAS* genes can produce an abnormal KRAS protein (KRAS^{G12C}) that can cause the uncontrolled growth of cancer cells. Sotorasib is known as a targeted therapy, which means that it has been designed specifically to attach to and prevent the abnormal KRAS protein from acting, by interrupting the chemical messages the cancer cells need to grow and to spread, and it also promotes processes that cause the cancer cells to die (2).

Sotorasib is given to patients when the cancer has progressed after receiving systemic therapy (treatment affecting the whole body) or when the patient has been unable to tolerate treatment with this therapy. Systemic therapy includes chemotherapy (specifically treatments containing platinum) and/or immunotherapy (specifically those called anti PD-1/PD-L1) (2).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Sotorasib received conditional marketing authorisation from the MHRA (the UK regulatory body responsible for medicines and medical devices) in the UK in September 2021, following positive data from the CodeBreak 100 trial (see Section 3d for further details). Marketing authorisation was conditional on additional data being collected.

In March 2022, sotorasib was recommended by NICE (3). While the NICE committee concluded that sotorasib fulfilled an unmet need in providing a targeted treatment for patients with *KRAS G12C*-mutated NSCLC, sotorasib was recommended for conditional reimbursement via the Cancer Drugs Fund to allow time for additional data to be collected. Sotorasib is now being reassessed by NICE as it is exiting the Cancer Drugs Fund.

The approved indication for sotorasib is:

‘LUMYKRAS is indicated as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy (2).’

The UK MHRA summary of product characteristics can be found here:

<https://products.mhra.gov.uk/product/?product=LUMYKRAS%20120%20MG%20FILM-COATED%20TABLETS>.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Please see list below for a list of grants made by Amgen to Roy Castle Lung Cancer Foundation.

- In 2021, Amgen Ltd (UK) provided a grant of £7,500 for them to develop and distribute information resources focused on molecular testing; impact of testing on treatment options and assist patients in advocating for the optimum treatment available for themselves.
- In 2022, Amgen Ltd (UK) provided a grant of £15,000 to help fund their Support Through Diagnosis: Ask the Nurse and Answering your Questions service.
- In 2023, Amgen Inc. (USA) provided sponsorship of £30,000 for support of the Global Lung Cancer Coalition (GLCC) in 2024.
- In 2024, Amgen Inc. (USA) provided sponsorship of £30,000 to support the Global Lung Cancer Coalition (GLCC) in 2024.
- In 2024, Amgen Limited (UK) provided a grant of £12,000 to enable Roy Castle Lung Cancer Foundation to improve and enhance support for and awareness of the needs of those affected by small cell lung cancer in the UK.
- In addition for honorarium & expenses of £1,481.34 was paid for a representative of the charity to participate in a panel discussion at an Amgen UK & Ireland internal meeting and a further honorarium of £330 for the provision of a recorded message for an Amgen internal educational meeting.

Alongside the grants, there was a patient booklet ‘Genomic testing in lung cancer’ co-developed with Roy Castle Lung Cancer Foundation. This was to provide patients and their carers/families information on genomic testing in lung cancer; it was last updated in 2024.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Lung cancer is the third most common cancer in the UK. Every year, more than 49,000 people in the UK are diagnosed with it, making up about 13% of all new cancer cases (4). NSCLC is a type of lung cancer which accounts for 80–85% of these cases (5). A specific genetic change, called the *KRAS G12C* mutation, occurs in around 13% of NSCLC cases (6, 7). This means that every year in the UK, over 5,000 people may be diagnosed with *KRAS G12C*-mutated NSCLC.

Around 70% of lung cancer cases are diagnosed at an advanced stage, when the cancer has already spread to lymph nodes and other organs in the chest (locally advanced disease) or to other parts of the body (metastatic disease) (8). Because it's often diagnosed late, lung cancer has a poor prognosis. Despite being the third most common cancer, lung cancer overall is the most common cause of cancer death in the UK, accounting for 35,000 deaths (21% of all cancer deaths) each year (4). One-year survival for patients with locally advanced (stage III) lung cancer is 52.5%, whilst 5-year survival is just 16.0% (9). For patients with metastatic (stage IV) lung cancer, 1-year survival is 21.7%, with only 4.3% of patients surviving 5 years (9).

Patients with advanced NSCLC carry a high symptom burden with associated reduced quality of life compared with other advanced cancers (10-13). These symptoms can get worse quickly and have a big impact on quality of life (14, 15). One common second-line treatment (treatment given if your first treatment fails, stops working, or cannot be tolerated) is called docetaxel, but it is associated with significant toxicity and poor quality of life, which add to the already high symptom burden (16-18). This is where newer treatments like sotorasib may be considered.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients will usually start by seeing their GP if they have symptoms that could be due to lung cancer (19). This may result in further tests, which may include imaging tests, such as a chest x-ray, computed tomography (CT) scan, and positron emission tomography (PET)-CT scan, as well as a bronchoscopy and/or biopsy, or referral to a specialist, such as a respiratory physician (19).

If lung cancer is diagnosed, a patient will be referred to a medical oncologist, who specialises in lung cancer (20). Further tests will help to find out what stage the lung cancer is, whether it has spread to other parts of the body, and determine the appropriate treatment. These tests may include various specialised imaging tests, biopsy, and bronchoscopy (20).

In addition, as advanced NSCLC can result from various gene changes or mutations, scientists may examine a sample of the lung cancer to search for particular mutations (20). Testing for mutations in the *KRAS* gene is typically conducted as part of this (20). A tissue sample will usually be taken during a needle biopsy as part of the initial cancer testing, and sent for testing in a laboratory (20).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Current treatment guidelines for patients with *KRAS G12C*-mutated NSCLC vary depending on the specific features of the cancer in a given individual, but typically involve anti-PD-1/PD-L1 immunotherapies alone or in combination with platinum-based chemotherapy as the first line of treatment (21). If the cancer comes back or doesn’t respond to the first treatment, doctors may try other options, including sotorasib, docetaxel, and platinum-based chemotherapy or anti-PD-1/PD-L1, if not already used (21). For people with a specific type of NSCLC called adenocarcinoma, another option is docetaxel combined with a drug called nintedanib (21). However, this combination is not used very often – only about 5% of patients receive it {Amgen Inc, 2025 #256}.

Figure 1: Current treatment pathway for *KRAS G12C*-mutated NSCLC, and positioning of sotorasib

```
graph TD
    subgraph 1L [1L]
        A[Platinum-based chemotherapy]
        B[Immunotherapy + platinum-based chemotherapy]
        C[Immunotherapy]
    end
    subgraph 2L [2L]
        D[Sotorasib or docetaxel +/- nintedanib†]
        E[Platinum-based chemotherapy or sotorasib]
    end
    subgraph 3L [3L]
        F[Sotorasib or docetaxel +/- nintedanib† (option not previously used)]
        G[Platinum-based chemotherapy or sotorasib or docetaxel +/- nintedanib† (option not previously used)]
    end
    A --> D
    B --> D
    C --> E
    D --> F
    E --> G
```

Abbreviations: NSCLC, non-small cell lung cancer.
†Nintedanib is only reimbursed for patients with adenocarcinoma. Other histologies will receive docetaxel monotherapy.
Note: Different immunotherapies (e.g. nivolumab, pembrolizumab, atezolizumab) are recommended in different patient groups (i.e. squamous vs non-squamous, and PD-L1 ≥50% vs <50%), however, for simplicity, these have been grouped in the schematic. Similarly, in some instances, the exact platinum-based chemotherapy is specified (e.g. carboplatin + paclitaxel). For detailed treatment pathways, please refer to NICE Guideline NG122.

2d) Patient-based evidence (PBE) about living with the condition

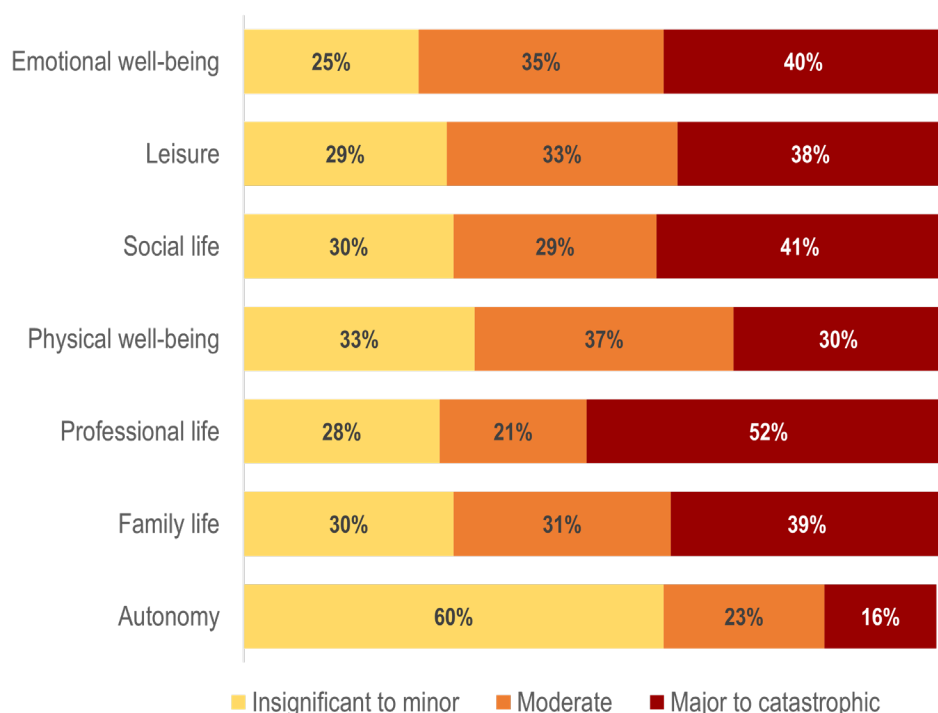
Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

To better understand how NSCLC affects people's daily lives and emotional well-being, Amgen conducted an online patient survey in collaboration with Lung Cancer Europe to capture data on seven key aspects of life: emotional well-being, leisure time, social life, physical well-being, professional life, family life, and autonomy (ability to live independently) (22). A total of 300 adults with NSCLC living in Europe completed the questionnaire between June and November 2020. The results showed that NSCLC had a negative impact on all seven areas, even for people diagnosed with early (stage I/II) disease. However, patients with advanced disease at diagnosis (n=159) tended to experience the strongest negative impacts. Among these patients, most said that the disease had had either a moderate or major to catastrophic impact on their emotional well-being (75%), professional life (73%), leisure (71%), social and family life (each 70%), and physical well-being (67%) (Figure 2).

Figure 2: Psychosocial impact of advanced NSCLC (n=159)



Abbreviations: NSCLC, non-small cell lung cancer.

Advanced NSCLC and its second-line treatment with conventional chemotherapy carry a high symptom burden that has been shown to significantly compromise the quality of life of patients (15, 22-24), their family and friends (25), and informal caregivers in particular (26). People with lung cancer often have multiple symptoms at the same time related both to the disease and its

treatment (27). Most patients with advanced NSCLC report at least one debilitating symptom at diagnosis, such as cough, shortness of breath, fatigue, pain, anorexia, and blood in sputum; more than half of the patients experience moderate or severe symptoms (13, 23). Uncontrolled symptoms and disease progression in advanced NSCLC reduce physical functioning, significantly reducing the quality of life of both patients and their caregivers (14, 24, 26, 28).

Advanced NSCLC is associated with a higher frequency of symptoms, symptom distress, and lower health-related quality of life compared with other advanced cancers (10-13).

As NSCLC is diagnosed at an advanced stage in most patients, it is particularly important to consider the impact of systemic treatment on symptom burden and quality of life (29, 30).

Patients who survive their first treatment are already fatigued, anorexic, and in pain. Therefore, it is important that further treatment does not worsen these symptoms or add to the symptom burden (31). Symptom control is a highly valued outcome by patients with advanced NSCLC, evident from patient preference studies (32, 33), and may allow patients to spend time with their families or undertake activities they enjoy (31). Patients with advanced *KRAS G12C*-mutated NSCLC that have progressed on first-line therapy often receive cytotoxic chemotherapy, such as docetaxel. Around half of these patients experience symptoms within 1 month of initiating treatment with docetaxel (34). Cytotoxic chemotherapy produces off-target symptoms because normal tissue is damaged as tumour cells are killed. By contrast, targeted treatments (like sotorasib) specifically destroy cancerous cells and cause less general (off-target) toxicity (although each novel targeted agent has its own unique toxicity profile) (35). Docetaxel is associated with a number of important toxicities, including neutropenia and febrile neutropenia, dyspnoea, fatigue, infection, anaemia, diarrhoea, stomatitis, and nausea and vomiting, that can lead to hospitalisation and severely compromise quality of life (16-18).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The specific changes to the *KRAS* gene present in patients with *KRAS G12C*-mutated NSCLC leads to the production of an abnormal *KRAS* protein that can cause the uncontrolled growth of cancer cells (2).

Sotorasib attaches to this abnormal *KRAS* protein inside cancer cells and prevents the protein from acting by interrupting the chemical messages the cancer cells need to grow and to spread, and it also promotes processes that cause the cancer cells to die (2).

Sotorasib was the first *KRAS*^{G12C} inhibitor to be made available in the UK. Adagrasib, another *KRAS*^{G12C} inhibitor, received conditional marketing authorisation from the MHRA in November 2023, however, guidance from NICE is still in development.

Sotorasib was previously granted an Innovation Passport under the Innovative Licensing and Access Pathway, and designated as a Promising Innovative Medicine under the Early Access to

Medicines Scheme (36, 37), both of which indicate recognition of sotorasib as a highly innovative treatment for patients.

More details can be found in the summary of product characteristics and the patient information leaflet for sotorasib here:

<https://products.mhra.gov.uk/product/?product=LUMYKRAS%20120%20MG%20FILM-COATED%20TABLETS>

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, sotorasib is prescribed as a single therapy and is not intended to be used in combination with other medicines for the treatment of *KRAS G12C*-mutated NSCLC (2).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Patients can only be treated with sotorasib with a prescription and treatment must be started by a doctor who is experienced in using cancer medicines. In addition, the patient's cancer must be tested before starting treatment to confirm that the *KRAS G12C* mutation is present (2).

Sotorasib is available as 120 mg and 240 mg tablets and is taken by mouth. The recommended dose is 960 mg taken once per day, at the same time each day, with or without food. Treatment is continued until the disease gets worse (disease progression) or side effects become too severe to tolerate (2).

If certain side effects develop, the doctor may decide to reduce the dose to 480 mg once per day and then, if needed, to 240 mg once per day. Treatment should be stopped if side effects are still too severe to tolerate at the lowest dose of 240 mg (2).

More details can be found in the summary of product characteristics and the patient information leaflet for sotorasib here:

<https://products.mhra.gov.uk/product/?product=LUMYKRAS%20120%20MG%20FILM-COATED%20TABLETS>

Alternative treatment with docetaxel, the main comparator for sotorasib in patients with *KRAS G12C*-mutated NSCLC, is more invasive, as it is administered intravenously i.e. as a drip into the bloodstream (38).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

CodeBreak 100 (NCT03600883)

CodeBreak 100 is an ongoing Phase 1/2, global, multicentre, single-arm, open-label trial of sotorasib in adult patients with *KRAS G12C*-mutated advanced NSCLC whose cancer had progressed following treatment with at least one prior systemic anticancer therapy. CodeBreak 100 was started on 27th August 2018 and is currently ongoing.

In total, 174 patients were treated with sotorasib.

Further details are available from the following sources:

- Hong et al. *N Engl J Med* 2020;383:1207-1217 (39)
- Dy et al. *J Clin Oncol.* 2023 Jun 20;41(18):3311-3317 (40)

CodeBreak 200 (Study 20190009; NCT04303780)

CodeBreak 200 is a Phase 3, global, multicentre, randomised, open-label study to measure the efficacy, safety, and tolerability of sotorasib compared with docetaxel in adult patients with *KRAS G12C*-mutated advanced NSCLC whose cancer had progressed following treatment with at least one prior systemic anticancer therapy. CodeBreak 200 was started on 4th June 2020 and is currently ongoing.

In this study, 345 patients were randomised to treatment with either sotorasib (n=171) or docetaxel (n=174).

Further details are available from the following sources:

- De Langen et al. *Lancet* 2023; 401: 733–46 (41)
- Waterhouse et al. *Lung Cancer.* 2024;196:107921 (42)

Cancer Analysis Set (CAS) real-world study

The prior recommendation made by NICE to provide sotorasib to patients on the NHS, via the Cancer Drugs Fund, has enabled evidence to be collected on the effectiveness of sotorasib in a real-world clinical practice setting. The CAS real-world study is a comparative analysis of data collected in the CAS database from patients treated with sotorasib or docetaxel in clinical practice in England. Eligible patients were adults with advanced NSCLC who had previously been treated with at least one prior systemic anticancer treatment, including platinum-doublet chemotherapy and/or anti-PD-1/PD-L1 immunotherapy. Patients had to have started treatment with either sotorasib or docetaxel monotherapy to be considered eligible. Patients treated with sotorasib were assumed to carry the *KRAS G12C* genetic mutation consistent with the conditions specified in the Managed Access Agreement for patients receiving sotorasib treatment in England.

The overall study period ran from 1st January 2013 to 31st May 2024.

In this study, data from 757 patients was available for analysis, 394 who were treated with sotorasib and 363 who received docetaxel {Amgen Inc, 2025 #270}.

Further details are available in Section 2 of the main submission dossier.

The **CodeBreak 100** study was used to support UK conditional marketing authorisation from the MHRA and the NICE recommendation in 2021/2022. Additional data collection to support full marketing authorisation was planned through the **CodeBreak 200** study. Similarly, the Managed Access Agreement for sotorasib noted **CodeBreak 200** as a planned primary source of further data collection, alongside longer-term data from **CodeBreak 100**. Real-world evidence collected via the Cancer Drugs Fund was anticipated as a secondary data source. However, regulatory feedback on the positive data reported in **CodeBreak 100** led to a reduction in the number of patients enrolled in the **CodeBreak 200** study, meaning that it no longer had a sufficient number of patients to detect a benefit in one of the key study outcomes, overall survival. As a result, data from the **CAS** study has been used as a primary data source in the NICE submission to demonstrate a clear benefit for patients treated with sotorasib versus docetaxel, with respect to overall survival.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

CodeBreak 200

In the Phase 3 study, CodeBreak 200, adult patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC whose cancer had progressed following treatment with at least one prior systemic anticancer therapy were treated with sotorasib (n=174) or the current standard of care treatment in the NHS, docetaxel (n=171). Patients treated with sotorasib lived significantly longer (median 5.6 months) than those treated with docetaxel (median 4.5 months), without their disease getting worse (progressing), known as progression-free survival (41). At 1 year, the number of patients treated with sotorasib who remained alive without their disease getting worse was more than double that of the docetaxel group (24.8% versus 10.1%) (41). Response to treatment (shrinkage in the size of the cancer or disappearance) was higher, time to achieve a response was shorter, and the duration of the response was longer with sotorasib (28.1%, 1.4 months, and 8.6 months) compared with docetaxel (13.2%, 2.8 months, and 6.8 months).

Although overall survival was not significantly different between sotorasib (10.6 months) and docetaxel (11.3 months), a change to the study as a result of feedback to Amgen from the regulatory authorities after positive data from the CodeBreak 100 trial (see below) meant that the number of patients enrolled was reduced, meaning that it no longer had enough patients to show a potential benefit of sotorasib on overall survival.

CodeBreak 100

In the single arm study CodeBreak 100, patients treated with sotorasib lived for a median of 6.3 months without their cancer getting worse and had a median overall survival of 12.3 months. Although there were some differences between the two studies in the locations of the patient populations enrolled into the studies and the treatments that patients had received prior to joining the study, the outcomes from CodeBreak 100 are broadly consistent with those from CodeBreak 200 and support the results observed in that trial.

CAS real-world study

With sotorasib being available on the NHS via the Cancer Drugs Fund, additional data has been collected on the effectiveness of the treatment on patients being treated in clinical practice in

England. This data shows that patients treated with sotorasib live significantly longer than patients treated with docetaxel (approximately 10.2 months versus 6.9 months) {Amgen Inc, 2025 #270}.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life in CodeBreak 200 was assessed using a number of questionnaires that were completed by participants at different time points during the study. These included questionnaires to assess the overall impact of cancer (EORTC-QLQ-C30), the impact of specific symptoms of lung cancer (EORTC-QLQ-LC13), and the impact on general health (EQ-5D), as well as questionnaires to assess the impact of treatment side effects on quality of life (FACT-G GP5) and the impact of treatment on symptoms (PRO-CTCAE).

The results of the questionnaires showed that sotorasib did not have a negative impact on participants' overall quality of life and the burden of specific cancer symptoms, whereas docetaxel resulted in measurements that significantly worsened, both immediately after treatment administration and during long-term treatment.

Patients treated with sotorasib were less bothered by treatment side effects than those receiving docetaxel, and their symptoms such as pain, aching muscles, aching joints, and mouth or throat sores were less severe (42). Patients treated with sotorasib found that their symptoms interfered less with their daily activities than patients who received docetaxel (42).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In the CodeBreak 200 trial, side effects (known as treatment-emergent adverse events), regardless of the cause, were reported in 166 (98%) patients in the sotorasib group and 148 (98%) patients in the docetaxel group. Treatment-related side effects (side effects that occur due to the treatment given) considered severe (known as grade 3 or worse) i.e. requiring hospitalisation or life threatening, were reported in 56 (33%) patients in the sotorasib group and in 61 (40%) patients in the docetaxel group.

In the sotorasib group, the most common severe (grade 3+) treatment-related side effects were diarrhoea (12%), alanine aminotransferase increase (8%), and aspartate aminotransferase increase (5%)†. All of these side effects resolved after dose interruption, reduction, or both. In the

docetaxel group, the most common severe treatment-related side effects were neutropenia (12%), fatigue (6%), and febrile neutropenia (5%).

Fatal treatment-related side effects were reported in one patient (<1%) in the sotorasib group (interstitial lung disease) and two patients (1%) in the docetaxel group (ileus and multiorgan failure).

In the sotorasib group, 60 (36%) dose interruptions, 26 (15%) dose reductions, and 16 (10%) discontinuations of sotorasib because of treatment-related side effects occurred; in the docetaxel group, 23 (15%) dose interruptions, 40 (27%) dose reductions, and 17 (11%) discontinuations of docetaxel because of treatment-related side effects occurred.

On average, patients were treated for longer with sotorasib compared to patients treated with docetaxel. An analysis showed that when the rates of side effects were adjusted to account for the amount of time patients were receiving treatment (exposure-adjusted), side effects were more common in patients receiving docetaxel than those who received sotorasib.

† Alanine aminotransferase and aspartate aminotransferase are enzymes typically found in the liver that may indicate liver damage if elevated in the blood.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The CodeBreak 200 trial showed that for people with advanced *KRAS G12C*-mutated NSCLC, sotorasib significantly increases the time that people remain alive without disease progression, relative to standard of care with docetaxel. At 1 year, the number of patients treated with sotorasib who remained alive without their disease getting worse was more than double that of the docetaxel group (24.8% versus 10.1%) (41). Response to treatment (shrinkage in the size of the cancer or disappearance) was higher, time to achieve a response was shorter, and the duration of the response was longer with sotorasib (28.1%, 1.4 months, and 8.6 months) compared with docetaxel (13.2%, 2.8 months, and 6.8 months).

In addition, the CAS RWE study showed that based on data from real-world UK clinical practice, patients treated with sotorasib had a significant improvement in overall survival compared with docetaxel (10.2 months versus 6.9 months).

Sotorasib also represents a less burdensome treatment option for patients, as it can be taken as tablets by mouth, as opposed to docetaxel, which is administered intravenously through a drip. In the CodeBreak 200 trial, treatment with sotorasib demonstrated better quality of life and reduced symptom burden compared with docetaxel. While quality of life measurements for subjects in the sotorasib group remained stable, for subjects in the docetaxel group, quality of life measurements significantly worsened, both directly after administration and long-term treatment. Patients treated with sotorasib were less bothered by treatment side effects than those receiving docetaxel. In addition, their symptoms were less severe and interfered less with their daily activities than patients who received docetaxel.

On average, patients were treated for longer with sotorasib compared to patients treated with docetaxel. When the rates of side effects in the CodeBreak 200 trial were adjusted to account for

the amount of time patients were receiving treatment (exposure-adjusted), the rates of side effects were higher for patients treated with docetaxel compared with those who received sotorasib.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Some side effects of any cancer treatment will require hospitalisation or can be life threatening (classified as severe side effects). Although 33% of patients treated with sotorasib in the CodeBreak 200 trial experienced severe side effects that were considered to be related to treatment, the rate with the comparator treatment, docetaxel, was higher (40%). When taking account of the fact that patients were also exposed to sotorasib treatment for longer on average than docetaxel, sotorasib provides a more tolerable option than standard of care when considering this aspect of cancer treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

The model simulates NSCLC by modelling different stages of the disease called 'health states'. In the model, hypothetical patients occupy a health state and can move between them over time. The health states that this model uses are:

- 'Progression-free' (the cancer is not getting worse)
- 'Progressed disease' (the cancer is getting worse)
- 'Death'

Patients experience different quality of life and accrue different costs depending on the health state they are in and the treatment they receive. Additionally, patients who are closer to death experience lower quality of life. The model works by simulating how patients move between the health states when they are given different treatments; the more effective the treatment, the more time patients will spend in the 'progression-free' health state.

Modelling how much a treatment extends life

Treatment with sotorasib extends life by delaying cancer progression. In the CodeBreak 200 trial and CAS RWE study, people lived longer without their disease progressing when treated with sotorasib compared with docetaxel. The CAS RWE study also showed that people treated with sotorasib lived longer overall compared with patients treated with docetaxel.

The base case of the economic model uses the data from the CAS RWE study. As data from the CAS RWE study were only available for a relatively short length of time, statistical models were used to estimate the proportion of patients who would be in each health state over their lifetime (maximum 20 years).

Modelling how much a treatment improves quality of life

The model uses a time to death utility approach, where patients will be assumed to have decreased quality of life as they get closer to death.

In addition, side effects from treatment were assumed to have a further negative impact on quality of life in a scenario analysis.

The model uses EQ-5D data from the CodeBreak 200 trial to estimate treatment-specific quality of life for different 'time to death' categories.

Modelling how the costs of treatment differ with the new treatment

Costs that were considered in the model include those associated with acquisition of medicines, treatment administration, resource use for disease monitoring and management, genetic testing, costs of treating side effects, costs of any subsequent treatments, and end of life costs.

Different medication costs are applied in the model for sotorasib and docetaxel, with sotorasib being more expensive. The oral administration of sotorasib is not assumed to incur a cost, however the intravenous administration of docetaxel is associated with a cost use of healthcare resources, with the cost obtained from standard NHS England reference cost sources.

Different costs for disease monitoring and management are applied to the different health states, and one-off costs are applied at treatment initiation and progression. Each side effect of treatment is associated with costs sourced from NHS England reference costs. Other costs include subsequent treatment costs, and a one-off cost for terminal care at death.

Uncertainty

Analyses were performed to test which inputs/assumptions in the model affected the results most. Scenario analyses were conducted:

- using data from the CodeBreak 200 trial instead of the CAS RWE study
- using real-world evidence from a US healthcare claims database
- using different approaches to modelling how much treatment improves quality of life
- including costs for genetic testing
- using an alternative source for end of life costs

These analyses did not change the conclusions of the cost-effectiveness results.

Additional factors

A severity modifier of 1.7x is applicable to this condition.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Sotorasib is an oral treatment taken once a day that has been designed to specifically target and stop the abnormal KRAS protein from acting, thus stopping the cancer cells from growing and spreading and promoting processes that cause the cancer cells to die (2). It is the first treatment that works in this way to receive marketing authorisation from the regulatory authorities in the UK (the MHRA), and was previously recognised as an innovative new treatment, being granted an Innovation Passport, and a designation as a Promising Innovative Medicine (36, 37). When NICE previously recommended sotorasib for patients under the Cancer Drugs Fund (3), they concluded that there was an unmet need for a targeted treatment for patients with *KRAS G12C*-mutated NSCLC.

With the clinical evidence from the CodeBreak clinical trials and the CAS real-world study indicating meaningful improvements in progression-free survival and overall survival, sotorasib is considered to be highly innovative and provides a step change in therapy for patients with *KRAS G12C*-mutated NSCLC who previously had no targeted therapy options available.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues [here](#)

Use of sotorasib is not expected to raise any equality issues.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Useful resources for lung cancer:

- Cancer Research UK: <https://www.cancerresearchuk.org/about-cancer/lung-cancer>
- Macmillan Cancer Support: <https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/non-small-cell-lung-cancer>
- European Medicines Agency: <https://www.ema.europa.eu/en/medicines/human/EPAR/lumykras>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event	Side effect
Alanine aminotransferase	Enzyme that may indicate liver damage if elevated in the blood
Anti-PD-1/PD-L1	A type of immunotherapy, a cancer treatment that harnesses the body's own immune system to fight cancer cells

Aspartate aminotransferase	Enzyme that may indicate liver damage if elevated in the blood
Cancer Drugs Fund (CDF)	‘Recommended for use within the CDF’ means that the medicine shows promising results in trials but there isn't enough evidence to recommend it at the moment. There is then more time to collect evidence about how well it works. Reviewers can also decide whether it meets the value for money criteria set out by NICE. After a limited period of time in the CDF, NICE reconsiders the medicine and makes a final decision whether to recommend it or not. The aim is to give doctors quicker access to new treatments for their patients.
Conditional marketing authorisation	The approval of a medicine that addresses unmet medical needs of patients, but where the evidence available is less comprehensive than usual. The available data must indicate that the medicine’s benefits outweigh its risks and the complete clinical data must be provided in the future.
EORTC-QLQ-LC13	Questionnaire to measure quality of life in patients with lung cancer
EORTC-QLQ-C30	Questionnaire to measure quality of life in patients with cancer
EQ-5D	A questionnaire on general health, used to assess quality of life
Exposure-adjusted	Adjusted to account for the amount of time patients received treatment
FACT-G GP5	Questionnaire assessing how much patients are bothered by symptoms
Febrile neutropenia	The presence of fever in a neutropenic patient
First-line treatment	The first treatment given for a disease
Grade 3 adverse events	Severe side effects (scale of 1 to 5, where 5 is fatal)
Intravenous	Treatment administered by a drip into the bloodstream
<i>KRAS</i>	A specific gene that controls the production of proteins that are involved in normal bodily processes of cell growth and cell survival
<i>KRAS G12C</i>	A specific genetic change or mutation in the <i>KRAS</i> gene that results in the production of abnormal protein that can cause the uncontrolled growth of cancer cells
Locally advanced disease	Where the cancer has spread into nearby tissues or lymph nodes; also known as stage III
Metastatic disease	Where the cancer has spread to other organs in the body; also known as stage IV
MHRA	UK regulatory body responsible for medicines and medical devices
Mutation	A genetic change
Neutropenia	When the body has too few neutrophils, a type of white blood cells
PRO-CTCAE	Questionnaire used in cancer clinical trials to help patients report how they feel during treatment, and includes assessment of the severity, frequency, and interference of treatment-related symptoms

QALY	One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale)
Second-line treatment	The second treatment a patient receives , if the first treatment fails, stops working, or cannot be tolerated
Systemic therapy	Treatment affecting the whole body
Targeted therapy	Designed specifically to attach to and prevent cancer cell growth
Treatment-emergent adverse events	Side effects that occur during the clinical trial
Treatment-related adverse events	Side effects considered to be related to the treatment given

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:	
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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]

Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID6287 sotorasib clarification questions_FINAL [redacted]	1.0	Yes	1 st August 2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A 1. The search strategies for single arm trial studies (Appendix B; Tables 15-26) include search terms for colorectal cancer as well as for non-small cell lung cancer.

Please explain the inclusion of these search terms in the strategies.

The original single arm trial (SAT) systematic literature review (SLR) (2020) was conducted for both non-small cell lung cancer (NSCLC) and colorectal cancer (CRC), and the same search strategy was used for all updates. However, the 2025 update was scoped solely for NSCLC as per the PICO (table 31, Appendix B). Although the search terms still included CRC, these records were excluded during the title and abstract screening stage based on the indication. Full-text screening was performed only for NSCLC studies. Please, refer to table 32, Appendix B, for a full list of references for included studies from the SAT SLR.

Decision problem

A 2. Priority question. The decision problem excludes docetaxel with nintedanib. The reason given is partly the low percentage and number of patients with KRAS-mutated NSCLC who received chemotherapy (monotherapy or combination) in 2L+ who received docetaxel + nintedanib according to the Cancer Analysis System (CAS) database.

- a) Please provide an explanation as to why patients were prescribed docetaxel + nintedanib, and if they have any clinical characteristics that might make them eligible for this treatment as opposed to docetaxel.**

There was no information available in the Cancer Analysis System (CAS) on the reasons why patients were prescribed specific treatments; it is only possible to infer the reasons, for example, patients treated with docetaxel + nintedanib must have NSCLC with adenocarcinoma cytology.

- b) Is there evidence that the use of docetaxel + nintedanib is declining? Please provide data showing the year that each of the patients received docetaxel + nintedanib.**

It is not possible to investigate the trend of docetaxel + nintedanib use over time using the CAS real-world evidence (RWE) dataset. Due to NHS Digital reporting rules, data points informed by small numbers ($n \leq 5$) of patients are “masked”, meaning the true number of patients is not reported. This is to prevent the potential identification of patients. Due to the small number of patients who received docetaxel + nintedanib over the time horizon of the study (<10 patients; ~5%), the patient numbers are too small to be reported when the results are stratified by year.

Clinical effectiveness evidence

A 3. Priority question. The company submission (CS) notes that:
“Due to challenges arising from crossover between treatment groups, in the primary analysis, OS [overall survival] was not significantly different between the sotorasib group (median 10.6 months) and the docetaxel group (median 11.3 months).

However, adjusted analyses accounting for crossover (including off-protocol crossover) yielded an OS HR [hazard ratio] of 0.820 (95% CI [confidence interval]: 0.315, 1.309).” (p. 34)

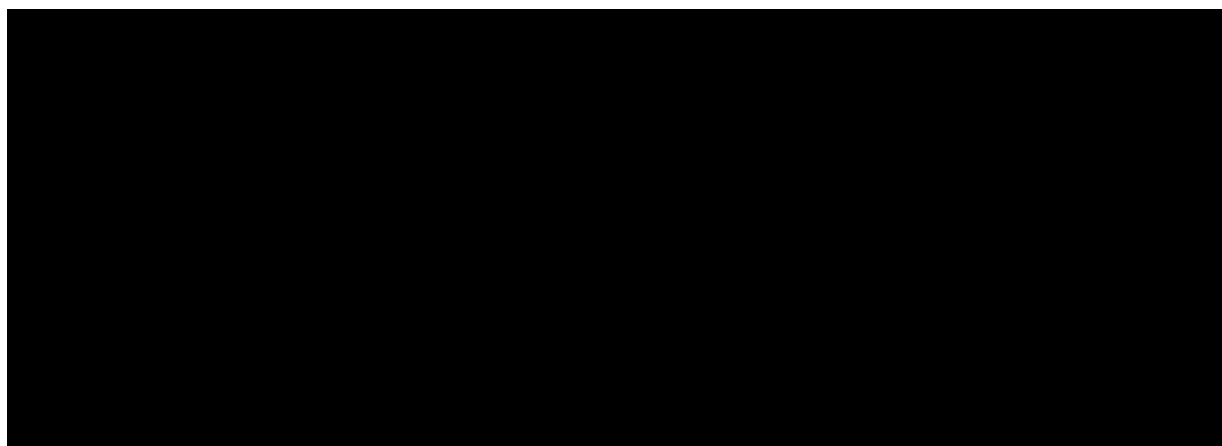
- a) Please confirm that the main explanation for the similarity in OS between the two arms is the crossover to sotorasib from docetaxel.**
- b) Please discuss the possibility that this result might indicate an advantage to treating with docetaxel before treating with sotorasib.**
- c) Please present OS data separately for those who crossed over to sotorasib and those who did not cross over.**

AMGEN can confirm that the main reason for the similarity in overall survival (OS) between the two arms is the crossover to sotorasib from docetaxel.

The intent-to-treat (ITT) analysis of CodeBreak 200 demonstrates a numerically superior OS for patients randomised to receive sotorasib (rather than docetaxel) which makes the EAG's hypothesis (that this result might indicate an advantage to treating with docetaxel before treating with sotorasib) highly unlikely.

Treatment durations, response to treatment and OS outcomes for patients who crossed over to sotorasib per protocol are provided in Figure 1. Table 1 reports key baseline characteristics of these patients. Please note that outcome data are aggregated for the total number of patients (n=46) who crossed over to receive sotorasib on protocol. These patients switched to sotorasib before (n=19) or after (n=27) blinded independent central review (BICR) confirmed progression.

Figure 1: Outcomes for patients in docetaxel arm who crossed over to sotorasib per protocol



Abbreviations: CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival.

Table 1: Key baseline characteristics of patients from docetaxel arm who crossed over to sotorasib per protocol

Abbreviations: BICR, blinded independent central review; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; SLD, sum of longest diameter.

A 4. Priority question. As recommended in the NICE Decision Support Unit (DSU) technical support document (TSD) 17, please complete the QuEENS checklist.

The QuEENS checklist was proposed by the NICE Decision Support Unit (DSU) as part of technical support document (TSD) 17. A thorough critical appraisal of all

available clinical effectiveness evidence, including the CAS RWE study, is presented in Section 2.5 of the company submission (CS). Quality assessment results for the CAS RWE study are provided in Table 24 in the CS. The study design and analytical approaches were informed by the target trial emulation framework, which provides a formal methodology for designing studies aimed to estimate causal effects using real-world data and is the preferred approach of NICE.

A 5. Priority question. Section 2.3.3.5.2 states that patients in the docetaxel cohort with available follow-up exceeding 39 months were censored at 39 months. Please perform sensitivity analyses where censoring at 39 months does not occur and incorporate the results into the cost effectiveness analysis.

The cut-off of 39 months was applied to prevent any bias which having different durations of follow-up for each treatment may introduce. It is not possible to re-analyse the CAS data as the analyses were pre-specified and the Company does not have access to the patient-level data used to generate the CAS analyses.

A 6. Priority question. In Section 3.3.3.1 of the CS it states: “As *patient-level data were not available for the time-to-event outcomes from the CAS RWE [real-world evidence] study, it was necessary to digitise KM [Kaplan-Meier] plots (after propensity score weighting, as described in Section 2.4.5.2 and Appendix K) for OS, TTDD [time to treatment discontinuation or death], and TTNTD [time to next treatment or death] to generate pseudo patient-level data to allow the fitting of parametric models.*” However, this seems to contradict the methodology as described in the Technical report where it states in Section 8.9.3.2.1: “*In adjusted analyses, the Kaplan-Meier analysis was performed using a weighted analysis set to account for baseline confounding...*”, and in Section 8.9.3.2.2: “*For all study objectives, the effect of sotorasib monotherapy versus docetaxel monotherapy was estimated using a Cox proportional hazards regression model. In adjusted analyses, the Cox model was fitted in the weighted analysis set to account for baseline*

***confounding.*” Please explain why the CS states that there was no access to patient-level data when the Technical report suggests that there was i.e. to produce K-M curves and to estimate the treatment effect using a regression model.**

The Company does not have access to the original patient-level data used to generate the results of the CAS RWE study. The original study did have access to the patient-level data in order to generate Kaplan-Meier (KM) data and perform Cox regression analyses, but these data were not available or accessible for the fitting of the parametric models, so it was necessary to digitise the KM outputs of the study to allow the fitting of parametric models.

Section B: Clarification on cost-effectiveness data

Systematic Literature Review

B 1. The systematic literature review (SLR) for studies reporting health-related quality of life (HRQoL) focused on patients with the KRAS mutation. Please provide an updated search comparing HRQoL in patients with (previously treated) locally advanced or metastatic non-small cell lung cancer, irrespective of mutation status.

Unfortunately, due to time and resource constraints, it is not possible to produce a new SLR using the parameters requested. It is worth noting that this search strategy of focussing on patients with the *KRAS* mutation, is the same strategy as used by the manufacturer in TA1071 and in the original submission for TA781.

B 2. For each conducted SLR (economic evaluations, HRQoL, resource use and costs), please provide a table specifying which studies were excluded from the economic model and provide reasons for their exclusion.

The list of excluded studies, alongside the reasons for their exclusion, from the economic SLR was provided as part of the reference park, please see the file ‘List of excluded studies - economic SLR’.

For the summary of studies identified via the SLR which were considered eligible based on the PICO criteria, please see Table 2. The table summarises the reasons for including or excluding studies for the economic model.

More information for economic evaluation, costs and resource use, health-related quality of life (HRQoL) studies identified as part of the 2025 SLR update is reported in the CS, Sections 3.1.2, 3.5 and 3.4, respectively.

Table 2: Studies identified via the SLR

Author	Reported outcomes	Reason
Original 2020 search		
Arnaud, A. (1) [abstract]	Cost / Resource use	Exclude: not relevant to the UK setting
Drawz, S. (2) [abstract]		
Drezet, A. (3) [abstract]	Economic evaluation	
Legras, A. (4)	Cost / Resource use	
Loubiere, S.(5)	Economic evaluation	
Loubiere, S. (6) [abstract]	Cost / Resource use	
Pennell, N. A. (7) [abstract]		
Perdrizet, K. (8) [abstract]		
Tan, A. (9) [abstract]		
Walther, Z. (10) [abstract]		
Yang, Y. (11) [abstract]	HRQoL/HSUV	Exclude: unclear whether relevant to the UK setting; HRQoL scale not reported
SLR update 2021		
Dall'Olio (12)	Cost / Resource use	Exclude: not relevant to the UK setting
SLR update 2025		
Berardi, A. (13) [abstract]	Economic evaluation, Cost / Resource use	Exclude: not relevant to the UK setting
Chopra, D. (14) [abstract]	Cost / Resource use	
Chouaid, C. (15)	HRQoL/HSUV	
El Saadany, T. (16)	Economic evaluation, Cost / Resource use	
Felip, E. (17) [abstract]	HRQoL/HSUV	Exclude: not relevant to the UK setting; limited information in the abstract
Fernandez-Barcelo, C. (18) [abstract]	Cost / Resource use	Exclude: not relevant to the UK setting; no additional details about disease costs
Jiang, Y. (19)	Economic evaluation, Cost / Resource use	Exclude: not relevant to the UK setting
Kang, D. W. (20)		Exclude: not relevant to the UK setting; intervention /

Author	Reported outcomes	Reason
		comparator not relevant for the model (focused on next generation sequencing)
Karim, N. (21) [abstract]		Exclude: not relevant to the UK setting; no additional details about disease costs
Keeping, S. (22) [abstract]		Exclude: not relevant to the UK setting; abstract only; focused on hepatotoxicity management
Pennell, N. A. (23)		Exclude: not relevant to the UK setting; intervention / comparator not relevant for the model (focused on next generation sequencing)
Reguart Aransay, N. (24) [abstract]	Cost / Resource use	Exclude: not relevant to the UK setting; no additional details about disease costs
Sheffield, B. (25) [abstract]	Economic evaluation, Cost / Resource use	Exclude: not relevant to the UK setting; intervention / comparator not relevant for the model (focused on next generation sequencing)
Vanderpoel, J. (26)		
Waterhouse, D. M. (27)	HRQoL/HSUV	Exclude: reported data from CodeBreak 200, but not in the format required for the model
Yang, S. C. (28)	Economic evaluation, Cost / Resource use	Exclude: not relevant to the UK setting; intervention / comparator not relevant for the model (focused on next generation sequencing)
Zhu, Y. N. (29)	Economic evaluation, Cost / Resource use, HSUV	Exclude: not relevant to the UK setting, however, the study highlighted the new source of AE disutilities (Nafees 2017 (30))

Abbreviations: AE, adverse event; HRQoL, health-related quality of life; HSUV, health state utility value; SLR, systematic literature review.

Model structure

B 3. Priority question. A partitioned survival model (PSM) with three distinct health states (progression-free [PF], progressed disease [PD] and death) was developed in Microsoft Excel®. The National Institute for Health and Care Excellence (NICE) DSU TSD 19 recommended the use of state transition models (STMs) alongside PSMs to verify the plausibility of PSM extrapolations and explore key clinical uncertainties in the extrapolation period. Moreover, the use of a PSM was considered a key issue in the original technology appraisal (TA; TA781). In NICE DSU TSD 19 it is further mentioned that state-transition modelling has advantages over PSM “with respect to extrapolation because the changing health state occupancy mix is explicitly modelled, stakeholders should note that the validity of the extrapolation remains dependent upon within trial trends in individual transition rates being representative of post-trial trends”. Specifically, extrapolated mortality in a PSM model is “determined by prior trends in mortality rates whereas extrapolated mortality in a state transition model is determined by a structural link between mortality and earlier disease-related events such as cancer progression”.

a) Please provide further insight into the decision to adopt a PSM instead of an STM.

Several factors were considered when identifying a partitioned survival approach as the structure to be used in the cost effectiveness model. These included:

- The suitability of the model structure to utilise the available evidence
- How the limitations of each model structure interact with the available evidence
- Alignment with the work conducted in TA781

As discussed in Document B, evidence was available from CodeBreakK 100, CodeBreakK 200, and the CAS RWE study, however the granularity of the evidence differed between sources. For the CodeBreakK trials patient level data was available,

whereas only aggregate data was available from the CAS RWE study. This restricted the analyses that could be conducted on the CAS RWE study. For instance, it was not possible to derive post-progression survival, which would be used to inform a state-transition model. Post-progression survival is calculated as the time from the point of disease progression to the date of death from any cause, its derivation relies on knowing both when a specific patient progressed and died. This was not possible from the CAS RWE study as time to next treatment or death (TTNTD; as a surrogate for progression-free survival [PFS]) and OS were only available on an aggregate level. A partitioned survival model structure on the other hand utilises both endpoints from the CAS RWE study directly. This means that the evidence from each source could be used to inform the same approach. In turn, the structural uncertainty related to the source of efficacy data could then be explored as part of scenario analysis.

Given that the CAS RWE study was preferred in the base case, the value of developing a state-transition model purely to validate model outcomes is then significantly reduced. The development of this secondary model structure would only have allowed validation of results informed by the CodeBreakK trials, which are only considered in scenario analyses.

It is acknowledged that the use of a partitioned survival model is associated with structural limitations, as is true of any model structure. These limitations are outlined in NICE DSU TSD 19 and the key limitation of interest, extrapolation of OS, has been highlighted by the EAG in the question. It is the company's belief that this limitation is largely mitigated by the maturity of the evidence used to inform efficacy outcomes. At the maximum follow-up of 38 months survival was █████ in the sotorasib arm and █████ in the docetaxel arm. This means that the extrapolated period informs the outcomes of a small proportion of patients and is informed by the prior events observed in the majority of patients. The company's belief is also supported by the conclusions of NICE DSU TSD 19 that states "*The extent to which the PartSA approach over- or under-estimates the true incremental life years and QALYs will be difficult to predict for any specific context, although the extent of differences between predicted and actual outcomes is expected to be less significant as the maturity of the data increases*".

The NICE DSU also highlights potential bias in the relative OS benefit estimated by a partitioned survival model in scenarios where most patients in both arms reside in the progressed health state. The DSU states that in scenarios where the benefit of an intervention is primarily derived from slowing progression, assuming continued OS benefit when most patients have progressed would bias results in favour of that intervention. However, this scenario is not reflective of the CAS RWE study where of the [REDACTED] sotorasib patients still alive at the end of follow-up, [REDACTED] were progression-free. A much greater proportion than in the docetaxel arm [REDACTED] of the [REDACTED] alive at the end of follow-up. It therefore follows that this limitation is not directly applicable to the modelling of the CAS RWE dataset even in the instance where the benefit of sotorasib is solely limited to delaying progression.

Finally, the methodology used in TA781 was considered, in line with the expectation of updating the analyses conducted prior to entry into the Cancer Drugs Fund (CDF). A partitioned survival model structure was used for this appraisal and although it highlighted as a key issue by the EAG during TA781, it is important to note that the topic was not discussed during the appraisal committee meeting. From this the company interpreted that the model structure was not prohibitive to decision making and, given the previously outlined points related to the evidence base, there was no reason to revise this approach.

Considering all these points the company did not believe there was sufficient justification to develop the cost-effectiveness model using a state-transition framework in place of a partitioned-survival analysis framework. A state-transition model would not allow for the incorporation of the CAS RWE study as the post-progression survival transitions could not be derived from the aggregate level data. The limitations of a partitioned survival model approach were also considered to be mitigated by the maturity of the efficacy data observed in both the CodeBreakK trials and the CAS RWE study.

- b) According to the EAG, state transition modelling would have clear advantages in the current application, as it would allow to optimally use available evidence from CodeBreak 200 (i.e. the only randomised comparator between the intervention and the primary comparator), that is not affected by cross-over. Particularly because progression-free**

survival (PFS) and pre-progression survival are not affected by cross-over, CodeBreak 200 could robustly inform these endpoints, while post-progression survival could be informed by the CAS RWE study. Please clarify why the above-described approach is not adopted in the CS.

As described in response to sub question B3.a post-progression survival cannot be informed by the CAS RWE study, as the aggregate level data does not allow for the identification of when specific patients progress and then die.

c) Please discuss the rationale and explore the implications of this choice, particularly in light of the issues highlighted in NICE DSU TSD 19.

As discussed in the previous responses, there is limited rationale in developing a state-transition model to meet this decision problem. Such a structure would not be informed by the base case efficacy source, the CAS RWE study, as post-progression survival cannot be derived from aggregate data. The previous response also highlights that the maturity of the CAS RWE study and the high proportion of patients that remain progression-free in the sotorasib arm suggest that many of the limitations of the model structure described in TSD 19 are not relevant to this evaluation.

d) Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11). Specifically, explore the approach described above by leveraging PFS/pre-progression survival data from CodeBreak 200 and post-progression survival from CAS RWE.

The company did not develop a state-transition model as part of the evidence submission for all of the reasons outlined in response to sub-question B3.a. There was then insufficient time to develop this approach during the responses to clarification questions, meaning it has not been possible to action this clarification.

Regardless, a state-transition model would likely provide limited benefit as a validation tool given the base case evidence source, the CAS RWE study, could not be used to populate the model. This means that the state-transition structure could

only be used to verify the outcomes of the partitioned survival model informed by CodeBreak 200, which is of limited use due to cross-over within the trial.

As previously described, the uncertainty in the extrapolation period is significantly reduced by the maturity of the data collected in the CAS RWE study, this is supported by NICE DSU TSD 19 which states *“the extent of differences between predicted and actual outcomes is expected to be less significant as the maturity of the data increases”*.

Population

B 4. Priority question. According to the CS “the patient population for the economic analysis is adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy”.

- a) The population as defined in the final scope is slightly different than quoted above: “Adults with previously treated KRAS G12C mutated, locally advanced or metastatic NSCLC”. Please elaborate on the differences (particularly regarding specification of previous treatment) and the implications of these differences.**

There is no difference between the populations; the first definition is specific regarding the prior treatments received; the second definition omits the mention of platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy, but these are the treatments which patients would have received as the “previous treatment”. The population described in the CS is aligned with the specific wording in the SmPC.

- b) According to CS Figure 1, sotorasib can be positioned either 2nd or 3rd line. Moreover, according to CS Table 70, sotorasib is positioned in 2L+.**

- i. Please provide the proportion of 2nd, 3rd and 4th+ line patients in CodeBreak 100, in CodeBreak 200 and in the CAS RWE study.**

The proportion of patients in each line of therapy from CodeBreak 200, CodeBreak 100 and the CAS RWE study were provided in Table 10, Table 12 and Table 16 of the CS respectively.

- ii. Please justify that it is appropriate to combine 2nd and 3rd line in the CS base-case, in (relative) effectiveness, health-related quality of life (HRQoL) as well as resource use and costs.**

The 2nd and 3rd-line populations are appropriate to combine as this is the patient population who would be treated with sotorasib in real-world clinical practice, i.e. patients who have been previously treated with PD-1/PD-L1 inhibitors or platinum-based chemotherapy.

- iii. Please provide subgroup analyses for 2nd and 3rd line patients ('previous treatment' is specified in the scope for defining subgroups).**

As described in the response to question B4.b.i, it is not possible to re-analyse CAS RWE data for subgroup analyses. However, one of the subgroup analyses presented in the CAS RWE results file showed similar outcomes for patients treated with prior immunotherapy, which may be a more appropriate interpretation of the 'previous treatment' subgroup as defined in the scope. Please see Section 2.8.2.2 of the CS.

- c) According to the CS “Subgroup analyses were not included in the cost-effectiveness analysis given there were no subgroups observed with substantially different efficacy to the whole population in CAS RWE”. The EAG considers the justification provided for not performing subgroup analyses insufficient. Even in the absence of differential efficacy, differences in cost-effectiveness may arise from variations in baseline risks, HRQoL, resource use or cost. Therefore, please provide subgroup analyses as specified in the final scope (based on disease stage, histology, previous treatment, and whether disease is newly diagnosed or recurrent).**

It is not possible to re-analyse the CAS data as requested, as the analyses were pre-specified and the Company does not have access to the patient-level data.

- B 5. The CS stated that “the patient population is also aligned with that in the Phase 3 CodeBreak 200 randomised controlled trial (RCT), and the sotorasib arm of the CAS RWE study, as described in Section 3.3.1”. Baseline

characteristics for the CAS RWE study and CodeBreak 200 are provided in CS Table 40.

a) Please also provide these baseline characteristics for CodeBreak 100.

Baseline characteristics for patients in CodeBreak 100 are provided in Table 12 in the CS. Please refer to TA781 (Section B.3.3.1) for the baseline characteristics used in the previous submission (31). The data in Table 40 of the CS presents the baseline characteristics in CodeBreak 200 and the CAS RWE study.

b) Please confirm whether baseline characteristics for the CAS RWE study as reported in Table 40 address the joint patient population. If based on sotorasib or docetaxel only, please provide an update of CS Table 40 and the economic model including baseline characteristics for the joint population of CAS RWE.

The baseline characteristics for the CAS RWE study address the joint patient population.

c) For the CAS RWE study, age and gender values reported in CS Table 40 seem inconsistent with those reported in CS Table 16. Please justify these inconsistencies and provide corrections as well as an updated economic model and results if required.

The values in Table 16 are the unadjusted baseline demographics for the CAS RWE study. The values presented in Table 40 are the adjusted baseline demographics following propensity score weighting. No updated model or results are required.

d) Please provide baseline characteristics for the subset of UK patients in CodeBreak 100, CodeBreak 200, and CAS RWE. For each of these, indicate the number of UK patients (N)

In CodeBreak 100, a country-specific breakdown of all patients is not available, however there were 9 patients from Europe enrolled in the study. In CodeBreak 200, 5 of the 345 enrolled patients were from the UK, as described in table 14.1.1.3 in the CodeBreak 200 clinical study report (CSR) in the reference pack. All patients in CAS RWE were from the UK, and the baseline demographics are reported in the CAS RWE study results Excel file in the reference pack accompanying the CS.

- e) There is currently a mismatch between the primary source used to inform patient characteristics (CodeBreak 200) and the primary source used to inform treatment effectiveness (CAS RWE). Please elaborate on appropriateness and implications of this approach and provide scenarios aligning the sources for patient population and effectiveness.

Not all of the baseline demographics required to accurately calculate body surface area-based drug dosing (i.e. for docetaxel) were available in CAS RWE – specifically, body weight and body surface area (BSA) were not available. As the baseline demographics of CodeBreak 200 and CAS RWE are very similar in terms of age and proportion of females (as shown in Table 40 of the CS), the decision was made to use a single source for baseline demographics rather than mixing the sources used to inform age, sex distribution, body weight, and BSA.

Intervention and comparators

B 6. According to the CS, the primary comparator was docetaxel and, although specified as a comparator in the scope, nintedanib plus docetaxel was not explored in the CS as only a small proportion of patients might receive it in clinical practice (based on the RWE from the CAS database, only ~5% (n<5) of patients with KRAS-mutated NSCLC received docetaxel + nintedanib in the 2L+ setting between 2017 and 2021). However, excluding nintedanib plus docetaxel is inconsistent with the original TA (TA781). Given that nintedanib plus docetaxel is listed as a comparator in the final scope and continues to be used in UK clinical practice, its exclusion requires stronger justification. Please provide scenario analyses and update the economic model to include nintedanib plus docetaxel, consistent with TA781.

It remains AMGEN's position that docetaxel and nintedanib is NOT routinely used in UK clinical practice for patients who would be considered eligible for sotorasib and therefore a full exploration of such a scenario analysis is unwarranted. However, we note that in the original appraisal for sotorasib in this indication (TA781), the incremental cost-effectiveness ratios (ICERs) compared with docetaxel and nintedanib were lower than those compared with docetaxel alone. Similarly, in the recent appraisal of adagrasib in the same patient population (TA1076), the

manufacturer's submission produced base case ICERs of adagrasib compared to docetaxel monotherapy of £29,107/QALY compared to an ICER of just £413/QALY compared to docetaxel and nintedanib. The respective EAGs for these appraisals did not disagree with the direction of these estimates in either case.

Given that any scenario analysis considering docetaxel and nintedanib would rely on relative effectiveness estimates derived from the LUME Lung 1 study, which informed both TA781 and TA1076, it is clear that all ICERs would be lower than those calculated for sotorasib compared to docetaxel alone. A full discussion of the strengths and weaknesses of LUME Lung 1 has been provided in both TA781 and TA1076.

Effectiveness

B 7. Priority question. To inform treatment effectiveness of sotorasib and docetaxel, the company used the CAS RWE in their base-case and the CodeBreak 200 RCT and Flatiron RWE in scenario analyses. In the CAS RWE, OS was available, but PFS was approximated by TTNTD.

a) Please discuss all advantages and limitations of each evidence source (i.e., CAS RWE, CodeBreak 200 and Flatiron RWE) for informing treatment effectiveness, and justify the decision of using CAS RWE to inform the CS base-case.

The Company selected the CAS RWE study as the primary data source for the base case analysis as it has numerous advantages over the other data sources. The strengths and limitations of the CAS RWE study and CodeBreak 200 are discussed in detail in Section 2.13 of the CS.

The primary advantage of the CAS RWE analysis is that it utilises real-world data captured directly by NHS Digital. The CAS RWE analysis has the longest maximum follow-up duration (39 months), the largest sample size (n=757), and features exclusively NHS patients who live in England, which is the same population that sotorasib is seeking baseline commissioning in. In addition, propensity score weighting was used to minimise any potential differences between the populations who received sotorasib and docetaxel. The main disadvantages of the CAS RWE

study are that PFS is not captured in the CAS database, and so TTNTD was used as a proxy for this outcome; however, as the marketing authorisations for the intervention and comparator restrict the use to “treatment until progression”, it is logical to assume that real-world PFS and TTNTD would be similar. Section 2.13.2.2.5 of the CS discusses the limitations in regards to selection bias for patients who were treated with docetaxel, in that *KRAS G12C* mutation status was not known for the majority of patients; the worse prognostic impact of the *KRAS G12C* mutation compared to patients without this mutation may mean that outcomes for docetaxel patients may be overestimated and the analysis may be systematically biased in favour of docetaxel. CAS RWE is also an observational study and may be considered lower quality evidence than a fully randomised controlled trial, although every effort has been made to mimic the design of an RCT where possible (e.g. restriction of follow-up to 39 months for both treatment arms, use of propensity score weighting to align patient populations).

Flatiron RWE is similar in concept the CAS RWE study, with a patient population composed of US patients, who differ in both baseline demographics and prior therapy compared to English patients. This results in uncertainty around the generalisability of the Flatiron RWE analysis to English NSCLC patients. A further limitation of the Flatiron dataset was that PFS was not available, and unlike in the CAS dataset there was not a suitable proxy; only OS was assessed.

CodeBreak 200 is a phase III, randomised, open-label trial comparing the efficacy of sotorasib versus docetaxel monotherapy in patients with previously treated *KRAS G12C* mutated NSCLC. Generally, a phase III study would be considered the highest-quality evidence to assess the efficacy and safety of a treatment, but there were several issues in the CodeBreak 200 trial design which mean that this is not the case. Patients’ enrolment was reduced from the originally-planned 650 to approximately 330 patients and were randomised in a 2:1 ratio of sotorasib to docetaxel as requested by the FDA. The trial design also allowed for crossover from docetaxel to sotorasib upon centrally confirmed radiologic progression. This combination of factors meant that the ITT analysis of CodeBreak 200 was not powered to detect comparative efficacy in terms of OS. Due to the relatively low patient numbers in the docetaxel arm and the extent of crossover, crossover-

adjustment methods were unable to reliably estimate OS due to the high stochastic uncertainty introduced by the trial design. Further confounding may have been introduced by the open-label design of the study (necessary due to the different administration routes of sotorasib and docetaxel) and concerns raised by the FDA in regard to the BICR assessment of PFS. CodeBreak 200 was also a global trial, with limited numbers of UK patients enrolled.

After all of the above factors were taken into consideration, the decision was made to utilise the CAS RWE study as the primary evidence source for the submission. The long follow-up duration, high number of patients, low stochastic uncertainty around outcomes, and maturity of outcome data combine to make the CAS RWE study the highest-quality source of evidence for decision-making.

b) Please elaborate on how PFS and OS for both sotorasib and docetaxel as observed in CodeBreak 200 compare to TTNTD and OS in the CAS RWE.

As discussed in section 2.13 of the CS, it is challenging to make conclusions on the level of OS benefit for patients on sotorasib and docetaxel in the CodeBreak 200 study due to the confounding introduced by the trial design and the fact that CodeBreak 200 was not powered to assess comparative efficacy in regard to OS.

Among patients who received sotorasib in the current study, median OS was 10.18 months (95% CI: 9.10-12.02) and median TTNTD was 8.51 months (95% CI: 7.33-9.43). These real-world findings are broadly consistent with results from other published studies in patients with previously treated *KRAS* G12C-mutated NSCLC. A real-world study of long-term outcomes for patients with advanced *KRAS* G12C-mutated NSCLC treated with sotorasib from the global expanded access program reported a median OS of 9.5 months (95% CI: 8.6-12.0) and a median real-world PFS of 6.3 months (95% CI: 5.0-7.3) (32), with outcomes reported from other single-country real-world studies also in broad alignment ((33-38)).

Median PFS in the CodeBreak 200 trial was 5.62 months for patients on sotorasib and 4.47 months for patients treated with docetaxel with an HR of 0.664 (95% CI: [0.509, 0.864]). In the CAS RWE study, median PFS estimated via TTNTD as a proxy was 8.51 months for patients treated with sotorasib and 5.62 months for

patients treated with docetaxel following standardised mortality ratio weighting (SMRW), with an HR of 0.567 (95% CI: [0.485, 0.663]). The fact that the median PFS for patients on docetaxel in CodeBreak 200 was similar to the median TTNTD for patients on docetaxel in CAS RWE lends credence to TTNTD being a valid proxy for PFS.

For additional information on the OS and real-world PFS outcomes, please see Table 5 of the CS reporting the results of the AACR project GENIE and Flatiron analysis.

c) Please elaborate on how representative TTNTD and OS from CAS RWE, and PFS and OS from CodeBreak 200 are for PFS and OS in UK clinical practice, supported by additional evidence and clinical as well as health economic expert opinion.

The OS estimates from CAS RWE are highly relevant for UK clinical practice as the study was conducted in the same patient population as those who would be eligible for treatment with sotorasib in UK clinical practice; the data were captured directly by NHS Digital as part of the CDF managed access agreement. To our knowledge, the CAS RWE study is unprecedented in its applicability to the UK NSCLC population. It covers approximately 95% of patients in England who receive systemic cancer treatments (39) and offers the largest sample size for sotorasib globally. The OS outcomes captured from CAS RWE are the best possible estimate of the treatment benefit of sotorasib and docetaxel due to the large sample size (n=394 and n=363 respectively) and the longer maximum follow-up (39 months) compared to CodeBreak 200. It is difficult to comment on the applicability of CodeBreak 200 to UK clinical practice due to the global nature of the study and the high stochastic uncertainty the trial design imparted on the OS outputs.

The TTNTD outcomes for docetaxel captured in CAS RWE were closely aligned with the PFS outcomes in CodeBreak 200 for docetaxel (5.62 months median TTNTD in CAS RWE, 4.47 months median PFS in CodeBreak 200).

d) To explore the suitability of using TTNTD as a proxy for PFS in CAS RWE, please provide:

i. An overview of how many patients discontinued before disease progression, at disease progression and post disease progression (absolute and relative numbers) in CodeBreak 200.

Unfortunately, this information is not available in the CodeBreak 200 CSR and it is not possible to perform these analyses in the timeframe for EAG clarification question responses, however the hazard ratios for time to treatment discontinuation or death (TTDD) versus PFS as provided in the economic model are close to 1, suggesting that PFS and TTDD are similar.

ii. An assessment of whether TTDD might be more suitable as a proxy for PFS in CAS RWE.

TTDD is not likely to be a superior proxy for PFS as it risks underestimating PFS; treatment end dates were not recorded in the systemic anticancer therapy (SACT) database, so the end date of the current line of therapy was derived using the recorded start date and the number of cycles received. Consequently, a degree of outcome misclassification can be expected in TTDD analyses. The start of the next line of therapy requires fewer assumptions in regard to disease progression, as it is logical to assume that a patient will have progressed if they have started on a new line of treatment; this is not necessarily the case for a patient who has discontinued their current line of treatment.

iii. An updated health economic model, exploring ii. in a scenario analysis.

Such an analysis is likely to produce unrealistic results as using TTDD as a proxy for PFS lacks face validity. The health state occupancy trace lacks face validity, with a high proportion of patients remaining in the disease progression state.

e) There seems to be a mismatch between OS, and PFS (TTNTD) hazard ratios from CAS RWE in the CS Table 35 and the health economic model.

i. Please justify and correct these inconsistencies in hazard ratios.

Inconsistencies in the hazard ratios (HRs) were corrected in the latest version of the model. For OS, the values from Table 35 of the CS are now available in the model. Please see the 'ModelChangesJuly2025' tab for full details.

Please note that the HR included in Table 35 for PFS (TTNTD used as a proxy) is incorrect. The HR of 0.252 refers to the value estimated for TTDD, an exploratory outcome. Table 53 should report the value of 0.567 (0.485, 0.663) presented in Table 29 of the CS.

Considering above, the correct PFS (TTNTD) values are now included on the PFS tab. Please note that the model allows to select the PFS values for IA or BICR hence there are two sets of the data for CAS RWE (AJ28:AO28 and AS28:AX28). There is only one result for the CAS RWE study hence the new values are identical for both sets.

- ii. Please justify the mismatch between headings and reported HRs in the economic model (Sheet “OS”: X30, X33, X38, AB35, AB40), and align the information provided in an updated health economic model.**

The mismatch between headings was the company's error which is now corrected in the latest version of the model.

- iii. Please explain whether these hazard ratios are used for the CS base-case and/or scenario analyses.**

The base case of the model utilises restricted parametric distributions that are independent of HRs. Similarly, none of the scenarios described in Section 3.9.3 of the CS rely on HRs from the CAS RWE study. Therefore, the reported results are not affected by the corrections made.

- iv. Please provide an updated health economic model, taking all changes due to clarification question B7.e) into account.**

The model is provided alongside this document.

B 8. Priority question. For the assessment of parametric survival models, insufficient details were provided for some criteria reported in the guidance from NICE DSU TSD 14 and 21. Please provide, for OS and PFS (TTNTD) both for the CodeBreak 200 RCT and CAS RWE separately for sotorasib and all relevant comparators:

- a) For CodeBreak 200, please report missing tables with the numbers of patients at risk and adjust available ones for 3-month intervals.**

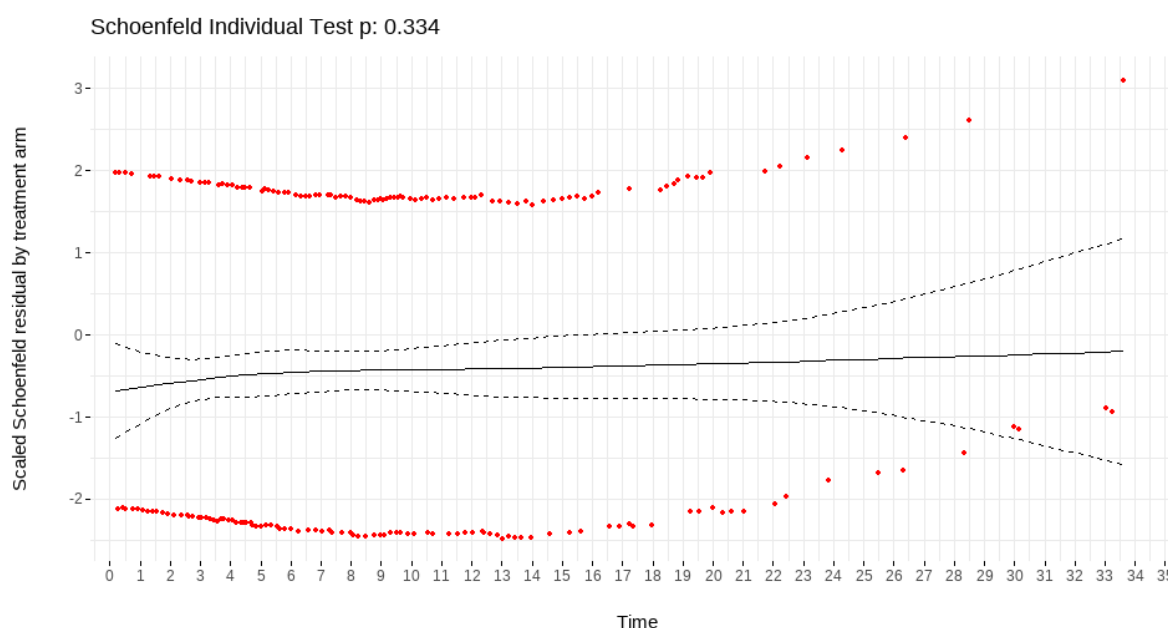
Unfortunately, it is not possible to re-analyse the CodeBreak 200 patient-level data in the timeframe for EAG clarification question responses.

- b) To examine the proportional hazard assumption:**

- i. Plot the scaled Schoenfeld residuals versus time, addressing the flaws in the CS; namely, detailed figure legends, ensuring that the x-axes are consistent with the Kaplan-Meier data by clear labelling, and that sotorasib as well as all relevant comparators are clearly identified as such.**

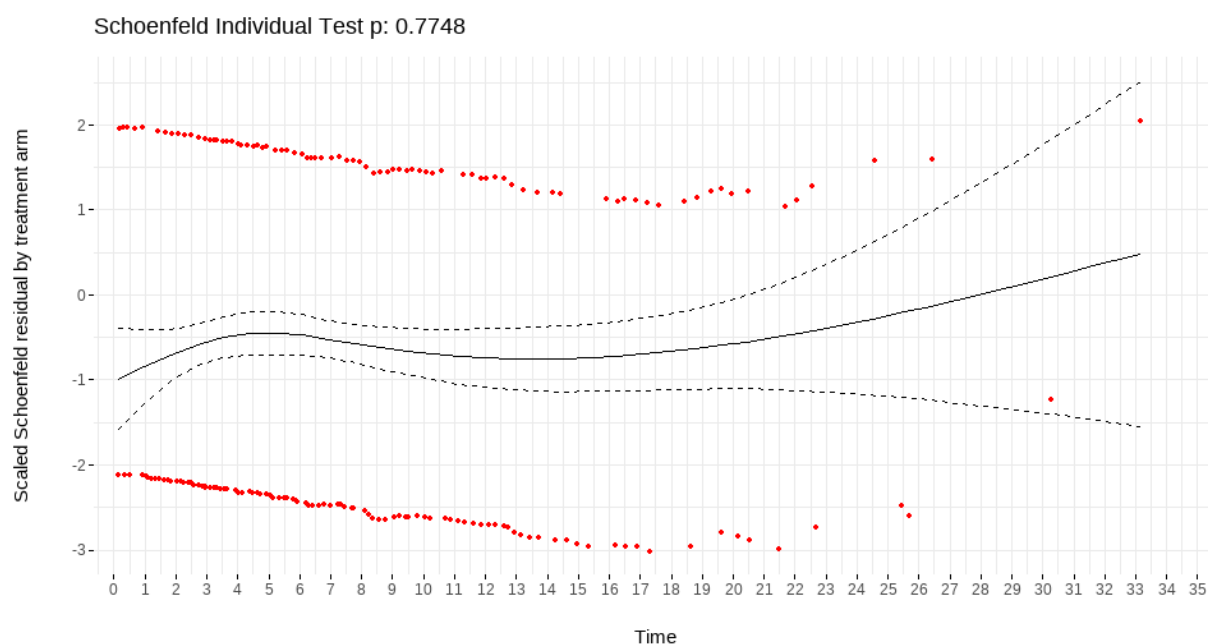
The irregular spacing of the X-axis tick marks in the originally presented Schoenfeld residual plots was by design, to allow for even spacing of Schoenfeld residuals and to avoid grouping in the left side of the plot where there are more observations. It is unclear what further labelling is required, as the Schoenfeld residuals plots are interpreted by assessing whether the effect of a covariate (in this case, treatment arm) is independent of time. Please see below for updated Schoenfeld residual plots with uniform X-axes (Figure 2 to Figure 4).

Figure 2: Updated Schoenfeld residual plot for Cox model fit to OS from CAS RWE



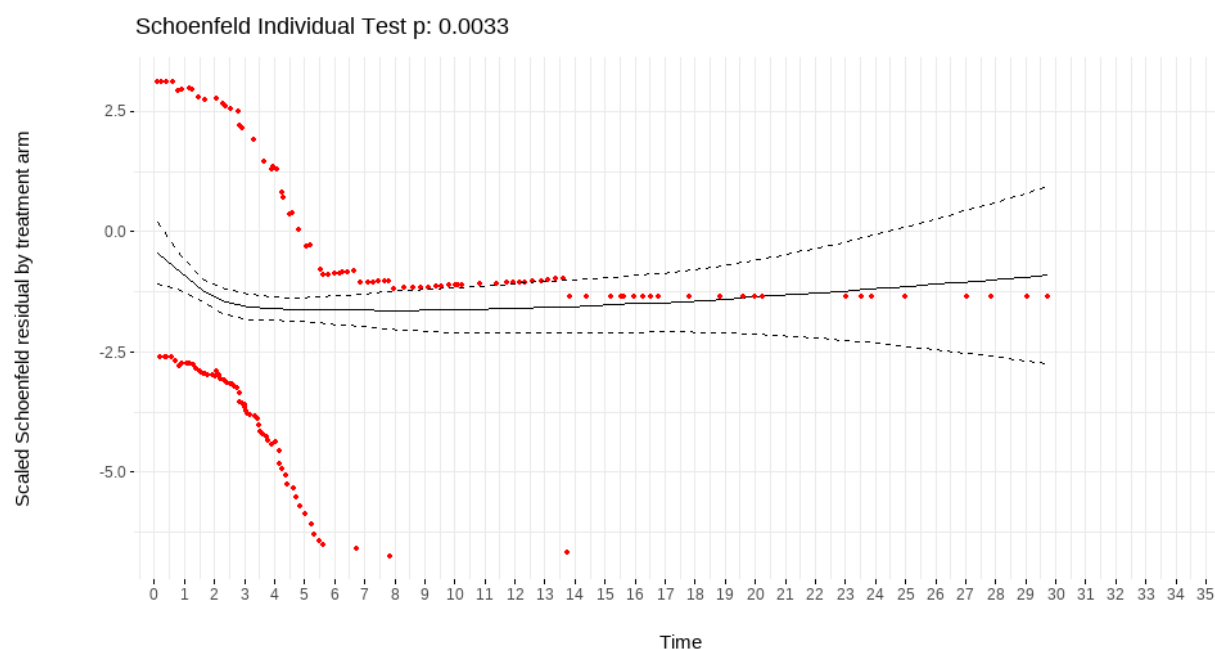
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real world evidence.

Figure 3: Updated Schoenfeld residual plot for Cox model fit to TTNTD (proxy for PFS) from CAS RWE



Abbreviations: CAS, Cancer Analysis System; PFS, progression-free survival; RWE, real world evidence; TTNTD, time to next treatment or death.

Figure 4: Updated Schoenfeld residual plot for Cox model fit to TTDD from CAS RWE



Abbreviations: CAS, Cancer Analysis System; RWE, real world evidence; TTDD, time to treatment discontinuation or death.

- ii. Plot the log cumulative hazard versus log time, addressing the flaws in the CS; namely, correct figure legends/axes labelling.**

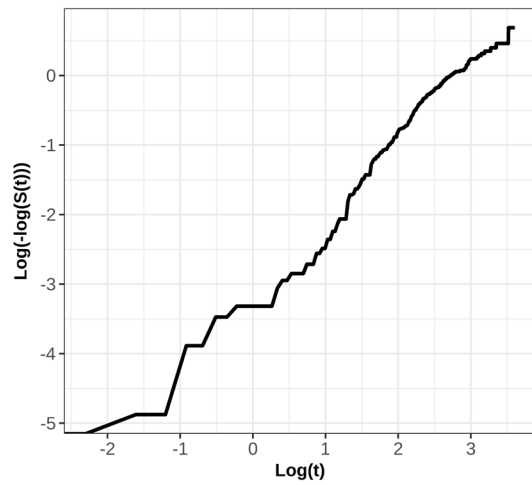
Log-cumulative hazard plots are presented below in the response to Question B8.c.

- c) To examine the heuristics of the hazard function over time, please plot the smoothed hazards over time**

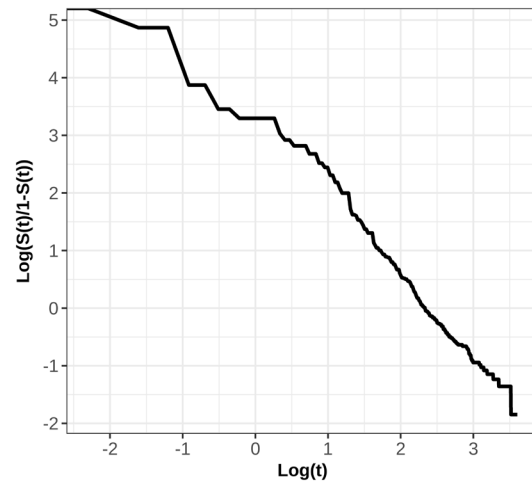
This response contains answers to several of the preceding and subsequent questions, including B8.b.ii and B8.d. Diagnostic plots for OS for sotorasib and docetaxel in CAS RWE are shown below in Figure 5 and Figure 6 respectively. Diagnostic plots for TTNTD for sotorasib and docetaxel in CAS RWE are shown below in Figure 6, Figure 7 and Figure 8 respectively. Diagnostic plots for TTDD for sotorasib and docetaxel in CAS RWE are shown below in Figure 8, Figure 9 and Figure 10 respectively.

Figure 5: Diagnostic plots for OS in the sotorasib arm of CAS RWE

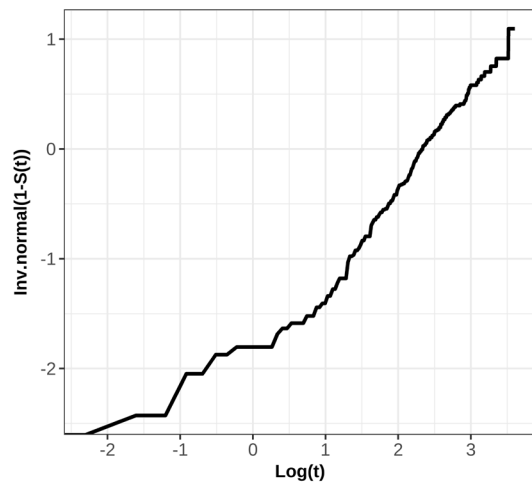
A: Log-cumulative hazard plot



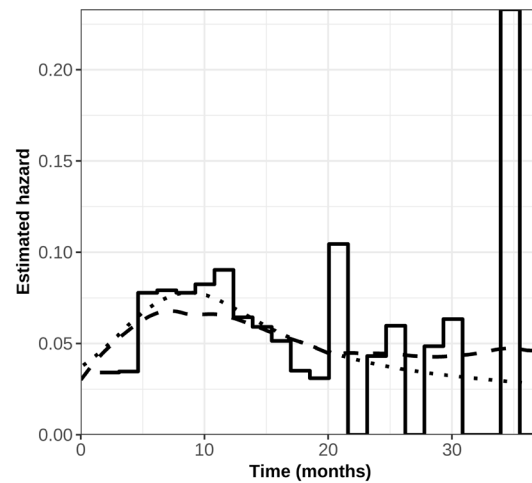
B: Logit survival plot



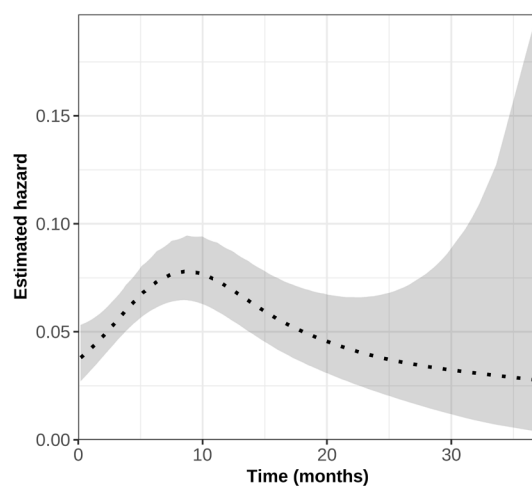
C: Inverse normal survival plot



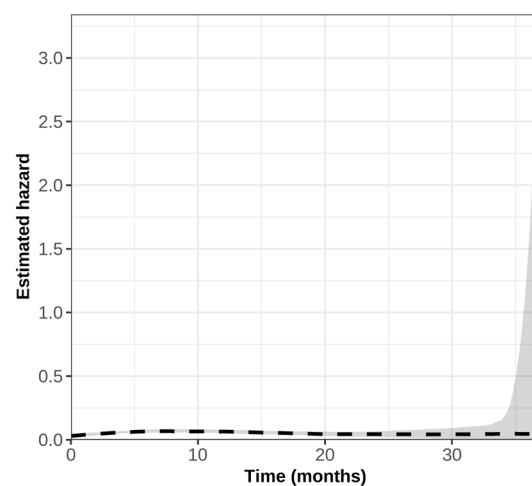
D: Unsmoothed (solid) & smoothed (dotted = 'bshazard' & dashed = 'muhaz') hazards



E: Smoothed hazard plot ('bshazard' with 95% CI)



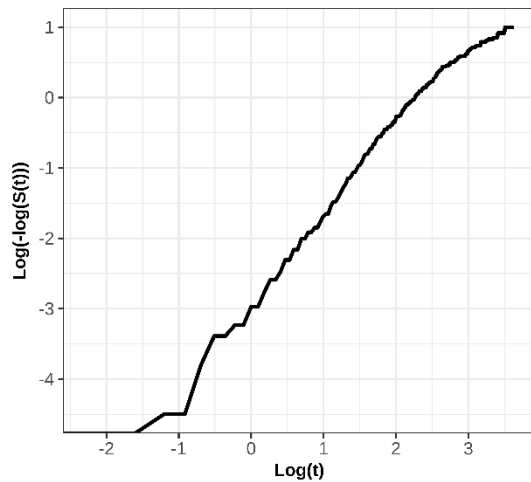
F: Smoothed hazard plot ('muhaz' with 95% CI)



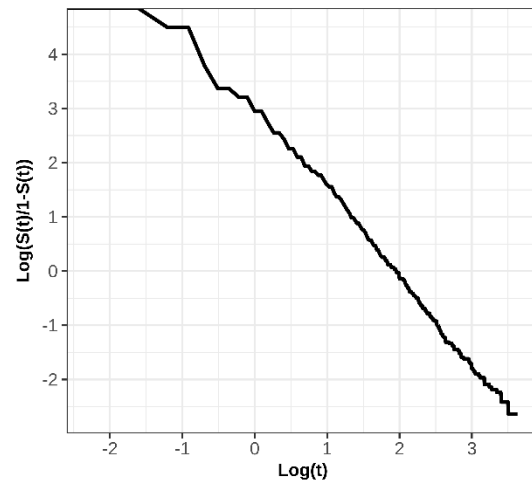
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real world evidence.

Figure 6: Diagnostic plots for OS in the docetaxel arm of CAS RWE

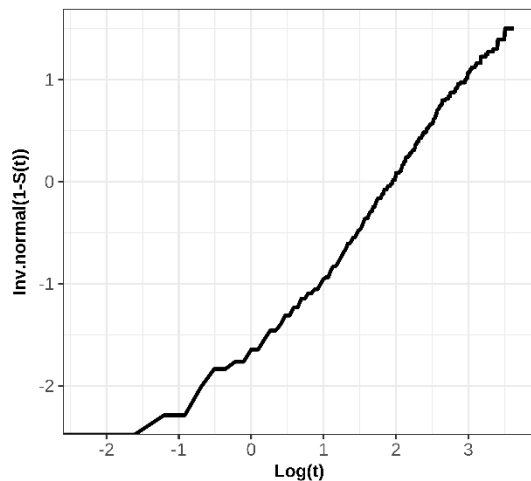
A: Log-cumulative hazard plot



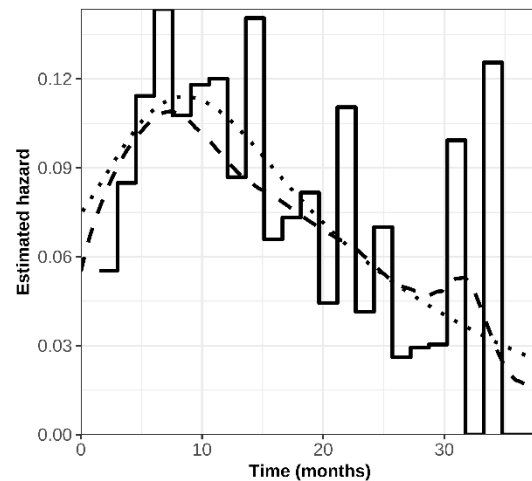
B: Logit survival plot



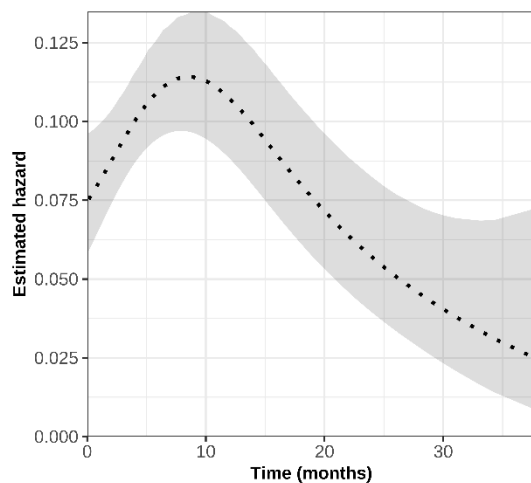
C: Inverse normal survival plot



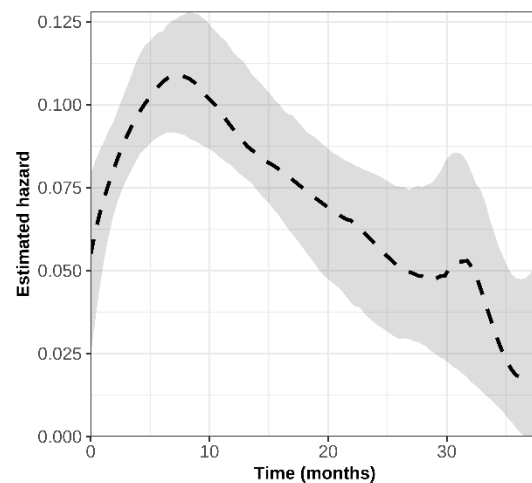
D: Unsmoothed (solid) & smoothed (dotted = 'bshazard' & dashed = 'muhaz') hazards



E: Smoothed hazard plot ('bshazard' with 95% CI)



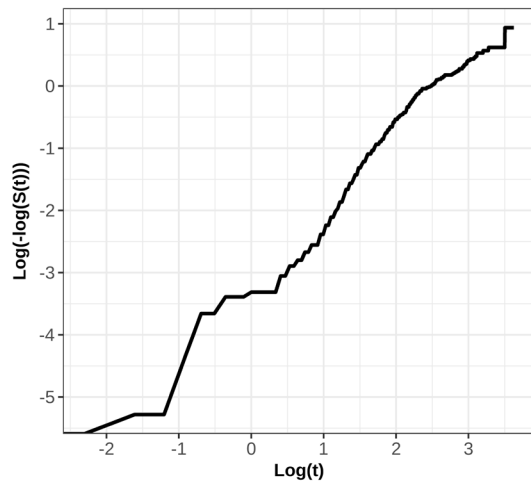
F: Smoothed hazard plot ('muhaz' with 95% CI)



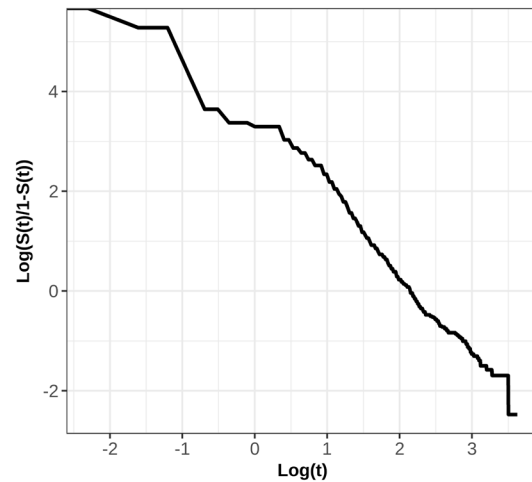
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real world evidence.

Figure 7: Diagnostic plots for TTNTD in the sotorasib arm of CAS RWE

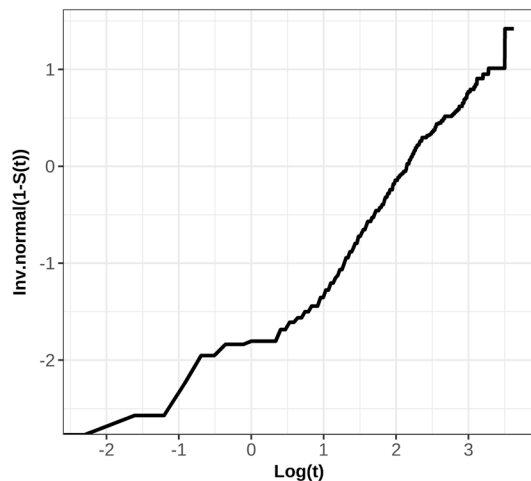
A: Log-cumulative hazard plot



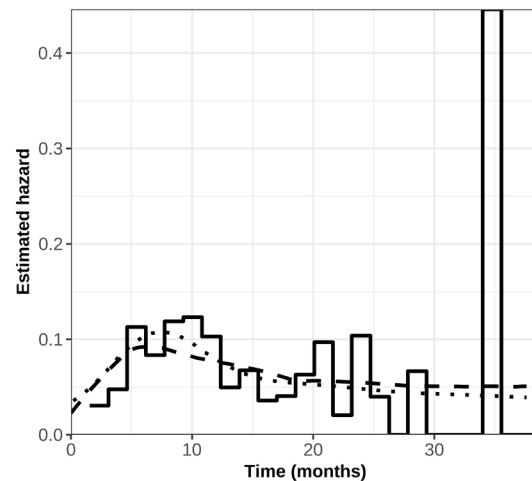
B: Logit survival plot



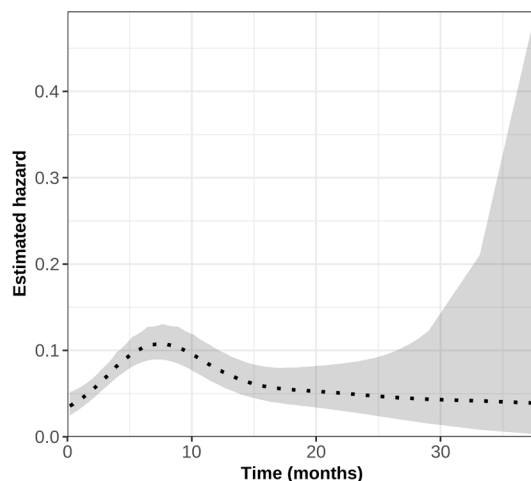
C: Inverse normal survival plot



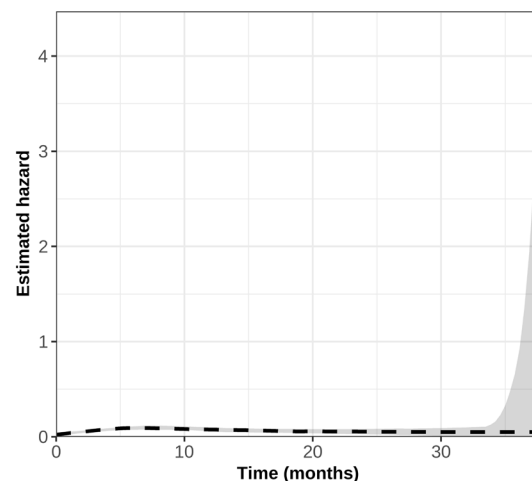
D: Unsmoothed (solid) & smoothed (dotted = 'bshazard' & dashed = 'muhaz') hazards



E: Smoothed hazard plot ('bshazard' with 95% CI)



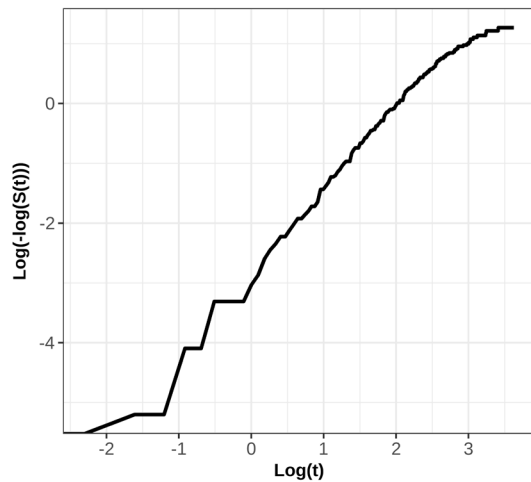
F: Smoothed hazard plot ('muhaz' with 95% CI)



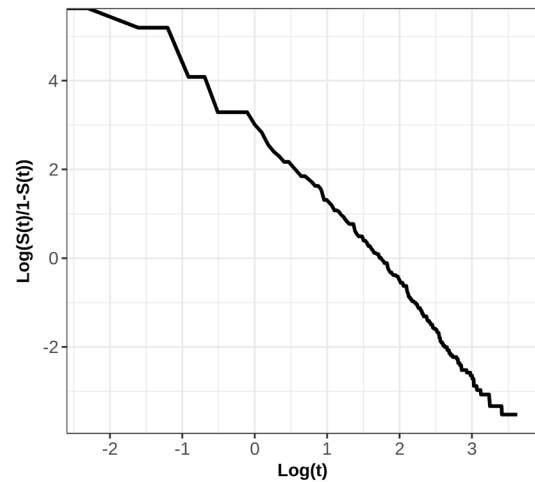
Abbreviations: CAS, Cancer Analysis System; RWE, real world evidence; TTNTD, time to next treatment or death.

Figure 8: Diagnostic plots for TTNTD in the docetaxel arm of CAS RWE

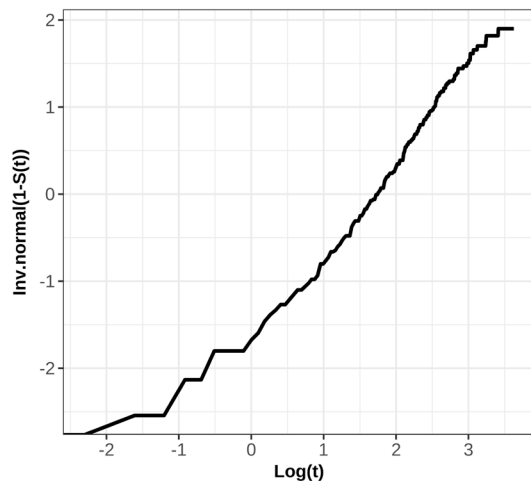
A: Log-cumulative hazard plot



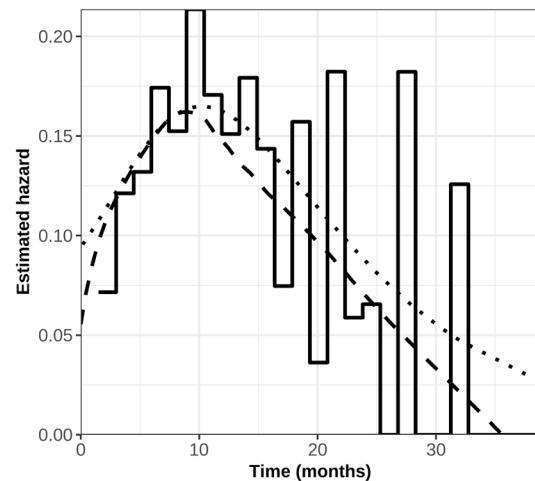
B: Logit survival plot



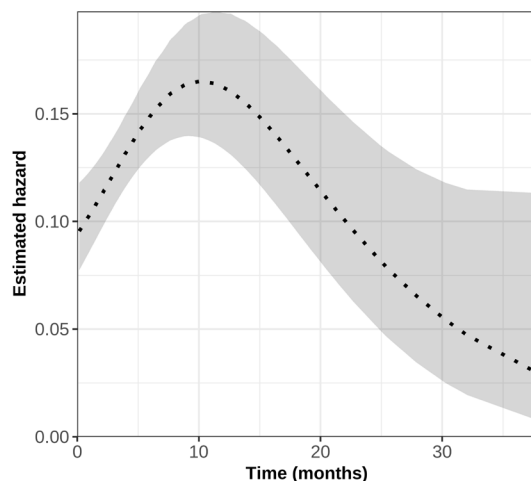
C: Inverse normal survival plot



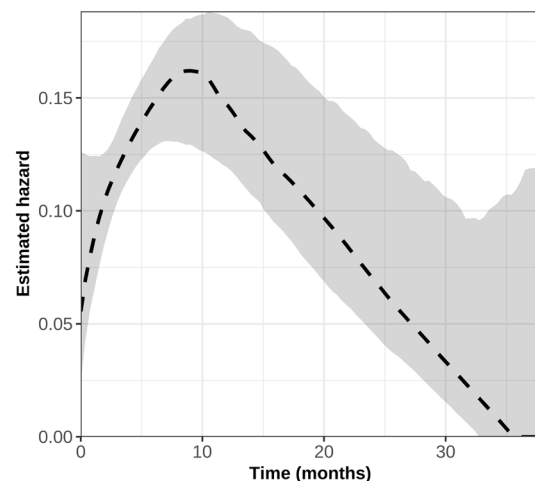
D: Unsmoothed (solid) & smoothed (dotted = 'bshazard' & dashed = 'muhaz') hazards



E: Smoothed hazard plot ('bshazard' with 95% CI)



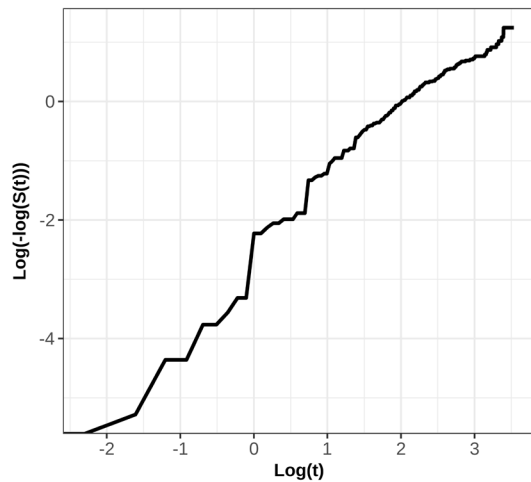
F: Smoothed hazard plot ('muhaz' with 95% CI)



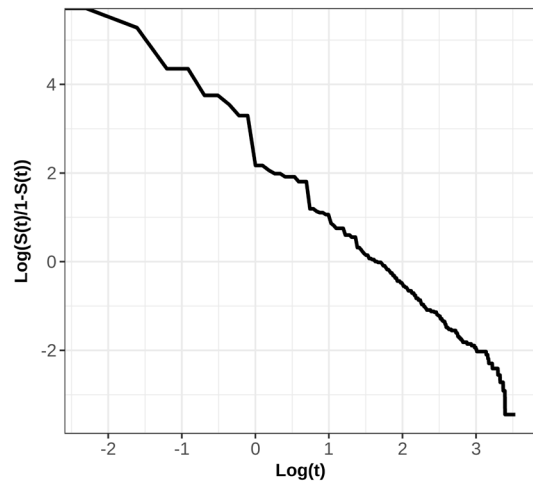
Abbreviations: CAS, Cancer Analysis System; RWE, real world evidence; TTNTD, time to next treatment or death.

Figure 9: Diagnostic plots for TTDD in the sotorasib arm of CAS RWE

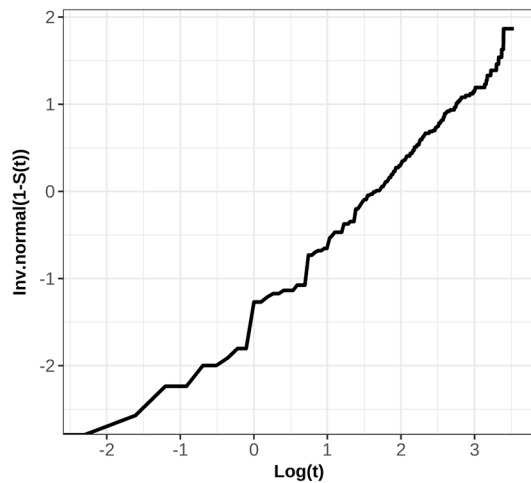
A: Log-cumulative hazard plot



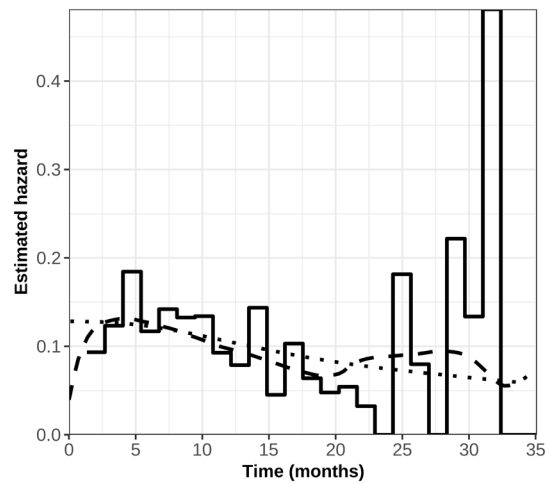
B: Logit survival plot



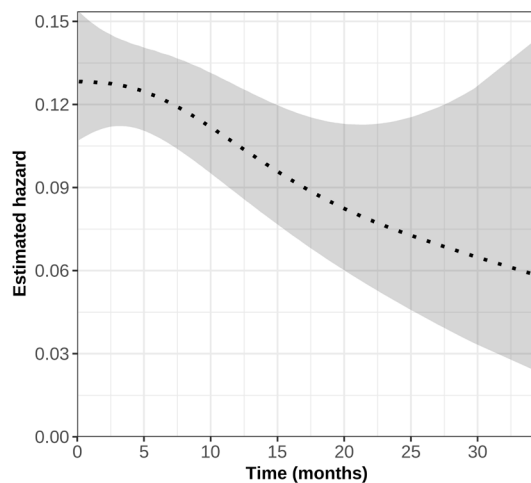
C: Inverse normal survival plot



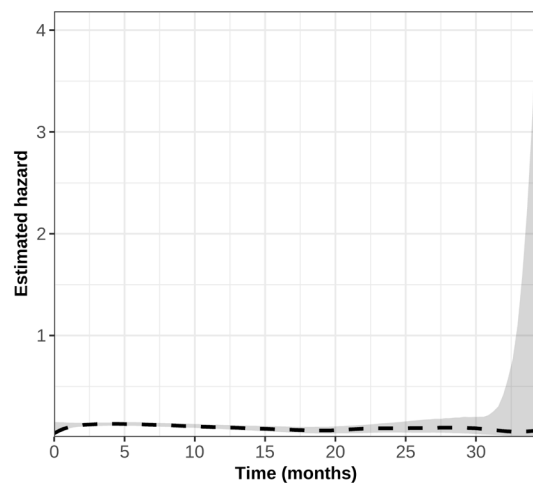
D: Unsmoothed (solid) & smoothed (dotted = 'bshazard' & dashed = 'muhaz') hazards



E: Smoothed hazard plot ('bshazard' with 95% CI)



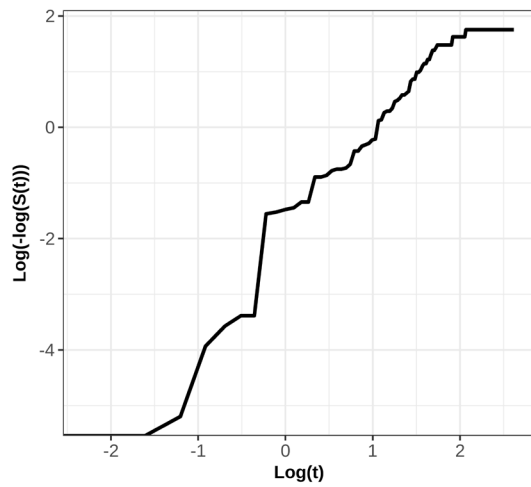
F: Smoothed hazard plot ('muhaz' with 95% CI)



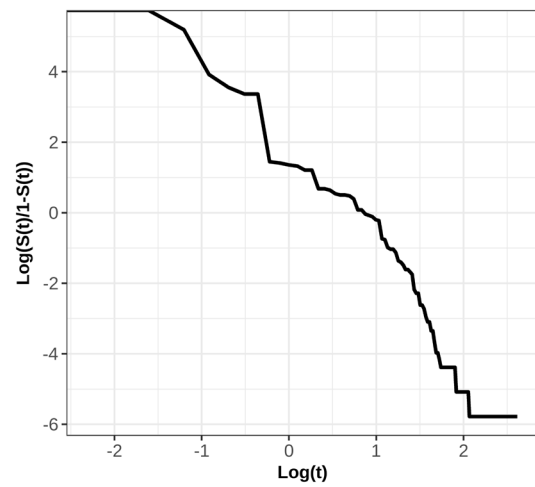
Abbreviations: CAS, Cancer Analysis System; RWE, real world evidence; TTDD, time to treatment discontinuation or death.

Figure 10: Diagnostic plots for TTDD in the docetaxel arm of CAS RWE

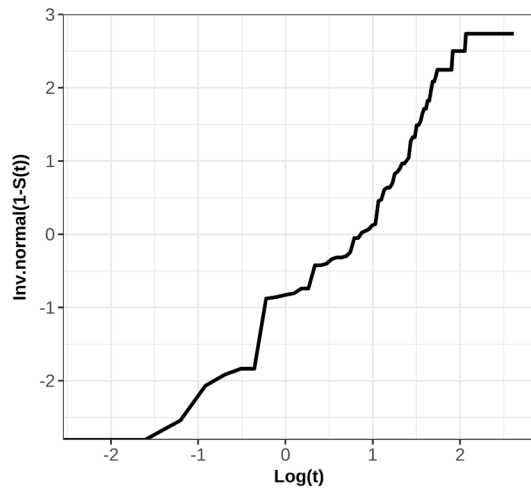
A: Log-cumulative hazard plot



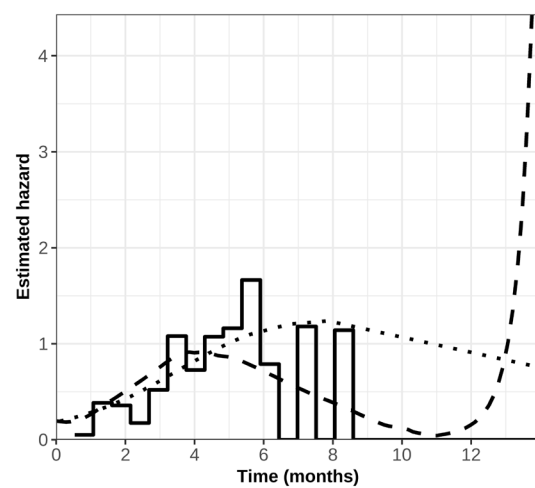
B: Logit survival plot



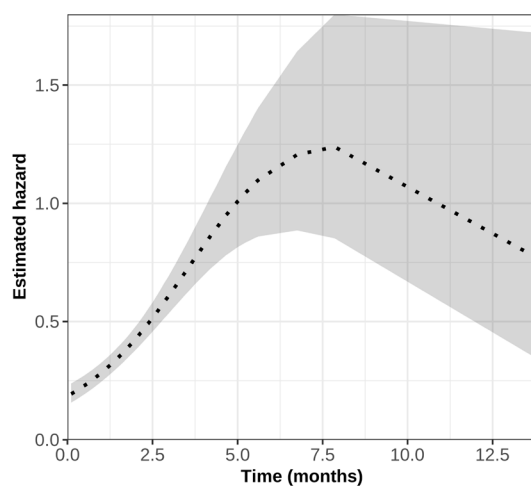
C: Inverse normal survival plot



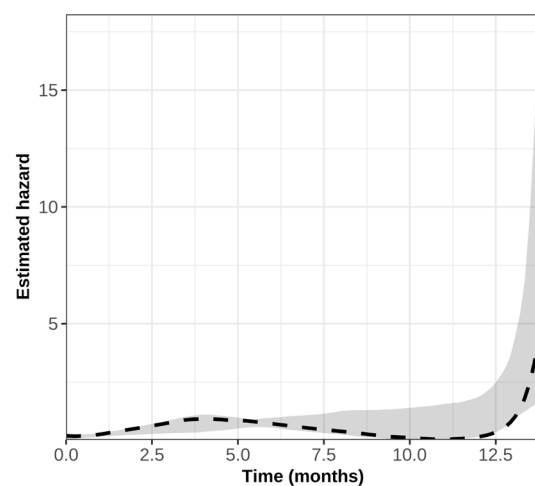
D: Unsmoothed (solid) & smoothed (dotted = 'bshazard' & dashed = 'muhaz') hazards



E: Smoothed hazard plot ('bshazard' with 95% CI)



F: Smoothed hazard plot ('muhaz' with 95% CI)



Abbreviations: CAS, Cancer Analysis System; RWE, real world evidence; TTDD, time to treatment discontinuation or death.

d) To examine diagnostics of parametric survival models (using the observed data):

i. Plot the cumulative hazard versus time.

Please see the response to question B8.c.

ii. Plot the log smoothed hazard versus time.

Please see the response to question B8.c.

iii. Plot the standard normal quantiles versus log time.

Please see the response to question B8.c.

iv. Plot the log survival odds versus log time.

Please see the response to question B8.c.

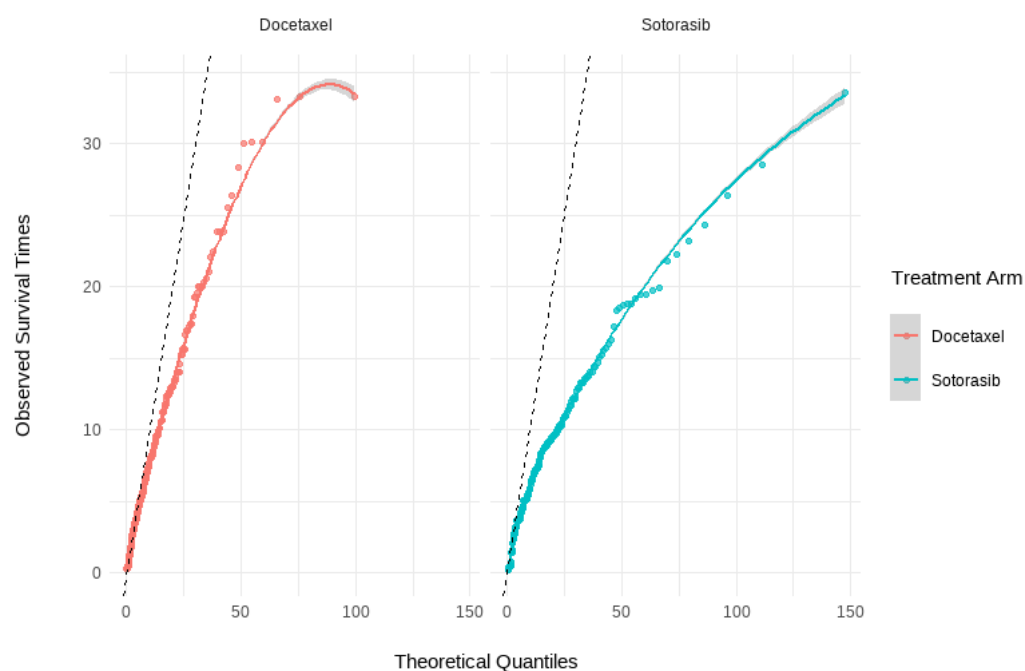
v. Provide a table of observed absolute OS and PFS data at various time points as well as their estimations per parametric model.

This information can be obtained via the “trace” worksheets of the economic model; to limit the length of the response, the results are not presented in this clarification question response, but all information required by the EAG for this question is present in the economic model.

e) To examine the accelerated failure time assumption, please provide quantile-quantile plots.

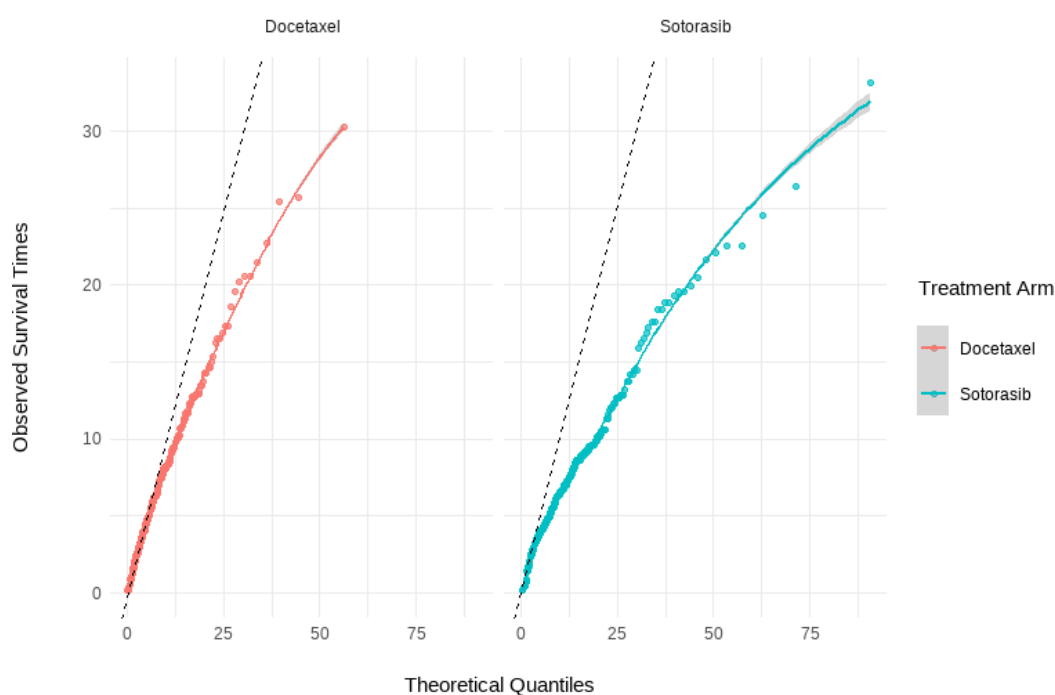
Quantile-quantile plots are presented below for the base case CAS RWE models used in the CS. Loess smoothing was used to calculate smoothed confidence bands. As in the CS, jointly-fitted models (using treatment as a covariate) were used for OS and TTNTD (Figure 11 and Figure 12) whereas independently-fitted generalised gamma models were used for TTDD for sotorasib and docetaxel respectively (Figure 13 and Figure 14).

Figure 11: Q-Q plot for jointly-fitted generalised gamma model for OS from CAS RWE



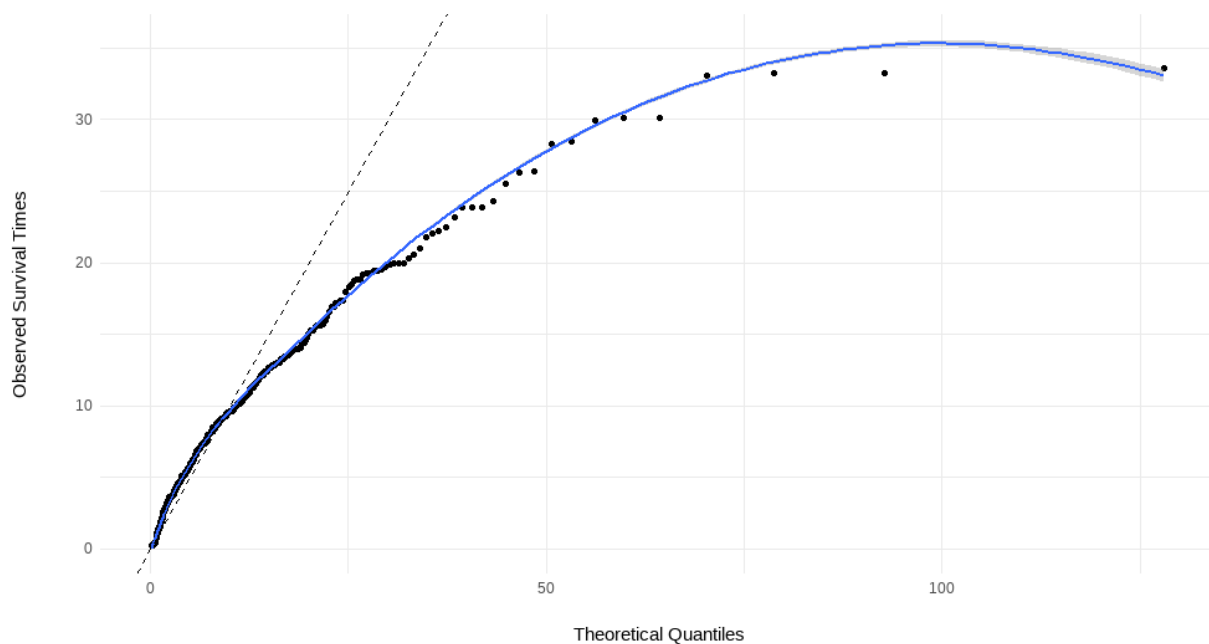
Abbreviations: CAS, Cancer Analysis System; OS, overall survival; Q-Q, quantile-quantile; RWE, real world evidence.

Figure 12: Q-Q plot for jointly-fitted generalised gamma model for TTNTD from CAS RWE



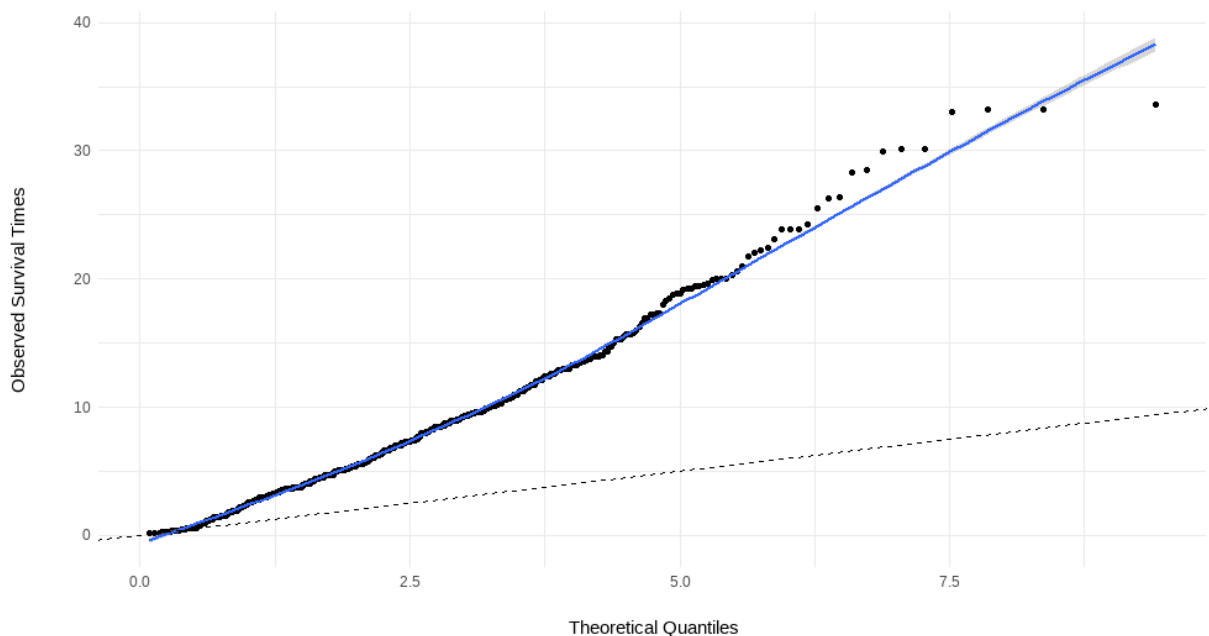
Abbreviations: CAS, Cancer Analysis System; Q-Q, quantile-quantile; RWE, real world evidence; TTDD, time to next treatment or death.

Figure 13: Q-Q plot for independently-fitted generalised gamma model for TTDD for sotorasib from CAS RWE



Abbreviations: CAS, Cancer Analysis System; Q-Q, quantile-quantile; RWE, real world evidence; TTDD, time to treatment discontinuation or death.

Figure 14: Q-Q plot for independently-fitted generalised gamma model for TTDD for sotorasib docetaxel from CAS RWE



Abbreviations: CAS, Cancer Analysis System; Q-Q, quantile-quantile; RWE, real world evidence; TTDD, time to treatment discontinuation or death.

- f) To examine the validity of the long-term extrapolations beyond the observed data, please provide supporting evidence that the extrapolations are consistent with relevant external data and expert opinion. For expert opinion, please provide a full description of the methods and results of the expert consultation conducted.**

Whilst the extrapolations were validated by a clinical expert, this was performed in an informal setting (i.e. a video call) and not via formal elicitation methods, for example, the SHELF elicitation framework or a Delphi panel. There are no other external data sources beyond what has been presented in the CS (i.e. CodeBreak 200 and Flatiron). The expert's feedback was that all parametric extrapolations are plausible, and so the parametric model selections were informed by a combination of goodness-of-fit and visual inspection. The document reporting the discussion with the clinical expert is provided alongside the clarification questions (40).

- g) Please justify the selection of the parametric survival models to estimate and extrapolate OS and PFS, taking into account the responses to the preceding questions as well as the "Survival Model Selection Process Algorithm" provided in NICE DSU TSD 14.**

Following the survival model process algorithm in NICE DSU TSD 14, there is sufficient evidence to suggest that a proportional hazards/accelerated failure time (AFT) approach is justifiable for the modelling of both OS and TTNTD (proxy for PFS). For TTDD, the proportional hazards and AFT assumptions were not met, and so individual model fitting was performed. The survival data were mature albeit not complete, so visual inspection, statistical goodness-of-fit, and clinical validity (a clinician interview) were used to inform curve selections submitted in the CS base case.

- B 9. Priority question. Treatment waning was not explicitly modelled by the company in its base-case, stating that the length of patient follow-up in the main source of clinical effectiveness was sufficient to capture any decline in treatment effectiveness.**

- a) Please justify the statement that the length of patient follow-up in the main source of clinical effectiveness was sufficient to capture any**

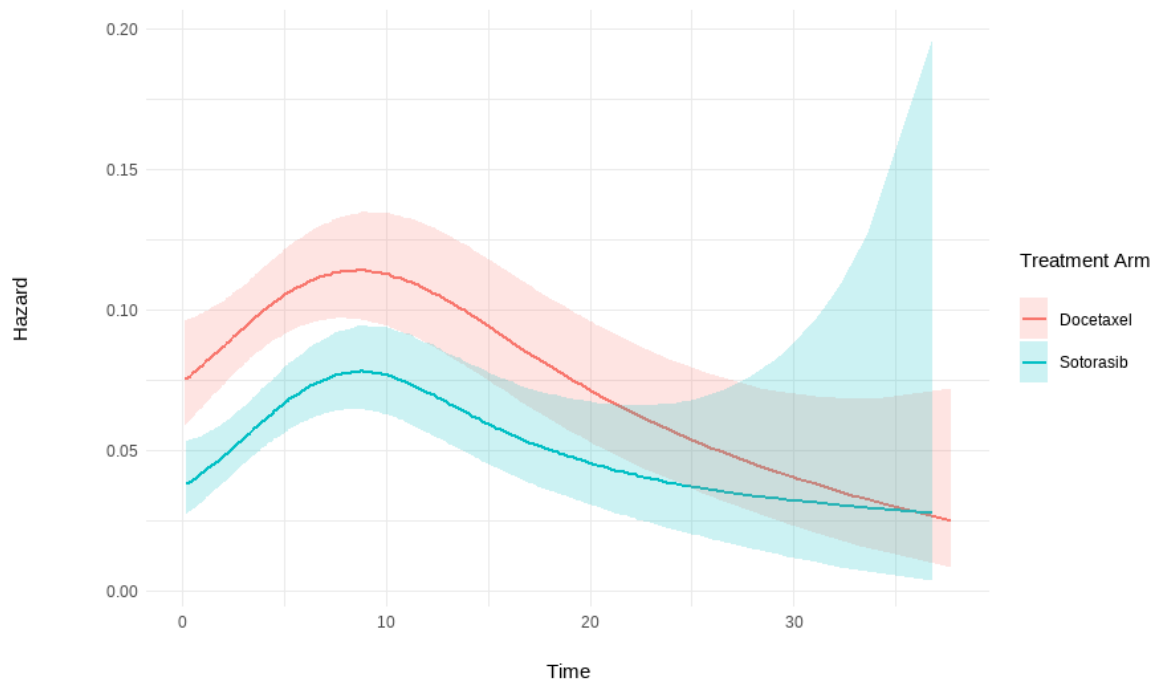
decline in treatment effectiveness, and elaborate on how treatment waning was captured in the current economic modelling.

The smoothed hazard functions provided in response to question B8 show high uncertainty in the estimate of the hazard function towards the end of the time horizon due to the number of patients at risk decreasing as time increases. It is difficult to make a definitive statement about treatment waning from these data alone, however the shape of the smoothed hazard functions appears to be similar for both sotorasib and docetaxel for OS (graph E in Figure 5 and Figure 6), suggesting that the hazard of death spiked at approximately 10 months in both arms, followed by a decrease in the hazard thereafter, albeit with high uncertainty.

b) Please provide additional evidence that assesses treatment waning for sotorasib and docetaxel in the observed data by plotting the smoothed hazards over time of both treatments (in one plot) separately for OS and PFS (TTNTD), both for CodeBreak 200 and the CAS RWE.

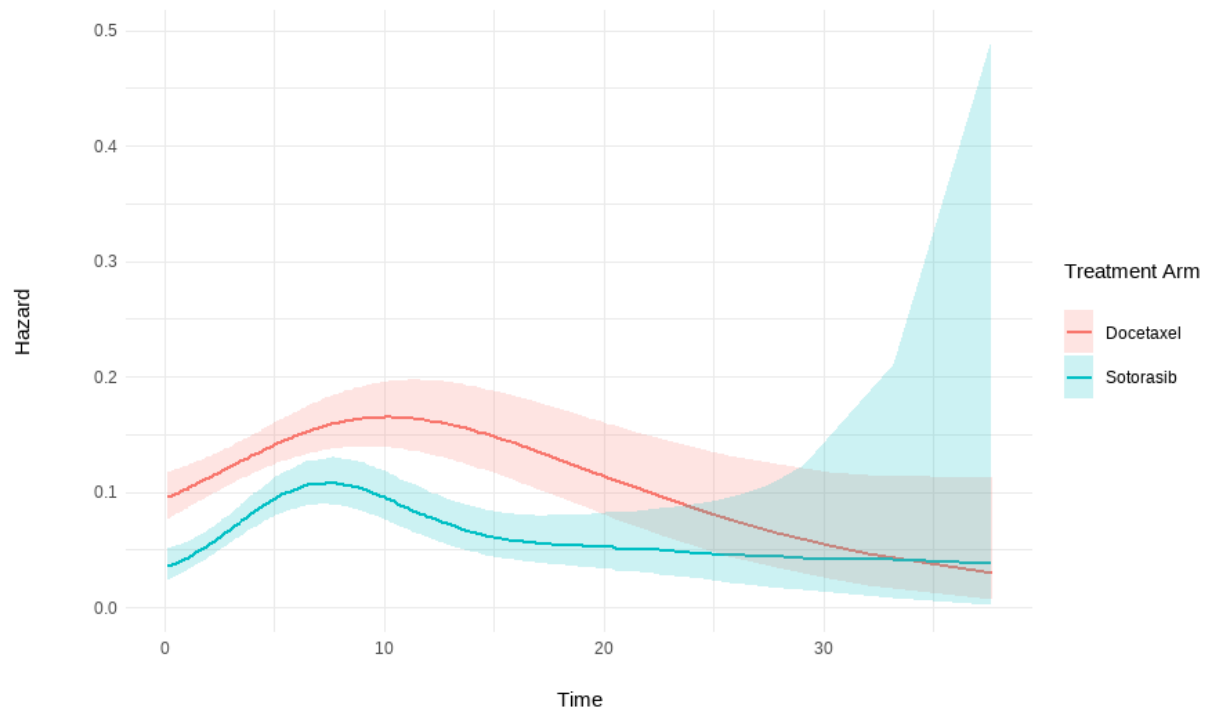
Separate smoothed hazard plots are provided in the Company response to question 8c, however for ease of interpretation smoothed hazard plots for the jointly-fitted OS and TTNTD survival data are shown in Figure 15 and Figure 16 below. The high uncertainty towards the end of the time horizon due to low patient numbers make any assessment of treatment effect waning highly uncertain. Unfortunately it was not possible to generate these plots for CodeBreak 200 in the timeframe for EAG clarification question responses.

Figure 15: Smoothed hazard plots (using bshazard) for OS from CAS RWE



Abbreviations: CAS, Cancer Analysis System; OS, overall survival; RWE, real world evidence.

Figure 16: Smoothed hazard plots (using bshazard) for TTNTD from CAS RWE



Abbreviations: CAS, Cancer Analysis System; RWE, real world evidence; TTNTD, time to next treatment or death.

B 10. Priority question. Time to treatment discontinuation or death (TTDD) was used to capture time on first line treatment. For CodeBreak 200, TTDD was derived by applying a HR to PFS as described in section 3.3.7.1.3. The EAG would like to receive further information on this approach, which falls short on the company's response in TA781 to EAG clarification question B7, stating that "It is important to note that a CDF [Cancer Drugs Fund] recommendation would facilitate further reduction in uncertainty in this parameter: a fully mature CodeBreak 100 TTD curve would be available, mature TTD for sotorasib vs docetaxel would be available from CodeBreak 200, and time on treatment data would be available from real world use of sotorasib in the NHS."

a) Please discuss all advantages and limitations of each evidence source (i.e., CAS RWE, CodeBreak 200) for informing TTDD, and justify why CAS RWE was preferred to inform TTDD in the CS base-case.

CAS RWE was used to inform TTDD in the economic model as it uses the same data source as the two other main outcomes in the model – OS and TTNTD (proxy for PFS). The main advantage to using CAS RWE is that the treatment discontinuation patterns identified are representative of the exact patient population who would receive sotorasib or docetaxel in UK clinical practice. As was the case for OS and TTNTD, the CAS TTDD dataset is larger and more mature than the CodeBreak 200 dataset. The CodeBreak 200 TTDD data has the advantage of being captured under clinical trial conditions, whereas the CAS RWE TTDD outcomes were estimated due to treatment end dates not being recorded in CAS – only the start dates of subsequent treatments were recorded. TTDD was calculated using the recorded start date of the current line of therapy and the number of cycles administered according to the rules described within the line of therapy algorithm in the CAS RWE study technical report included in the CS reference pack. CodeBreak 200 TTDD data were not used in combination with CAS RWE OS and TTNTD (proxy for PFS) as this would introduce additional uncertainty and heterogeneity of patient populations in regards to their geography.

b) Please elaborate on how TTDD for both sotorasib and docetaxel as observed in CodeBreak 200 compare to TTDD in the CAS RWE.

TTDD was captured in CodeBreak 200. For the sotorasib group the median duration of treatment was 19.86 weeks, and for the docetaxel group the median duration of treatment was 12.0 weeks. In CAS RWE, the median duration of treatment for the sotorasib group was 20.24 weeks and was 9.2 weeks for the docetaxel group. The estimates of TTDD for CAS RWE utilise larger patient numbers than CodeBreak 200 and demonstrate that the method used to estimate TTDD (based on the recorded date of the start of treatment and the number of cycles of treatment) generates plausible estimates of TTDD.

c) Please elaborate on how representative TTDD from CAS RWE and CodeBreak 200 are for TTDD in UK clinical practice, supported by additional evidence and clinical as well as health economic expert opinion.

The TTDD captured in CAS RWE closely resembles the duration of treatment in CodeBreak200, and is representative of UK clinical practice as it comprises of real-world outcomes of UK patients.

d) In the CS health economic model sheet “Trace interv” and “Trace comp1”, in columns X and Y a (currently turned off) feature “Preliminary time to discontinuation” was included which was not mentioned in the CS. Please explain the function of this feature, and its hard-coded multiplier.

This functionality is a vestigial feature of the Global model from which the UK-specific model was adapted and is non-functional in the model submitted by the Company. It was not used to perform any analyses and as a result was not described in the CS.

e) For CodeBreak 200, please explain the chosen approach to generate TTDD in more detail for sotorasib and relevant comparators, and highlight any differences.

The TTDD curves for the CodeBreak 200 scenario analysis were generated via pairwise Cox regressions performed on PFS versus TTDD for each treatment arm in CodeBreak 200 to generate time-varying HRs. This is distinct to the approach taken for the CAS RWE TTDD as it does not involve the use of parametric models. The

hazard ratios for PFS versus TTDD from CodeBreak 200 are close to 1 for sotorasib, suggesting that treatment continued to close to disease progression. For docetaxel, the HRs are lower, suggesting that patients discontinued treatment earlier than they experienced disease progression. The HRs are presented on the “TTD” sheet of the model in cells E32:E38.

f) Please justify the approach of using PFS as a proxy for TTDD for CodeBreak 200 and elaborate on why this approach was deemed more suitable than directly using available TTDD data from CodeBreak 200.

PFS was used directly as this is representative of how patients would be treated in a real-world scenario in line with the marketing authorisations of sotorasib and docetaxel; specifically, treatment until disease progression.

g) Please provide a scenario analysis and updated economic model directly informing TTDD using parametric survival modelling based on the TTDD data from CodeBreak 200. For the assessment of model suitability, please also provide details of all criteria as reported in NICE DSU TSD 14, including the EAG’s requests in clarification question B8.

These analyses have not been performed for the TTDD data from CodeBreak 200, and unfortunately it is not possible to perform these analyses and incorporate them into the model before the deadline to respond to the EAG clarification questions. The similarity between the median TTDD outcomes as described in the response to question B10.b suggests that the results are likely to be similar; the CAS RWE study also captured TTDD directly in the UK patient population and is a superior source of evidence.

B 11. In the CS health economic model sheet “Settings”, OS, PFS and TTD curves can be split into different time intervals. Please confirm that the cells in columns F (period last cycle) and G (HR vs docetaxel) of the settings tab in the economic model were originally (in TA781) used to inform the piecewise modelling of sotorasib versus nintedanib + docetaxel. Please clarify the function of these cells in the current submission, and if piecewise modelling is also applicable, please provide all relevant details in line with NICE DSU TSD 21.

The purpose of the cells is to allow for time-varying HRs to be used for comparisons between sotorasib and docetaxel. The cells in question are a holdover from the Global economic model which was utilised to develop the economic model included in the CS. The purpose of the cells was to allow for exploratory analyses which may have been relevant for other geographies but were ultimately not used in the CS. The comparison versus docetaxel + nintedanib from the original submission was implemented via HRs, but these were stored on the “OS”, “PFS”, and “TTD” sheets of the model.

Adverse Events

B 12. In the CS, treatment emergent, treatment-related adverse events with a grade 3 or 4 incidence $\geq 5.0\%$ (CodeBreak 200) were included. Disutilities pertaining to adverse events were excluded from the base-case and included in a scenario analysis. Further, no differentiation for costs or disutilities were made between grade 3 or 4 adverse events and all adverse events were assumed to last for a duration of four weeks.

- a) Treatment-related AEs were defined as occurring in $> 10\%$ of subjects in either group. Please provide justification and supporting evidence for the chosen cut-off and why AEs with an incidence equal or below 10% were not considered relevant for inclusion.

Section 2.11.1.3.2 of the CS reports the most commonly treatment-related adverse events (AEs) occurring in $>10\%$ of subjects in either group. For the incidence of treatment-related AEs for a lower cut-off of 5% please see the publication by de Langen 2023 (41). Note that in the publication, ‘neutropenia’ and ‘neutrophil count decreased’ in combined into one category ‘neutropenia’ (41).

To clarify, the model includes the AE incidence of treatment-emergent treatment-related grade ≥ 3 occurring in $>5\%$ of subjects in either group as reported in Table 34 of the CS.

- b) Please provide justification and supporting evidence for excluding grade 1 and 2 adverse events, as well as grade 3 and 4 adverse events with an

incidence < 5.0%. Please provide an updated economic model and scenario analysis including all adverse events, irrespective of grade or incidence rate.

Grade 1 and 2 AEs are considered low grade, therefore, they are associated with low costs and unlikely to change the conclusions of the economic modelling.

- c) Please provide justification and supporting evidence to suggest that the impact of adverse events on health-related quality of life would already be captured in the CS base-case, particularly provided the decision to exclude patients with missing data.

The impact of AEs on HRQoL is captured in the CS base case through the use of time-to-death utilities. As highlighted in Section 3.4.4 of the CS, time-to-death utilities more accurately reflect changes in HRQoL, including those due to adverse events, than a progression-based approach. Based on this evidence, the model base case applies time-to-death utilities by treatment arm, which appropriately reflects the impact of adverse events on patient quality of life.

With regards to missing data, only patients with a non-missing utility index at any time during the study were included as discussed in Section 3.4.1 of the CS. This approach ensured that only complete and reliable data were used, while still capturing a broad representation of patient experience over time. For more information on completion rates, see Appendix J.3.

- d) Please provide justification and supporting evidence for the approach to include the same costs and disutilities for grade 3 and 4 adverse events. Further, please provide an updated economic model and scenario analysis including grade-specific disutilities and costs per adverse event.

Grade 3 and 4 AEs are considered severe and typically require medical attention. Both grades are often evaluated together in economic analyses.

The unit costs used in the model, as described in Section 3.5.4, captured a range of costs associated with the management of adverse events, with the complexity of patients' conditions reflected in the variation of CC scores across the included HRGs for most of adverse events.

Moreover, the reported sources of disutility values typically present a combined value for grade 3 and 4 AEs and therefore do not support the request to provide an updated economic model.

- e) Please provide justification and supporting evidence for the assumption that all adverse events would last for four weeks, irrespective of grade or type. Further, please provide an updated economic model and scenario analysis, utilising durations based on adverse event type and grade.

To maintain consistency between the current submission and TA781 (31), the current model applies the same assumption of 4 weeks at baseline as that used in the previous appraisal, including a lower bound of 3.2 weeks and upper bound of 4.8 weeks. This assumption reflects a pragmatic and accepted approach previously considered appropriate by the ERG and committee.

Therefore, no further analysis was performed focusing on duration based on adverse event type and grade. The impact of varying AE duration was explored through sensitivity analysis using the above bounds mentioned which sufficiently captures the uncertainty around this parameter.

B 13. Disutilities and costs related to adverse events are reported in CS Tables 59 and 63 respectively. The EAG noted that the type of adverse events (e.g. inclusion of anaemia and exclusion of pleural effusion), their disutility and unit costs, and sources in the current appraisal differ from the ones reported in TA781. The EAG further noted that the reported unit cost for code 800 Clinical Oncology Service in CS Table 63 (£159.94) to inform decreased neutrophils, decreased white blood cells, increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) is lower than the unit cost reported in [tarlatamab for previously treated advanced small-cell lung cancer \[ID6364\] NICE GUID-TA11423](#) (£303).

- a) Please provide justification for the observed differences in type, disutility, cost and source of adverse events between the current appraisal and TA781.

The base case of the submitted model utilises Grade ≥ 3 treatment-related AE profile from CodeBreakK 200 as the CAS RWE did not collect any safety data. The safety

profile in TA781 was based on the data collected in CodeBreak 100. Therefore, some differences in the included AE are due to a different source of the data.

The company aimed to maintain consistency between the current submission and TA781. Therefore, disutility values for most of the AE were the same as in TA781. For diarrhoea, fatigue, febrile neutropenia and neutropenia, the SLR identified a relevant paper by Nafees et al. 2017 (30) which was used instead of the previous publication by the same author (Nafees et al. 2008 (42)). A new source for disutility for anaemia was required; an AE not included in the original submission.

The approach for estimating unit costs for majority of the AE was based on recent committee papers for NICE GID-TA11423 (in development) (43) in the same disease area. For dyspnoea, an alternative approach was used instead of assumption. Please see section 3.5.4 of the original submission for more information.

- b) Please justify and correct the inconsistency related to the code 800 Clinical Oncology Service unit cost.

To maintain consistency between the source of the unit costs, the current submission utilises the NHS Reference Costs whereas NICE GID-TA11423 (in development) utilised the NHS Payment Scheme. NHS Reference Costs are more appropriate source of the unit costs as they reflect the prices paid in the NHS as specified in NICE PMG36 (section 4.4.4) (44).

- B 14. For diarrhoea, fatigue, febrile neutropenia and neutropenia, standard errors for adverse event disutilities were assumed to be 5% of the input value due to lack of reporting. However, for other inputs, 20% variation was assumed when no uncertainty estimate was available. Please provide an updated economic model and (cost-effectiveness) results having consistently set all to 20% (where uncertainty estimates are not available).

Thank you for flagging, and the company agrees that 20% should be used instead of 5%. The issue has now been corrected in the model. Please see 'ModelChangesJuly2025' tab. As AE disutilities are not included in the base case, they do not affect the deterministic or probabilistic base case results.

Health-related quality of life

B 15. Priority question. The CS analysis calculates utility values using descriptive statistics by time-to-death (base-case) and progression status (scenario analysis). The EAG would like to see further detail regarding the calculation of utility values utilised in the base-case and scenario analysis.

a) The analysis consists of subjects in the phase 3 full analysis set with a non-missing utility index for at least one timepoint across the study period. Please provide/specify:

i. Details regarding patterns of missingness with respect to treatment arm, progression status, time-to-death, and adverse reaction prevalence and include an overview of the number of patients for which data was available at each time point.

Please note that the base case analysis for EQ-5D analyses used the French value set to calculate utilities, so any following diagnostic plots utilise French utility values; the UK value set was used for the submission, however, as per the NICE reference case. Completion of the EQ-5D-5L at baseline comprised 97% of the full analysis set. Completion rates of the EQ-5D-5L were lower at day 5 for cycles 1-3 compared to visits in day 1. A table of completion rates is presented in Table 3.

Table 3: CodeBreak 200 EQ-5D-5L completion rates by assessment time point

Assessment points	Phase 3 FAS (N=345)		Phase 3 FAS-Sotorasib (N=171)		Phase 3 FAS-Docetaxel (N=174)	
	Number completed	% of visit set	Number completed	% of visit set	Number completed	% of visit set
Baseline*	320	92.754	166	97.076	154	88.506
Cycle 1 Day 5	270	87.662	144	79.121	126	76.829
Cycle 2 Day 1	263	90.068	149	83.708	114	79.720
Cycle 2 Day 5	239	83.860	128	73.563	111	70.701
Cycle 3 Day 1	251	94.361	140	90.323	111	88.095
Cycle 3 Day 5	192	80.335	105	69.079	87	64.925
Cycle 4 Day 1	206	94.495	119	90.840	87	87.879
Cycle 5 Day 1	187	95.897	107	93.043	80	90.909
Cycle 6 Day 1	165	95.930	94	93.069	71	91.026
Cycle 7 Day 1	151	96.795	90	94.737	61	92.424

	Phase 3 FAS (N=345)		Phase 3 FAS-Sotorasib (N=171)		Phase 3 FAS-Docetaxel (N=174)	
Assessment points	Number completed	% of visit set	Number completed	% of visit set	Number completed	% of visit set
Cycle 8 Day 1	140	95.890	82	93.182	58	90.625
Cycle 9 Day 1	120	94.488	71	91.026	49	87.500
Cycle 10 Day 1	113	94.167	67	90.541	46	86.792
Cycle 11 Day 1	109	97.321	66	95.652	43	93.478
Cycle 12 Day 1	100	94.340	60	90.909	40	86.957
Cycle 13 Day 1	101	97.115	60	95.238	41	93.182
Cycle 14 Day 1	91	95.789	55	93.220	36	90.000
Cycle 15 Day 1	87	97.753	53	96.364	34	94.444
Cycle 16 Day 1	83	98.810	50	98.039	33	97.059
Cycle 17 Day 1	76	97.436	47	95.918	29	93.548
Cycle 18 Day 1	72	97.297	42	95.455	30	93.750
Cycle 19 Day 1	66	97.059	43	95.556	23	92.000
Cycle 20 Day 1	62	100.000	41	100.000	21	100.000
Cycle 21 Day 1	51	96.226	35	94.595	16	88.889
Cycle 22 Day 1	44	100.000	33	100.000	11	100.000
Cycle 23 Day 1	39	97.500	29	96.667	10	90.909
Cycle 24 Day 1	26	96.296	20	95.238	6	85.714
Cycle 25 Day 1	17	94.444	14	93.333	3	75.000
Cycle 26 Day 1	15	93.750	13	92.857	2	66.667
Cycle 27 Day 1	14	100.000	12	100.000	2	100.000
Cycle 28 Day 1	11	100.000	9	100.000	2	100.000
Cycle 29 Day 1	8	100.000	7	100.000	1	100.000
Cycle 30 Day 1	8	100.000	7	100.000	1	100.000
Safety Follow-Up	116	100.000	65	100.000	51	100.000
Safety Follow-Up After Crossover	9	100.000	-	-	9	100.000
Long-Term Follow-up 1	56	100.000	27	100.000	29	100.000
Long-Term Follow-up 2	24	100.000	10	100.000	14	100.000
Long-Term Follow-up 3	10	100.000	4	100.000	6	100.000
Long-Term Follow-up 4	4	100.000	2	100.000	2	100.000
Long-Term Follow-up 5	2	100.000	1	100.000	1	100.000

Abbreviations: FAS, full analysis set.

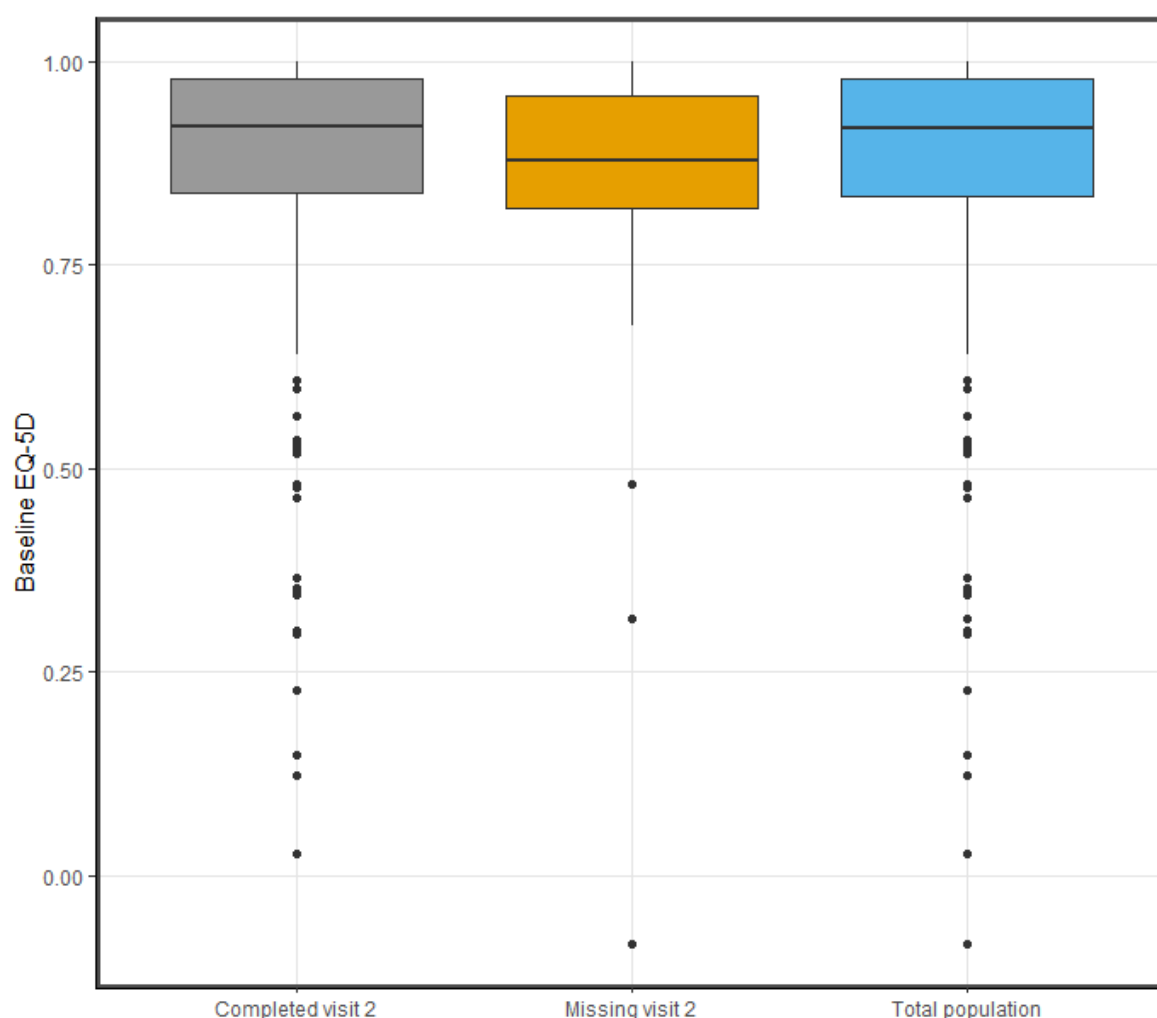
Parallel boxplots assessed whether French utility index scores are lower for subjects who did not provide data in the following cycle (i.e. data is missing-at-random).

Clarification questions

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These generally show that median scores of baseline EQ-5D-5L scores were similar between groups with observed and missing data at subsequent treatment cycles (see Figure 17). The missing-at-random assumption was therefore considered appropriate.

Figure 17: Parallel box plots for French utility scores at baseline by missingness at cycle 1



- ii. Whether missing data imputation was considered. If applicable, please indicate which method of missing data imputation was used and provide justification for this decision in light of the response to clarification question B14a)i. If not, please provide justification for not incorporating such imputation into the present analyses.

Imputation of missing values was not performed and a complete case analysis approach was used. Due to the low number of missing values, and the fact the values were missing at random, the impact on results, should imputation be performed, is expected to be negligible. The complete case approach used also allows for greater reproducibility.

b) The current approach for estimating utility values does not account for repeated measures within patients. Further, within patients with non-small cell lung cancer, Hatswell *et al.*, 2024 (see: <https://doi.org/10.1007/s40273-023-01314-2>) found the use of continuous models provide a statistically better fit compared to the use of grouping time-to-death as discrete periods.

i. Please clarify the exact approach taken to estimating utility values by providing clear details regarding both time-to-death and health state approaches.

For the time-to-death approach, date of death was derived from CodeBreak 200 OS data, in addition to the last known alive date. EQ-5D-5L assessments were performed for the following health states:

- Less than 1 month to death (defined as within 30 days of death)
- Between 1 and 3 months to death (defined as 31-90 days until death)
- Between 3 and 6 months to death (defined as 91-183 days until death)
- More than 6 months to death (defined as ≥ 184 days until death)

For the health state approach, the date of progression was derived from PFS data, using the Investigator Assessment (IA) definition. PFS-IA was applied, as IA triggered sotorasib discontinuation and crossover. Patient reported outcome measures (PROM) assessments were defined as pre-progression or post-progression.

ii. Please provide justification and supporting evidence for the decision to analyse HRQoL data descriptively rather than a regression-based analysis (i.e., mixed effects models).

Both a regression-based approach and descriptive approach were investigated and the results were similar for both analyses; for ease of interpretation of methods, the descriptive approach was chosen. This approach was considered appropriate for capturing key trends in HRQoL without overfitting the data.

iii. Please clarify why and how the chosen groupings of time-to-death periods were selected and provide justification for the decision to not model time-to-death as a continuous function. Further, please provide an updated economic model and scenario analysis utilising a continuous time-to-death approach to deriving utility values.

We appreciate the reference to Hatswell et al (2024) (45). However, this publication was not available at the time the utility analysis was planned. The selected groupings of time-to-death periods were based on the previous utility analysis conducted using the HRQoL data from CodeBreak 100 as was used in the original NICE STA. These categories were based on an earlier analysis by Hatswell et al and were validated by clinicians as described in the original TA781 clarification questions (46). Modelling time-to-death as a continuous function would have also required assuming a specific (linear or non-linear) functional form. As the true shape of the relationship is unknown, grouping was preferred to minimise bias due to potentially incorrect extrapolation assumptions. Whilst grouping may introduce some imprecision, we note this is likely to be conservative and bias results in favour of docetaxel rather than sotorasib. Further to this, it is unfortunately not possible to perform another utility analysis which uses a continuous time-to-death approach in the timeframe for responses to the EAG clarification questions. However, we have performed mixed model for repeated measures (MMRM) analyses based on the grouped time-to-death approach, which are presented below. The MMRM outputs are shown in Table 4 and the cost-effectiveness results using the updated base case model are shown in Table 5.

Table 4: MMRM-based utility analysis from CodeBreak 200 (primary data cut)

Treatment arm	Time-to-death	Estimate	SE	p-value	Lower CI	Upper CI
Sotorasib	Intercept (i.e. Time-to-death > 6 months)	████	████	████	████	████
	Time-to-death- Below 1 month	████	████	████	████	████
	Time-to-death -Between 1 and 3 months	████	████	████	████	████
	Time-to-death -Between 3 and 6 months	████	████	████	████	████
Docetaxel	Intercept (i.e., Time-to-death > 6 months)	████	████	████	████	████
	Time-to-death- Below 1 month	████	████	████	████	████
	Time-to-death -Between 1 and 3 months	████	████	████	████	████
	Time-to-death -Between 3 and 6 months	████	████	████	████	████

Abbreviations: CI, confidence interval; MMRM, mixed model for repeated measures; SE, standard error.

Table 5: Updated deterministic results utilising MMRM-based utility analysis from CodeBreak 200 (primary data cut)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	11,731	████	████	-	-	-	-	-
Sotorasib	████	████	████	████	████	████	████	26,998

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MMRM, mixed model for repeated measures; QALY, quality-adjusted life year.

- c) The CS suggests that progression status and time-to-death utility approaches could not be combined due to the structure of PSM models. Please provide an updated economic model and scenario analysis informing health state utility values with a full model (i.e., mixed effects model) including (but not limited to) treatment arm, disease progression, and time-to-death. Here, the health state utility value approach can incorporate a disutility “penalty” based on time-to-death weighted at each cycle. Please include covariate coefficients (and associated 95% confidence intervals) and full model diagnostics.

It is unfortunately not possible to perform this analysis and incorporate it into the economic model in the timeframe for responses to the EAG clarification questions.

- d) Please clarify whether age and sex adjustment was applied to utility calculations in both the time-to-death and health state utility value approaches. If not, please provide an updated economic model and scenario analysis incorporating age and sex adjustment.

No separate age and sex adjustment for utility values (e.g. using the Ara and Brazier algorithm (47)) was performed, although it should be noted that the time-to-death utility approach used in the model base case does incorporate patient age as part of the time-to-death analysis. The impact of incorporating the Ara and Brazier age and sex adjustment in the previously submitted model had a minor impact on the ICER, and the same would be true for this analysis.

B 16. Priority question. The CS utilises the crosswalk algorithm by Van Hout *et al.* (2012) to map EQ-5D-5L outcomes to EQ-5D-3L. The latest version of the NICE health technology assessment manual (section 4.3.16) stipulates that the mapping function developed by the DSU (Hernández Alava *et al.* 2017), using the EEPRU dataset (Hernández Alava *et al.* 2020), should be used for reference-case analyses. Please provide an updated economic model and (cost-effectiveness) results utilising the mapping function by Hernández Alava *et al.* 2017. Please also update impacted scenario analyses and the quality-adjusted life year (QALY) shortfall analysis.

It is unfortunately not possible to repeat this analysis using the Hernandez Alava et al crosswalk algorithm in the timeframe given for EAG clarification question responses.

B 17. Utility values utilised in the CS base-case (time-to-death) and health state utility value (HSUV) scenario analyses are treatment-dependent.

- a) Please discuss the plausibility of this approach (also considering the coefficient of the treatment covariate in the mixed effects regression model requested in clarification question B14c) and discuss (if any) treatment-specific factors that may impact HRQoL that would justify the use of treatment-dependent utility values.

The treatment-dependent approach allows for any HRQoL differences between the sotorasib and docetaxel arms to be captured. Differences in utility values may be driven by different patient outcomes and different rates and severities of adverse events. The model also separately considers a utility decrement for intravenous (IV) administration, and AE-specific disutilities sourced from systematic reviews, although these options are disabled by default to prevent any double-counting of disutilities this approach may introduce. The Company recognises that a treatment-independent approach may also be valid and has provided results for this scenario in the response to question B17.b.

- b) Please provide an updated economic model and scenario analyses utilising treatment independent utilities for both the time-to-death approach and HSUV approach.

The updated model will be provided alongside this document.

None of the changes in the model, included in the response to questions B14, B7.e.i, or B18 and summarised in “ModelChangesJuly2025” tab of the model, impact the deterministic base case results or scenario results. The change to docetaxel RDI, discussed in question B18.a, was included before running analyses reported below.

The company acknowledge that AE disutilites were unintentionally left out of Scenario 6 included in Table 74 of the CS. The updated results, now including these

disutilities, are shown in Table 6 below. Please note that this analysis constitutes the base case for all scenarios included in Table 7.

The deterministic results for the scenario analyses using utilities by progression status and AE disutilities are reported in Table 6.

The results do not differ substantially from the scenario results reported in Table 75 of the CS. Utilising per progression status approach of modelling utilities led to decrease in incremental quality-adjusted life years (QALYs) across all scenarios, except scenario #5. Increase in incremental QALYs in scenario #5 was due to using alternative best fitting distributions from the CAS RWE study which was considered not appropriate for the base case of the model as described in Section 3.3.4.2 and 3.3.5.2 of the CS.

Table 6: Updated deterministic results for scenario #6 included in the CS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	11,731	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	27,461

Abbreviations: CS, company submission; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 7: Deterministic scenario analyses results utilising per progression status approach of modelling utilities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Scenario #1: Source of clinical data: CAS RWE study with Flatiron analysis OS for docetaxel								
Docetaxel	11,709	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	26,889
Scenario #2: Source of clinical data: CAS RWE study with PFS from CodeBreak 200								
Docetaxel	11,389	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	28,751
Scenario #3: Source of clinical data: CodeBreak 200 with Flatiron analysis OS for docetaxel								
Docetaxel	12,883	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	18,832
Scenario #4: Source of clinical data: CodeBreak 200 primary analysis								
Docetaxel	13,538	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	31,510

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Scenario #5: Distributions used for the CAS RWE study								
Docetaxel	12,444	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	28,274
Scenario #6: not required (per progression utilities were tested in this scenario)								
Scenario #7: Inclusion of genetic testing costs (Hamblin 2017(48))								
Docetaxel	11,731	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	29,727
Scenario #8: Alternative source of terminal costs								
Docetaxel	12,945	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	27,434

Abbreviations: CAS, Cancer Analysis System; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RWE, real-world evidence.

Costs

B 18. Priority question. The model applies a relative dose intensity (RDI) for sotorasib (86.42%) and docetaxel (90.40%) to account for temporary treatment interruptions, dose reductions, and/or missed doses. The RDI for both treatments was obtained from the CodeBreak 200 CSR using the safety analysis set.

a) Please provide the definition of RDI in the current submission.

The definition of relative dose intensity (RDI) was reported in CodeBreak 200 CSR (Table 12-1): *“actual dose intensity/planned dose intensity*100, where actual dose intensity is the actual cumulative dose divided by the actual duration of IP administration (days), planned dose intensity is 960 mg/day and 75 mg/m²/day for sotorasib and docetaxel, respectively”* (49).

Please note that the company crosschecked the results with the CSR for CodeBreak 200 and identified inconsistencies with the model. Those include (1) difference in point estimate for RDI for docetaxel at 2 decimal places; (2) standard errors (SEs) for RDI for both docetaxel and sotorasib. The updated SE are much lower than originally included.

The changes in the model inputs do not affect the results of the deterministic base case results (please see 'ModelChangesJuly2025' tab for more details). However, the updated deterministic sensitivity analysis indicated that RDI for sotorasib is no longer the most influential model parameter.

b) Please explain whether RDI is applicable to both oral and intravenous treatments.

Yes, RDI is applicable to both oral and intravenous treatments. RDI is used in calculations related to number of tablets or vials used for patients on treatment.

c) Please provide details on how RDI was calculated for sotorasib and docetaxel separately, and whether there were differences due to their different mode of administration.

Please see the response to Question B18.a for a full definition which was used for both treatments.

d) Please justify the differences (also the incremental differences) in RDI between the current submission and those in the initial submission (TA781).

TA781 used CodeBreak 100 trial as the source of the evidence whereas the current submission utilises CodeBreak 200 trial. As those are two separate studies, and separate patient populations, the differences in RDIs are expected.

The company reviewed the results reported in Table 37 in TA781 (31) and Table 60 in the current CS. RDIs for both docetaxel (90.3% vs 90.4%, respectively) and sotorasib (89.2% vs 86.4%, respectively) are closely aligned and not expected to meaningfully alter the model's outcomes.

e) Please provide a scenario analysis assuming equal RDIs for sotorasib and docetaxel, as recommended by the EAG in TA781.

The deterministic base case results, assuming the same RDI for both sotorasib and docetaxel, are presented in Table 8. RDI was assumed at 88.41% which is the average of observed RDIs for sotorasib and docetaxel as suggested in TA781 (31).

Overall, the ICER was not substantially affected and increased by £597 from the deterministic base case in the CS. The calculations consider the severity modifier of 1.7.

Table 8: Base case results (deterministic) assuming the same RDI for sotorasib and docetaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	11,730	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	26,873

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; RDI, relative dose intensity.

B 19. Priority question. Drug wastage and vial sharing were not clearly discussed within the CS. The EAG noted various costing options in the economic model, including “per treatment day” and “per opened pack” to calculate treatment costs. The latter seems to include wastage, if a pack is not finished at the end of treatment or if a vial is not fully used per administration.

a) Please clarify whether drug wastage and vial sharing are applicable to sotorasib and docetaxel.

As mentioned by the EAG, the latter option of “per open pack” includes wastage as the full pack or vial cost is accounted for in the model, despite the amount being used.

b) Please elaborate on the different costing options (i.e. per treatment day and per opened pack) within the economic model.

Both options contribute to the calculation of drug acquisition costs and differ by the time when the costs are accounted for in the model. When the method “per treatment day” is selected, the model includes the drug acquisition costs at each model cycle; when the method “per open pack” is selected, the model accounts for the drug acquisition costs at the time when the new pack is required.

c) Please clarify and justify what the current approach is and, whether this is similar or different between sotorasib and docetaxel.

The same approach is used for both sotorasib and docetaxel as the model settings “Method to calculate treatment costs” applies to both comparators.

The company acknowledges that the selected approach does not account for wastage and may therefore underestimate the true cost of the treatments included. When the “per open pack” option is selected, the drug acquisition costs of sotorasib and docetaxel increase by [REDACTED] and £11, respectively. This corresponds to an approximate increase of [REDACTED] for sotorasib and 20.5% for docetaxel. Although the ICER increases by £1,755, when applying a severity modifier of 1.7, the relative impact of the costing method is greater for docetaxel. Therefore, the “per open pack” approach is considered to favour sotorasib in comparative terms. Please see Table 9 below for full results of the scenario analysis.

d) Please discuss the potential implications of oral (i.e., sotorasib) versus intravenous (i.e., docetaxel) administration of treatment for drug wastage and vial sharing.

The route of drug administration might have an important implication for drug wastage and resource use. There is a lower likelihood of wastage with oral treatments, such as sotorasib, as the unused doses are more likely to be used by a patient. With vials, as for docetaxel, must be prepared in the clinical setting which can lead to wastage if the required dose not align with the size of the vial. There is, however, a possibility of vial sharing with intravenous treatments like docetaxel, but the extent to which this practice is used in clinical settings remains uncertain.

e) Please provide a scenario where the treatment cost for sotorasib is based on per pack basis, considering that NICE now takes a more standardised approach for modelling oral treatments to help ensure consistency of cost calculations and better reflect how treatments are dispensed in clinical practice

(<https://www.nice.org.uk/process/pmg24/chapter/cost-effectiveness>).

Please see the results scenario analysis utilising “per open pack” method of calculating treatment costs in Table 9 below. Please note that the change to docetaxel RDI, discussed in question B18.a, was included before running analyses reported below.

Table 9: Scenario analysis results (deterministic) utilising "per open pack" method of calculating treatment costs

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental QALYs (x1.7)	ICER incremental (£/QALY)
Docetaxel	11,786	■	■	-	-	-	-	-
Sotorasib	■	■	■	■	■	■	■	28,031

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

B 20. The company stated in section 3.5.2 that “disease monitoring and management costs were based on previously accepted values from TA781 for sotorasib.”

- a) Please confirm that values from TA428 and TA347, which were used in TA781 to calculate the disease monitoring and management costs, are also used in the current submission.

For consistency with the original submission, the company used the same approach to calculate disease management costs in the current submission i.e., the items included, the number of resources per cycle, and the proportion of patients requiring each resource. However, the unit costs were updated using the most recent sources, as detailed in Appendix M, Tables 69 to 72.

- b) Please justify the appropriateness of sourcing disease monitoring and managements costs from TA428 and TA347, also considering their year of publication (2017 and 2015 respectively).

No studies identified via the SLR were judged as relevant for the CS due to a lack of reporting of healthcare resource usage for patients with previously treated *KRAS* G12C mutation-positive NSCLC in NHS practice. For the full list of identified studies, see Appendix G of the CS and the response to question B2.

Due to the lack of new evidence, maintaining consistency with TA781 (31) and TA1076 (terminated) (50) in the same disease area was considered sufficient justification for including the approach to cost the disease management costs from TA781.

- c) Please provide a scenario analysis exploring more recent literature and/or TAs to inform disease monitoring and management costs in the economic model.

Please see the response to the previous point (question B20.b).

B 21. The distribution of subsequent treatments for patients who progress on sotorasib and docetaxel were informed by TA781 (UK clinical experts) and TA347, respectively. However, the EAG in TA781 commented that the subsequent treatment costs for sotorasib were likely underestimated and

recommended using data from CodeBreak 100. Currently, data from the CodeBreak 200 RCT have also become available.

- a) Please justify the approach of informing the distribution of subsequent treatment for patients who progress on docetaxel based on TA347, also considering its year of publication (2015).

The approach of informing the distribution of subsequent treatment for patients who progressed on docetaxel was judged as appropriate due to a lack of data from a larger cohort of patients receiving subsequent treatments and to maintain consistency with the original submission (TA781 (31)) and TA1076 (terminated) (50)

- b) Please clarify whether the types of subsequent treatments for patients who progress on sotorasib were also informed by UK clinical experts, and if not, please explain how the types of subsequent treatments were informed.

As reported in TA781 (31), the distribution of subsequent treatments for patients who progress on sotorasib were informed by UK clinical experts who advised that a greater proportion of patients are likely to be able to tolerate active treatment and that subsequent docetaxel would be preferred over re-challenge with platinum-based chemotherapy regimens.

Please note that TA1076 (terminated) (50) utilised the distribution of subsequent treatments from TA781 (31). Clinical advice received by the EAG for that appraisal indicated that the assumed treatment distribution aligns with the clinical practice, and the EAG considered the values appropriate.

- c) Please justify the approach of informing the distribution of subsequent treatment for patients who progress on sotorasib based on clinical expert opinion.

Please see the response above.

- d) Please provide more information on the clinical expert opinion used to inform subsequent treatments in the economic model. The NICE health technology evaluations manual (<https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741>) states that the reporting of expert opinion should contain information about "the

identification and selection of experts, and the reporting of results including the consensus of opinions or data aggregation."

These documents will be shared separately.

e) Please provide an updated economic model and scenario analyses informing the distribution of subsequent treatments for patients who progress on sotorasib and docetaxel based on:

i. CodeBreak 200

ii. CodeBreak 100

iii. CAS RWE

The information regarding the subsequent treatment distribution was not available from the CAS RWE study. For CodeBreak 200, the summary of subsequent treatments used is provided in Section 2.7.1 of the CS. Please note that the data is reported for all patients, including those who crossed over from docetaxel to sotorasib. The distribution of subsequent treatments in CodeBreak 100 might not reflect the current clinical practice.

The impact of the distribution of subsequent treatments is expected to be minimal, therefore, the scenario analyses were not provided.

f) Best supportive care was modelled as a subsequent treatment for which a zero cost was assumed. Please provide further justification and evidence to support this assumption.

Best supportive care was assumed to have no cost in the model in line with TA781 (31).

g) The total administration cost for docetaxel monotherapy as subsequent treatment in Table 53 of Appendix I is inconsistent with the economic model. Please correct this inconsistency and check all other input parameters for errors and inconsistencies.

The price for docetaxel in Table 53 of Appendix I and the model are both correct. Table 53 reports per pack unit price of docetaxel monotherapy. In contrast, the cost

of docetaxel monotherapy as a subsequent treatment within the model (cell Costs!E49) is based on calculations. Under the current model settings, i.e. per treated day method for calculations of treatment costs, the acquisition cost per dose is lower than per-pack price. However, the same unit cost, sourced from eMIT (51), is consistently applied to both the docetaxel monotherapy comparator and subsequence treatment.

B 22. In section 3.5.3 of the CS, the company mentioned that “*the genetic costs associated with KRAS testing are not included in the base case but were considered in a scenario analysis*”. The company’s justification for this was that KRAS testing is routinely commissioned by the NHS in NSCLC and no additional tests beyond those used in the routine diagnostic work up and management of patients with NSCLC are required. Please provide evidence to support this statement.

KRAS G12C is a gene target covered by M4.1 Test Code (available from: <https://www.england.nhs.uk/genomics/the-national-genomic-test-directory/>) which is indicated for all non-squamous NSCLC (and selected squamous patients) as part of routine diagnostics. All gene targets covered under M4.1 and M4.2 are mandatory to be reported by the Genomics Laboratory Hubs.

Severity

B 23. Priority question. The CS indicates that “QALY shortfall calculations were estimated using a reference case of the [QALY Shortfall] calculator, including Office for National Statistics (ONS)-reported general population mortality rates and general population utility values”. The EAG was unable to replicate the results with the likewise referenced [QALY Shortfall Calculator](#).

a) Please provide more information on the mentioned “reference case” and explain how the [QALY Shortfall Calculator](#) can be used to replicate the provided results.

As mentioned in Section 3.6 of the CS, the QALY shortfall calculations were estimated using a reference case of the calculator which can be selected under

'Select scenario' on the web page (QALY Shortfall Calculator **(52)**). The sources for the reference case can be explored by clicking on '(see sources for details)'.

The results can be replicated by utilising patients age at baseline and gender information (Table 66 of the CS), remaining QALY of untreated (discounted) from Table 71 of the CS and setting discount rate to 3.5% (as per NICE guidelines).

As noted in the footnote of Table 69 of the CS, the average for absolute and proportional shortfall was calculated based on population aged 63 and 64 years old to align with the population in the model (average age of 63.5 years). Please see Table 10 for the breakdown of the results.

Table 10: Summary of QALY shortfall analysis for the base case

Results	Treatment	Age used in calculations	% female used in calculations	QALY for untreated (discounted)	Absolute shortfall	Proportional shortfall	QALY weighting
Result #1	Docetaxel	63	41%		11.07	95.10%	x1.7
Result #2		64			10.71	94.95%	x1.2
Estimated (average of #1 and #2)		63.5			10.89	95.03%	x1.7

Abbreviations: QALY, quality-adjusted life year.

b) Please update the health economic model and report updated results based on i)-iv):

- i. For the severity calculation, patient baseline characteristics from CodeBreak 200 were employed. Please provide severity calculations for both CodeBreak 200 and CAS RWE patient population while aligning them with their source of clinical evidence, also considering clarification question B 5.**

The CAS RWE does not provide all baseline characteristics required in the model, thus, the baseline data from CodeBreakK 200 trial was used instead (see Table 40 in the CS). Please note that for the baseline characteristics that are available in both sources, i.e. age at baseline and % of females, there is minimal difference between the two only for age. Amending the age in the model to 64 years old, as per the CAS RWE data, does not impact the base case ICER.

For the results utilising the CAS RWE baseline characteristics, where patient population is 64 years old (Table 40 of the CS), and the clinical evidence, please see Results #2 in Table 10.

The QALY shortfall calculations were also performed for scenario #3 included in the CS (see Table 74 in the CS) where CodeBreakK 200 was used as the clinical source of evidence. To adjust for the crossover of patients in the docetaxel arm of CodeBreakK 200, HR from the Flatiron 2L+ RWE was used to estimate OS for docetaxel. The results are presented in Table 11.

Table 11: Summary of QALY shortfall analysis for scenario #3 from the CS

Results	Treatment	Age used in calculations	% female used in calculations	QALY for untreated (discounted)	Absolute shortfall	Proportional shortfall	QALY weighting
Result #1	Docetaxel	63	41%		11.00	94.50%	x1.2
Result #2		64			10.64	94.33%	x1.2
Estimated (average of #1 and #2)		63.5			10.82	94.42%	x1.2

Abbreviations: CS, company submission; QALY, quality-adjusted life year.

The results of QALY shortfall calculations for scenario #3 are at borderline of the severity modifier of 1.7. Please note that due to crossover of patients from docetaxel to sotorasib arm in CodeBreak 200, scenario #3 required adjustment for docetaxel OS utilising the RWE from Flatiron 2L+ US study. The clinical evidence included in the company's base case, the CAS RWE study, was based on patients treated within the NHS setting, therefore, it is the most relevant to the NHS in England.

ii. Please confirm whether the same life table as reported in the health economic model was used, i.e., ONS. National Life Tables, UK 2021-2023; Release date: 2025-03-18.

The sources for the reference case can be explored by clicking on '(see sources for details)' under 'Select scenario' on the web page (QALY Shortfall Calculator **(52)**). Based on the source referenced, the Office for National Statistics (ONS) National Life Tables for 2017 to 2019 (pooled) are used. Please note that the company does not have access or control over the sources included in the QALY Shortfall Calculator.

iii. Please use probabilistic instead of deterministic results as inputs for the QALY shortfall calculations.

The only input required from the model results for the QALY shortfall calculations is the remaining QALY of untreated (discounted). Since the deterministic and probabilistic results for this input are identical in the submitted model, the QALY shortfall calculations will also be identical to already reported in Section 3.6 of the CS.

iv. Please further validate the severity modifier by using the method for health state utility values by progression status instead of time-to-death categories, both for the CAS RWE and the CodeBreak 200 as sources for treatment effectiveness in scenario analyses.

The results of the base case and scenario #3 utilising per progression utility approach and including AE disutilities are reported in Table 12. As discussed in Section 3.4.4 of the CS, time-to-death utilities are more appropriate to use in the submission as they capture quality of life more accurately as patients approach the end of life, explaining significantly more variability in quality of life (QoL) estimates than traditional progression-based method.

Table 12: Summary of QALY shortfall analysis for base case and scenario #3 of the CS based on per progression status utility approach

Results	Treatment	Age used in calculations	% female used in calculations	QALY for untreated (discounted)	Absolute shortfall	Proportional shortfall	QALY weighting
Base case (utilising the age from the CAS RWE study), per progression status utility approach including AE disutilities							
Results	Docetaxel	64	41%	■	10.63	94.24%	x1.2
Scenario #3, per progression status utility approach including AE disutilities							
Result #1	Docetaxel	63	41%	■	10.92	93.81%	x1.2
Result #2		64			10.56	93.62%	x1.2
Estimated (average of #1 and #2)		63.5			10.74	93.72%	x1.2

Abbreviations: AE, adverse event; CS, company submission; QALY, quality-adjusted life year.

Results

B 24. Priority question. Considering the base case results.

- a) Please provide a comparison of the observed survival as well as PFS (e.g., using restricted mean survival time; RMST) and the undiscounted life years (LYs) as well as undiscounted progression free LYs (estimated in the model) by filling out the Table below using different periods/truncation points (with justification) to calculate the RMST.

An analysis of restricted mean survival time (RMST) and restricted mean progression-free survival time (RMPFST) have been carried out using a truncation point of 37 months. The maximum follow-up in the CAS RWE study varied slightly by endpoint and treatment arm but all were between 37 and 38 months, therefore truncating the results at 37 months allowed for a consistent comparison. The observed RMST and RMPFST were calculated using the area under the curve of the Kaplan-Meiers up to 37 months. The results of the analyses are presented in Table 13.

Table 13: Observed and modelled restricted mean outcomes

	Observed		Modelled		
	Restricted mean	Percentage at risk at truncation	Estimated restricted mean outcome	Estimated lifetime outcome	Proportion beyond observed data
OS – RMST truncated at 37 months					
Sotorasib	■	■	■	■	15.6%
Docetaxel	■	■	■	■	6.4%
Increment	■	-	■	■	32.1%
PFS – RMPFST truncated at 37 months					
Sotorasib	■	■	■	■	6.4%
Docetaxel	■	■	■	■	1.5%
Increment	■	=	■	■	13.6%

Abbreviations: OS, overall survival; PFS, progression-free survival; RMPFST, restricted mean progression-free survival time; RMST, restricted mean survival time.

b) Please elaborate on the plausibility of the differences between observed and modelled outcomes (proportion accumulated beyond observed data) for:

i. Sotorasib

ii. the relevant comparators

iii. the increment

We have provided the information requested by the EAG including the incremental difference. However, the percentage of incremental benefit accrued beyond the observed data is a difficult statistic to interpret. Assessment of each treatment arm individually is far more logical and if the outcomes for each arm are plausible then the increment must be plausible too.

First the alignment between the observed and modelled restricted mean values should be noted. Both outcomes are marginally overestimated for docetaxel and underestimated for sotorasib demonstrating the pragmatic selection of survival models.

It is not possible to review the plausibility of the proportion of outcomes accrued beyond the observed data in an objective manner. At best, the proportion of outcomes accrued through extrapolations can be compared to the proportion of patients at risk, and from this an extrapolation with an optimistic tail could be identified. This, however, is still a subjective interpretation. Broadly the proportion accrued beyond the observed data is consistent with the percentage of patients still at risk at the end of the follow-up. For both outcomes a greater proportion of the outcomes are accrued beyond the observed period in the sotorasib arm. This is consistent with the treatment being more efficacious and as a result there being more patients alive at the end of follow-up whose outcomes need to be extrapolated.

c) Regarding the model estimated differences between sotorasib and the comparator (in terms of PFS, LYs and QALYs); please provide an explanation of the mechanism by which the model generated these differences as well as a justification for why they are plausible based upon available evidence (see NICE DSU TSD 19).

It is unclear what clarification the EAG is looking to obtain from this question, the cost-effectiveness model uses a mechanism that is very common amongst oncology models and is described within Document B.

We believe the EAG would like us to discuss one of the limitations of partitioned survival models outlined in NICE DSU TSD 19. This limitation is that the OS hazard profile is generalised across the extrapolation period, but if the benefit of treatment relates to slowing progression, then the hazard ratio of OS will converge to 1 as a greater proportion of patients reside in the post-progression state. If this convergence is not captured, then OS would be overestimated.

In the model base case a jointly fitted generalized gamma model is used to model OS, assuming a constant treatment effect, so this limitation could be relevant. However, the scenario described in NICE DSU TSD 19 is not reflective of the evidence base in this appraisal and is therefore not a concern. The limitation described in NICE DSU TSD 19 is related to an instance where the treatment effect is limited to before progression and all patients reside in the post-progression state. This is not the case in the sotorasib model when utilising the CAS RWE study. At the end of follow-up the majority of alive patients in the sotorasib arm were progression-free (■■■■), a much greater proportion than in the docetaxel arm (■■■■). This means that even if the treatment effect is limited to slowing progression, and there is no evidence to support this assumption, the vast majority of patients in the sotorasib arm are still experiencing this benefit at the end of follow-up and it is therefore logical to continue it into the extrapolated phase.

Sensitivity/scenario analyses

B 25. Priority question. For the deterministic and probabilistic sensitivity analyses, when 95% confidence interval (CI) boundaries were lacking for input parameters, $\pm 20\%$ of the mean for all base case values was assumed. Statistical distributions were assigned to mirror model input properties. In some cases, model input parameters were assumed to be fixed (i.e., not varied deterministically and/or probabilistically). Please address the following aspects:

a) Derivation of standard errors: please provide a scenario analysis, applying $\pm 30\%$ for all input parameters lacking standard errors/95% CI information.

In the absence of data, applying $\pm 20\%$ of the mean to reflect uncertainty was considered sufficient for the current submission and consistent with the approach used in TA781 (31). The scenario analysis can be run by EAG by changing the mode input DSA_PSA_coeff_var on Settings tab of the model.

b) Choice of statistical distribution

- i. Please justify why for the model input parameters population cohort age and weight (kg) normal distributions are assumed. Please explore gamma or log-normal distributions in scenario analyses.**

Age and weight (kg) are both continuous variables, and the assumption of normal distribution is often justified in large cohorts.

Baseline characteristics included in the base case of the model were sourced from CodeBreak 200 trial. The full details regarding the age at randomization (in years) reported in Table 9-4 of CSR (49) and section 2.3.1.9 of the CS. The data for 345 patients suggests that the distribution is symmetric, and standard deviation (SD) does not indicate an extreme spread of the data. Therefore, the assumption of normal distribution is reasonable.

Given the relatively large cohort size, the company maintains the use of a normal distribution. As average patient weight does not influence the model outcomes, scenario analysis was not conducted.

- ii. Please explain and justify the use of gamma distributions for several utility (decrements), reported in the “Model parameters” sheet. Please explore beta distributions in scenario analyses.**

The distribution for utilities and disutilities have been changed from gamma to beta. Please see the cells affected reported on ‘ModelChangesJuly2025’ tab, row 34.

The latest version of the model will utilise beta distributions in the base case.

c) Assumption of fixed input parameters

- i. Please provide justification for every input parameter that was assumed to be fixed (e.g., KRAS-G12C testing inputs and input related to subsequent treatments).**

Certain parameters required fixed values to be included in the model. Inputs related to subsequent treatment reflect the current patient pathway, as supported by referenced sources in the model, and are not intended to be modified. The *KRAS-G12C* testing costs were sourced from the literature and adjusted for inflation to reflect current prices. In the new version of the model, those costs are linked to tab 'Intermediate calcs', cell row 151 where the calculations can be found (noted on 'ModelChangesJuly2025', row 28).

- ii. Please assign standard errors (or $\pm 20\%$ of the mean if not available) and appropriate distributions to the fixed input parameters, and include these in the deterministic and probabilistic sensitivity analyses.**

Where relevant, SE and distributions were assigned for the fixed parameters and included in both deterministic and probabilistic analyses.

- d) If additional parameters are included or updated in the health economic model in response to the clarification letter, please take into account the above-mentioned points. Please provide a separate justification for any parameter assumed to be fixed, in line with NICE DSU TSD 7, D1.**

No additional inputs were included following the response to this clarification letter.

- e) Issues with regard to the deterministic (DSA) and probabilistic sensitivity analyses (PSA): In the "Model parameters" sheet, whereas one can seemingly indicate preferences with regard to parameter inclusion in columns C, D; final DSA/PSA parameter inclusion is dependent on column inputs N, R, which feature IF-statements. This way, many relevant parameters in the DSA and PSA are excluded such as hazard ratios and time-to-death utilities. Please correct this setting. In cases where no correction is performed, please take action as detailed in d).**

Thank you for flagging the issues. Columns N and R have been reviewed and corrected, where necessary. The list of changes applied in the 'Model parameters' sheet is reported on tab 'ModelChangesJuly2025', rows 29 to 33.

B 26. CS Tables 74 and 75 provide overviews of performed scenario analyses and deterministic scenario analyses results respectively.

- a) The EAG was unable to replicate deterministic base case results for scenario analyses 3, 4, and 8. Please provide a more detailed description to facilitate implementation in the health economic model.

For scenario 3 and 4, please see Table 14 below for the changes in the inputs selected in the model.

Table 14: Selection of inputs for scenario #3 and #4

Model input	Location	Base case	Scenario #3	Scenario #4	Notes
Source for OS KM and parametric models	Settings!E48	UK CAS RWE study	CodeBreak 200 adjustment for crossover, TSE (primary analysis)	CodeBreak 200 adjustment for crossover, TSE (primary analysis)	-
Source for OS HRs	Settings!E49	UK CAS RWE study	Flatiron analysis 2L+ (weighted)	CodeBreak 200 adjustment for crossover, TSE (primary analysis)	Main difference between two scenarios
Sotorasib: OS distribution (only if selected method includes parametric models)	Settings!E55	Gen. Gamma	Log-normal	Log-normal	-
Docetaxel: OS modelling method in 1st OS period	Settings!E57	Restricted parametric distribution	HR vs Sotorasib	HR vs Sotorasib	Settings!E58 will update accordingly
Source for PFS	Settings!E63	UK CAS RWE study	CodeBreak 200 observed (primary analysis)	CodeBreak 200 observed (primary analysis)	-
Sotorasib: PFS distribution	Settings!E69	Gen. Gamma	Log-logistic	Log-logistic	Docetaxel will update automatically

Model input	Location	Base case	Scenario #3	Scenario #4	Notes
(only if selected method includes parametric models)					
Utilise CAS RWE TTD data?	Check Box 187 (in Settings!E76)	ticked	unticked	unticked	-

Abbreviations: CAS, Cancer Analysis System; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence; TSE, two stage estimation.

For Scenario 8, the alternative source of terminal care costs is reported on 'Intermediate calcs' tab, cell E132. The value should replace Costs!E87.

- b) In addition, please provide a separate sheet/overview in the health economic model where all scenarios, including those in response to the clarification letter, can be easily implemented.

Due to the time constraints, it was not possible to prepare a separate sheet which will enable the user to quickly implement the scenarios described in Table 74 the CS.

- c) Please also report probabilistic scenario analyses results in a separate overview.

Due to time constraints associated with responding to this clarification letter, probabilistic scenario analyses were not performed.

Validation and transparency

B 27. Priority question. In the CS health economic model, the “Model parameters” sheet provides an overview of input parameters included by the company in the CS. However, it is not the source of model inputs, instead it is updating when model input values originating from different sheets update. Please provide an updated health economic model, where all parameters and their respective distributional information origin and are linked from the “Model parameters” sheet. Please ensure that the probabilistic analyses run smoothly, also drawing model inputs from there.

Unfortunately, there isn't sufficient time to implement the changes in the model. However, please note that this will not impact the model's results or functionality.

B 28. The results of the validity assessments are not described in detail in CS section B.3.11 nor are performed validation exercises (i.e. specific black-box tests).

- a) Please provide a detailed description of the validity assessment performed as well as the results.

The current version of the model was populated with the inputs from TA781, including clinical and cost data, to evaluate whether the model generate consistent results. The company was able to recreate the original submission results with the current version of the model.

In addition, a health economist independent to the current submission performed a quality check of the model. The full model validation can be found in a separate document 'ID6287_Sotorasib in NSCLC_Economic model validation'. The document includes the questions from TECH-VER checklist.

- b) Please provide the cost-effectiveness model verification checklist referred to in CS section B.3.11.2.

Please see the response to point a) in the current question B 28.

- c) Please provide complete the TECH-VER checklist (Büyükkaramikli et al. 2019, <https://pubmed.ncbi.nlm.nih.gov/31705406/>) and provide the results.

Please see the response to point a) in the current question B 28.

B 29. The company performed a scenario analysis using CodeBreak 200 RCT clinical data, reporting “comparable results” with the current CS base case.

- a) Please indicate to which scenario analysis from CS Table 74 this finding refers, and otherwise detail the applied model settings and assumptions compared to the CS base case, specifically chosen parametric survival models.

The conclusions mentioned by the EAG are included in Section 3.11.1 of the CS. This refers to the scenario analysis #3 and #4, included in Table 74 of the CS, where the clinical data for the CodeBreak 200 trial was used with a different approach to estimate OS for docetaxel.

The total discounted costs for sotorasib and docetaxel are broadly comparable across the model's base case and Scenarios 3 and 4, as outlined in Section 3.9.3 of the CS. While there are some differences in QALYs between treatments due to variations in the evidence sources, the base case is considered more representative of clinical practice, as it is derived from real-world NHS patient data.

For model settings, and the differences vs base case, for scenario #3 and #4 please see Table 14.

- b) Please justify the chosen model settings in a) with additional evidence and/or expert opinion.

The selected model settings were based on the alternative comparative efficacy data source presented in the CS for CodeBreak 200. Please see Section 3.3.7.1 of the CS.

B 30. Please provide cross validations, i.e., comparisons with other relevant NICE TAs, including but not limited to those focussing on the broader (previously treated) locally advanced or metastatic NSCLC population, and elaborate on the identified differences regarding:

- a) Model structure and assumptions
- b) Input parameters related to:
 - i. Clinical effectiveness
 - ii. Health state utility values
 - iii. Resource use and costs
- c) Estimated (disaggregated) outcomes per comparator/ intervention
 - i. Life years

ii. QALYs

iii. Costs

Due to the time constraints of the current clarification question period, the company is unable to perform a full cross-validation with all relevant NICE TAs, including but not limited to those focussing on the broader (previously treated) locally advanced or metastatic NSCLC population.

However, Table 39 of the CS includes the comparison of features of the economic analysis with the ongoing NICE appraisal (TA1076 [terminated] (50)) in the same indication.

B 31. Further external validation of the health economic model would be desirable.

- a) Please perform and report on the face validity assessment of the model structure, model assumptions, model inputs, intermediate outcomes as well as final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).

For factors affecting the selection of the model approach, please see the response to question B 3a. Specifically, the current submission utilised the model approach, assumptions, the source of inputs as per TA781 (31). The same approach was utilised as part of terminated appraisal TA1076 (50) with no key issues identified which related to the model approach.

The company compared modelled OS and TTNTD, as summarised in Section 3.3.4 and 3.3.5 of the CS, and concluded the similarity in the reported values from the CAS RWE study. Several scenario analyses were also conducted, described in Section 3.9.3 of the CS and question B 29.

The results of the economic analysis were evaluated for clinical and economic plausibility. The results could not be compared to published literature due to the identified economic evaluations not being relevant to the UK setting due to inclusion of non-UK patient data and country-specific unit costs.

The model was considered appropriate for the UK setting despite its limited comparability with published literature. It is consistency with NICE methodology and utilises the most relevant data from the CAS database, based on patients treated within the NHS setting, making it generalisable to clinical practice.

- b) Please provide CS reference number 120 (Amgen Inc. Data on file: Clinical validation of parametric curves. 2025).

The document is provided alongside the clarification questions.

- c) Please provide the full minutes of any meetings held with clinical or health economic experts to inform the current CS, and prior TA781.

Unfortunately, the documents outlining any meetings held with clinical or health economic experts used to inform the current and previous submission TA781 cannot be provided within the timeframe for responding to the clarification questions.

- d) Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using:
 - i. evidence used to develop the economic model.
 - ii. evidence not used to develop the economic model.

The external validity of the model inputs, intermediate outcomes, and final outcomes was assessed primarily using the CAS RWE study, which reflects patients treated within the NHS setting and thus provides relevant and representative data for the UK context. An alternative clinical trial dataset was incorporated in scenario analyses to test the robustness of the model against evidence not used in its development. The model's intermediate outcomes were found to be comparable to those observed in the CAS RWE study, supporting consistency and relevance.

However, due to the lack of published UK-based economic evaluations or real-world studies, direct external validation of final outcomes was limited. Additionally, we were unable to perform a formal validity assessment with clinical experts due to time constraints for this submission. Despite these limitations, the model outcomes were clinically plausible and aligned with expectations, supporting the model's generalisability and external validity within the UK NHS setting.

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Maastricht University

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

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

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Contributions of authors

Nigel Armstrong acted as project lead and health economist on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Huiqin Yang also acted as project lead and systematic reviewer on this assessment and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Bram Ramaekers, Teresa Holly, Bradley Sugden, Sabine Grimm, Mabel Wieman and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Maria Katsipataki acted as

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Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
A&E	Accident & Emergency
AACR	American Association of Cancer Research
ACP	American College of Physicians
AE	Adverse event
AFT	Accelerated failure time
ALK	Anaplastic lymphoma kinase
AIC	Akaike information criterion
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATT	Average treatment effect in the treated
BIC	Bayesian information criterion
BICR	Blinded independent central review
BMI	Body mass index
BNF	British National Formulary
BRAF	V-Rad murine sarcoma viral oncogene homolog B1
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CAS	Cancer Analysis System
CC	Complications and comorbidities
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMR	Cochrane Methodology Register
CNS	Central nervous system
CON	Confidential
COSD	Cancer Outcomes and Services Dataset
CR	Complete response
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews in Effects
DCO	Data cut-off
DCR	Disease control rate
DLRT	Dose level review team
DMC	Data Monitoring Committee
DOR	Duration of response
DOWSA	Deterministic one-way sensitivity analysis
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EHR	Electronic health records

ELCC	European Lung Cancer Congress
EMA	European Medicines Agency
eMIT	Electronic market information tool
EOI	Events of interest
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	European Quality of Life-5 Dimensions 3 Levels
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Levels
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU	European Union
EUR	Erasmus University Rotterdam
FACT-G GP5	Functional Assessment of Cancer Therapy-General, Item 5
FAD	Final Appraisal Determination
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixing errors
FG	Final guidance
FV	Fixing violations
GEE	Generalised estimating equations
HCRU	Healthcare costs and resource utilisation
HES	Hospital Episode Statistics
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health State Utility Value
HTA	Health Technology Assessment
IA	Investigator assessment
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
IP	Investigational product
IPCW	Inverse probability of censoring weighting
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KRAS	Kirsten ras sarcoma
KRAS _m	Kirsten ras sarcome mutation
KSR	Kleijnen Systematic Reviews Ltd
LoT	Line of therapy
LS	Least squares
LTFU	Long-term follow-up
LYs	Life years
MAIC	Matching-adjusted indirect comparison
MDx	Molecular Diagnostics
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare products Regulatory Agency
MJ	Matters of judgement
MMRM	Mixed model for repeated measurement
MTA	Multiple Technology Appraisal
N/A	Not applicable
NCRAS	National Cancer Registration and Analysis Service
NDRS	National Disease Registration Service
NE	Not estimable

NHB	Net health benefit
NHS	National Health Service
NHS EED	National Health Service Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	Netherlands
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine kinase
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetics
PPS	Per protocol set
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PS	Propensity score
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q1	First quartile
Q3	Third quartile
Q3W	Every three weeks
QALY	Quality-adjusted life year
QD	Once daily
QLQ-C30	Quality of Life Questionnaire 30-Item Core Module
QLQ-LC13	Quality of Life Questionnaire Lung Cancer Module
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumours
ROBINS-I	Risk Of Bias In Non-randomised Studies – of Interventions
ROS	Proto-oncogene tyrosine-protein kinase
RPSFT	Rank preserving structural failure time
RTDS	Radiotherapy Data Set
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAS	Safety analysis set
SATs	Single arm trials
SD	Standard deviation

SE	Standard error
SFU	Safety follow-up
SLD	Sum of longest diameter
SLR	Systematic literature review
SMD	Standardised mean difference
SMQ	Standard MedDRA Query
SMRW	Standardised mortality ratio weighting
STA	Single Technology Appraisal
STM	State transition model
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TRAE	Treatment-related adverse event
TSD	Technical Support Document
TSE	Two-stage estimation
TTD	Time to treatment discontinuation
TTD(D)	Time to treatment discontinuation (or death)
TTNT(D)	Time to next treatment (or death)
TTP	Time to progression
TTR	Time to response
UK	United Kingdom
UMC+	University Medical Centre+
US	United States
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
WCLC	World Conference on Lung Cancer
WTP	Willingness-to-pay

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1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness (CE) with Section 1.6 highlighting modelling errors identified by the EAG. A summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (DP), 3 (clinical effectiveness) and 4 (CE) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Uncertainty as whether docetaxel with nintedanib is a comparator.	2.2
2	Uncertainty as which of the two main comparative analyses is the most valid.	3.2
3	Missing subgroup analyses.	4.2.3
4	Non-randomised study to inform the treatment effectiveness of sotorasib and docetaxel.	4.2.5
5	Incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreaK 200.	4.2.5
6	Issues related to the modelling of TTD(D).	4.2.5
7	Insufficient justification for treatment waning assumptions.	4.2.5
8	Suboptimal approach for the estimation of utility values.	4.2.7
9	Use of treatment-dependent utilities.	4.2.7
10	Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.	4.2.7
11	Suboptimal approach for the modelling of the acquisition costs.	4.2.8
12	Transparency issues related to insufficient responses to the clarification questions posed by the EAG.	5.2.1
EAG = External Assessment Group; EQ-5D-3L = European Quality of Life-5 Dimensions 3 Levels; EQ-5D-5L = European Quality of Life-5 Dimensions 5 Levels; TTD(D) = time to treatment discontinuation (or death)		

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The clinical source to inform sotorasib and docetaxel overall survival (OS), progression-free survival (PFS)/time to next treatment (or death) (TTNT[D]), and time to treatment discontinuation (or death) (TTD[D]).

- The selected approaches and parametric curves for the modelling of OS, PFS/TTNT(D), and TTD(D) for sotorasib and docetaxel.

1.2 Overview of key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length (OS) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing PFS: [REDACTED] and [REDACTED] life years accrued by sotorasib and docetaxel respectively in the PFS health state (incremental difference: [REDACTED] of total incremental life year gains).

Overall, the technology is modelled to affect costs by:

- Its higher drug acquisition costs. Drug acquisition costs were £[REDACTED] for sotorasib and £54 for docetaxel (incremental difference: £[REDACTED], [REDACTED] of total incremental costs).

The company's scenario analyses that have the greatest effect on the ICER are:

- Source of clinical data: CodeBreaK 200 with Flatiron analysis OS for docetaxel (scenario 3), decreased the ICER by 35.7%.
- Inclusion of genetic testing costs¹ (scenario 7), increased the ICER by 8.3%.
- Inclusion of per progression utilities (scenario 6), increased the ICER by 5.5%.

1.3 The DP: summary of the EAG's key issues

The DP addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on docetaxel with nintedanib (Table 1.2).

Table 1.2: Key issue 1: Uncertainty as whether docetaxel with nintedanib is a comparator

Report Section	2.2
Description of issue and why the EAG has identified it as important	Docetaxel with nintedanib is excluded as a comparator on the basis of lack of use in clinical practice and lack of advantage over docetaxel monotherapy. This is despite the FAD from TA781 concluding that it is a comparator. Evidence of lack of use was presented from the CAS RWE study. A conference abstract of a UK real-world study was presented to show the poorer outcomes with the combination than were observed in the LUME-Lung 1 RCT, which had been used to show its advantage over monotherapy. The EAG also noted slightly better outcomes from another real-world study, albeit it not from the UK and with overlapping 95% CIs. The outcomes for docetaxel from the CAS RWE study and the main RCT, CodeBreaK 200, are also similar to those of docetaxel with nintedanib from the real-world studies.
What alternative approach has the EAG suggested?	The EAG requested clarification as to whether its use was declining in clinical practice from the CAS RWE, and if there is a subgroup for whom it might be preferred over nintedanib monotherapy, and if there was a trend for declining use. The company responded that no information was available to answer the first, and too few patients were treated to answer the second question. The EAG clinical expert also agree to the exclusion of docetaxel with nintedanib as comparator.

Report Section	2.2
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Either some evidence or possibly further clinical expert opinion that docetaxel only used or exclusion of the subgroup for whom docetaxel with nintedanib might be used from the DP.
CAS = Cancer Analysis System; CE = cost effectiveness; CI = confidence interval; DP = decision problem; EAG = External Assessment Group; FAD = Final Appraisal Determination; RCT = randomised controlled trial; RWE = real-world evidence; UK = United Kingdom	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.3: Key issue 2: Uncertainty as to which of the two main comparative analyses is the most valid

Report Section	3.2 to 3.4
Description of issue and why the EAG has identified it as important	The company argues that the CAS RWE study is more valid than the CodeBreaK 200 RCT as evidence comparing sotorasib with docetaxel. This is for three main reasons: • there was a high rate of withdrawal from the docetaxel arm of the RCT • there was crossover from docetaxel to sotorasib in the RCT, which might be incompletely adjusted for • the CAS RWE study is UK based, efforts were made to ensure recruitment of most patients who received docetaxel in the same population as who received sotorasib, and statistical analyses were conducted to adjust for any remaining differences in prognostic factors/treatment effect modifiers • sensitivity analyses were also applied to address uncertainty in analysis population and statistical adjustment The EAG agrees with the company's arguments. However, there is always the possibility of remaining bias in the CAS RWE study, and the outcomes from this study favour sotorasib. Also, the EAG prefer the RCT data for PFS, given that this is unaffected by crossover.
What alternative approach has the EAG suggested?	The EAG requested some clarification as to the application of methods to identify and reduce any bias in the CAS RWE study, which the EAG was largely satisfied with, although the company stated that they do not have access to the patient-level data in order to perform any additional analyses.
What is the expected effect on the CE estimates?	ICER likely to be higher when using the RCT data.
What additional evidence or analyses might help to resolve this key issue?	It appears that some judgment, informed by clinical expert opinion, will be required to determine the most plausible estimates of treatment effect (sotorasib versus docetaxel) on PFS, OS and TTD. Fortunately, there seems to be considerable clinical experience of the use of docetaxel and some of the use of sotorasib in the UK, as shown by the CAS RWE study.
CAS = Cancer Analysis System; CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; RCT =	

Report Section	3.2 to 3.4
randomised controlled trial; RWE = real-world evidence; TTD = time to treatment discontinuation; UK = United Kingdom	

1.5 The CE evidence: summary of the EAG's key issues

A full summary of the CE evidence review conclusions can be found in Section 5.4 of this report. The company's CE results are presented in Section 5.1, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 5.2. The key issues in the CE evidence are discussed in the issue Tables below.

Table 1.4: Key issue 3: Missing subgroup analyses

Report Section	4.2.3
Description of issue and why the EAG has identified it as important	The company did not conduct subgroup analyses despite the final scope listing previous treatment, disease stage, histology, and metastatic disease status as potentially relevant subgroups. Evidence from CodeBreaK 200 and CAS RWE suggests heterogeneity, i.e., differential relative efficacy in outcomes depending on prior therapy, CNS involvement, and liver metastases.
What alternative approach has the EAG suggested?	Perform subgroup analyses using available data from CodeBreaK 200, particularly based on prior LoT, disease stage, histology, and metastatic disease characteristics (CNS/liver involvement). This trial-level data could help explore whether CE differs across clinically relevant subgroups.
What is the expected effect on the CE estimates?	Subgroup analyses may show that CE differs between groups. Not accounting for heterogeneity risks over- or under-estimating value in specific patient groups.
Could any additional evidence or analyses be provided to resolve this key issue?	Additional analyses from CodeBreaK 200 (subgroup analyses on treatment line, disease stage, histology, CNS/liver metastases) could address this key issue.
CAS Cancer Analysis System; CE = cost effectiveness; CNS = central nervous system; EAG = Evidence Assessment Group; LoT = line of therapy; RWE = real-world evidence	

Table 1.5: Key issue 4: Non-randomised study to inform the treatment effectiveness of sotorasib and docetaxel

Report Section	4.2.5
Description of issue and why the EAG has identified it as important	The company uses a non-randomised study (CAS RWE) to inform the treatment effectiveness in their economic model, risking bias due to (unmeasured) confounding.
What alternative approach has the EAG suggested?	The EAG alternatively prefers using the CodeBreaK 200 RCT to inform treatment effectiveness.
What is the expected effect on the CE estimates?	The impact of the chosen source to inform treatment effectiveness on the CE estimates differs depending on the preferred parametric survival curves. The EAG's base-case preferences for the modelling of OS substantially increased the ICER, whereas the EAG's base-case preferences for the modelling of PFS slightly decreased the ICER. Overall, the

Report Section	4.2.5
	EAGs preferred OS and PFS curves based on CodeBreak 200 substantially increased the ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	Conduct a risk of bias assessment for the non-randomised study using ROBINS-I to better inform the selection of the source to inform treatment effectiveness in the economic model.
CAS = Cancer Analysis System; CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; ROBINS-I - Risk Of Bias In Non-randomised Studies – of Interventions; RWE = real-world evidence	

Table 1.6: Key issue 5: Incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreak 200

Report Section	4.2.5
Description of issue and why the EAG has identified it as important	Information required for the parametric survival curve selection of OS and PFS (as outlined in NICE DSU TSD 14) was incomplete for CodeBreak 200. The EAG therefore selected parametric survival curves based on incomplete information.
What alternative approach has the EAG suggested?	In its clarification letter, the EAG requested details of all criteria from NICE DSU TSD 14 and 21 guidance for OS and PFS for CodeBreak 200, separately for sotorasib and all relevant comparators.
What is the expected effect on the CE estimates?	Unclear. The potential impact of the chosen OS curve on the ICER seems substantial, whereas the impact of the chosen PFS curve on the ICER seems minor.
Could any additional evidence or analyses be provided to resolve this key issue?	All information requested by the EAG in clarification question B8 should be provided for CodeBreak 200 to resolve this key issue.
CE = cost effectiveness; DSU = Decision Support Unit; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; TSD = Technical Support Document	

Table 1.7: Key issue 6: Issues related to the modelling of TTD(D)

Report Section	4.2.5
Description of issue and why the EAG has identified it as important	The company used time to TTD(D) data from CAS RWE to inform treatment costs in its economic model. The EAG is concerned that TTD(D) in CAS RWE was an exploratory endpoint that was estimated indirectly using a line of treatment algorithm, which could result in misclassification of TTD(D). Furthermore, the EAG considers the company's scenario analysis of indirectly estimating TTD(D) from CodeBreak 200 using Cox regressions performed on PFS versus TTD(D) to generate time-varying HRs to be suboptimal.
What alternative approach has the EAG suggested?	The EAG alternatively prefers informing TTD(D) directly by fitting parametric survival curves to the observed TTD(D) data in CodeBreak 200, which was requested in the clarification letter but not provided by the company.

Report Section	4.2.5
What is the expected effect on the CE estimates?	The expected impact of the EAG's preferred approach on the CE estimates is unclear. For now, the EAG uses the time-varying HRs from CodeBreaK 200 to inform the modelling of TTD(D) in its base-case, which substantially increased the ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	The potential misclassification of TTD(D) in CAS RWE cannot be solved. For the modelling of TTD(D) directly by fitting parametric survival curves to the observed TTD(D) data in CodeBreaK 200, the analyses requested by the EAG in clarification question B10 should be provided.
CAS = Cancer Analysis System; CE = cost effectiveness; EAG = External Assessment Group; HR = hazard ratio; PFS = progression-free survival; RWE = real-world evidence; TTD(D) = time to treatment discontinuation (or death)	

Table 1.8: Key issue 7: Insufficient justification for treatment waning assumptions

Report Section	4.2.5
Description of issue and why the EAG has identified it as important	Treatment waning was not explicitly modelled by the company in its base-case, stating that the length of patient follow-up in the main source of clinical effectiveness was sufficient to capture any decline in treatment effectiveness. The EAG considers this strong assumption insufficiently justified.
What alternative approach has the EAG suggested?	The EAG requested additional justification and evidence that assesses treatment waning in the observed data in clarification question B9, which was not provided for CodeBreaK 200.
What is the expected effect on the CE estimates?	The EAG's preferred approach of modelling treatment waning from 2 years onwards with gradual decline over 5 years resulted in a minor increase of the ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	The justification and analyses requested by the EAG in clarification question B9 should be provided to resolve this key issue.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.9: Key issue 8: Suboptimal approach for the estimation of utility values

Report Section	4.2.7
Description of issue and why the EAG has identified it as important	A time-to-death, rather than a progression-based approach to estimating utilities was adopted. While the EAG accepts the company's justification for including time-to-death into utility calculations, the EAG would prefer the time-to-death dimension to be incorporated into progression-based utilities.
What alternative approach has the EAG suggested?	The EAG requested a scenario analysis informing utilities with a full model (i.e., mixed effects model) including (but not limited to) treatment arm, disease progression, and time-to-death in clarification question B15. Here, a progression-based approach can incorporate a disutility penalty based on time-to-death weighted at each cycle. This was not provided.
What is the expected effect on the CE estimates?	Unclear.

Report Section	4.2.7
Could any additional evidence or analyses be provided to resolve this key issue?	Results of a fully fitted model (i.e., mixed effects model) informing health state utilities. This should explore including (but not be limited to) treatment arm, disease progression, and time-to-death. The suggested approach can incorporate a disutility penalty based on (continuous) time-to-death weights, applied at each cycle. Full model results including details regarding covariate selection, coefficients (and associated 95% CIs) and full model diagnostics should be provided.
CE = cost effectiveness; CI = confidence interval; EAG = External Assessment Group	

Table 1.10: Key issue 9: Use of treatment-dependent utilities

Report Section	4.2.7
Description of issue and why the EAG has identified it as important	The CS base-case utilises treatment-dependent utilities based on a descriptive analysis. The EAG questions whether this assumption is valid.
What alternative approach has the EAG suggested?	The EAG requested the results of a full regression model that explored treatment group as a covariate. The existence of a (statistically significant) difference in treatment group would support this assumption. The requested analysis was not provided. The EAG therefore included treatment-independent utilities in its base-case.
What is the expected effect on the CE estimates?	The inclusion of treatment-independent utilities increased the deterministic base-case ICER (1.7 x severity modifier) by £5,176.
Could any additional evidence or analyses be provided to resolve this key issue?	Results of a fully fitted model (i.e., mixed effects model) informing health state utilities. This should explore including (but not be limited to) treatment arm, disease progression, and time-to-death. The suggested approach can incorporate a disutility penalty based on (continuous) time-to-death weights, applied at each cycle. Full model results including details regarding covariate selection, coefficients (and associated 95% CIs) and full model diagnostics should be provided.
CE = cost effectiveness; CI = confidence interval; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.11: Key issue 10: Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.

Report Section	4.2.7
Description of issue and why the EAG has identified it as important	The CS utilises the crosswalk algorithm by Van Hout et al., 2012 to map EQ-5D-5L outcomes to EQ-5D-3L. The latest version of the NICE HTA manual stipulates that the mapping function developed by the DSU (Hernandez Alava et al., 2017), using the EEPRU dataset (Hernandez Alava et al., 2020), should be used for the reference-case analysis. The CS therefore deviates from the NICE reference case.
What alternative approach has the EAG suggested?	The EAG requested that the company update their analysis to be consistent with the latest guidance in clarification question B16. The request is outstanding as the company suggested the request could not be fulfilled in the timeframe given for EAG clarification question responses.

Report Section	4.2.7
What is the expected effect on the CE estimates?	Unknown.
Could any additional evidence or analyses be provided to resolve this key issue?	Analyses should utilise the mapping function developed by the DSU (Hernandez Alava et al., 2017), using the EEPRU dataset (Hernandez Alava et al., 2020) to map EQ-5D-5L outcomes to EQ-5D-3L.
CE = cost effectiveness; CS = company submission; DSU = Decision Support Unit; EAG = External Assessment Group; EQ-5D-3L = European Quality of Life-5 Dimensions 3 Levels; EQ-5D-5L = European Quality of Life-5 Dimensions 5 Levels; HTA = Health Technology Assessment; NICE = National Institute for Health and Care Excellence	

Table 1.12: Key issue 11: Suboptimal approach for the modelling of the acquisition costs

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	The company's per treatment day approach for the modelling of drug acquisition costs was not in line with the per pack approach as recommended in the NICE process and methods guide.
What alternative approach has the EAG suggested?	The EAG requested a scenario analysis using a per pack costing approach for sotorasib, in line with the NICE process and methods guide.
What is the expected effect on the CE estimates?	The analysis applying a per pack approach for the modelling of both sotorasib and docetaxel drug acquisition costs resulted in a moderate increase of the ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	N/A
CE = cost effectiveness; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; NICE = National Institute for Health and Care Excellence	

Table 1.13: Key issue 12: Transparency issues related to insufficient responses to the clarification questions posed by the EAG

Report Section	5.2.1
Description of issue and why the EAG has identified it as important	The company did on multiple occasions not comprehensively address the questions posed by the EAG, putting it in the position being unable to comprehensively assess the CS DP and methodology.
What alternative approach has the EAG suggested?	Share information requested during clarification phase.
What is the expected effect on the CE estimates?	Unclear, as perceived additional uncertainty with regard to assessment of CE.
Could any additional evidence or analyses be provided to resolve this key issue?	Share information as requested during clarification phase.
CE = cost effectiveness; DP = decision problem; EAG = Evidence Assessment Group	

1.6 Company's modelling errors identified by the EAG

The EAG noted some deviations from good modelling practice in the CS health economic models both at submission and after clarification:

- In the "Model parameters" sheet, user choices considering deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) parameter inclusion are not the final determinant of inclusion but columns N and R which feature if statements.
- Not all relevant parameters have been included in the DSA and PSA.

Further details regarding these issues are reported in Section 5.2.1.

1.7 Summary of the EAG's view

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £109,537 per QALY gained with a severity modifier of 1.2. The probabilistic EAG base-case analyses indicated CE probabilities of ■■■ and ■■■ at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were alternative assumptions regarding the choice of clinical source (and parametric survival curves) to inform the modelling of sotorasib and docetaxel OS and the choice of clinical source and approach to inform the modelling of sotorasib and docetaxel time to treatment discontinuation (TTD). The ICER increased most in the scenario analysis with alternative assumptions regarding relative dose intensity (RDI) for sotorasib and docetaxel.

There is large remaining uncertainty about the effectiveness and CE of sotorasib, which can be partly resolved by the company. For CodeBreaK 200, this includes providing additional subgroup analyses, details of NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 and 21 criteria for parametric survival curve selection, analyses directly fitting parametric survival curves to the observed TTD(D) data, additional justification and evidence that assesses treatment waning, and mixed effects regression models and the appropriate mapping algorithm for the estimation of utility values. Additionally, a risk of bias assessment for Cancer Analysis System (CAS) real-world evidence (RWE) and any remaining lacking responses and analyses in response to clarification should be provided. Therefore, according to the EAG, the CS nor the EAG report contains an unbiased estimate of sotorasib compared with docetaxel.

Table 1.14: Summary of EAG's preferred assumptions and ICER

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Deterministic results								
CS base-case								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£44,669	-0.53	-0.21
				1.2	████	£37,224	-0.45	-0.12
				1.7	████	£26,276	-0.23	0.09
EAG_1 FV: per pack costing approach for docetaxel and sotorasib acquisition costs (per treatment day in CS base-case)								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£47,653	-0.60	-0.25
				1.2	████	£39,711	-0.51	-0.17
				1.7	████	£28,031	-0.29	0.05
EAG_2 MJ: individually fitted Gamma from CodeBreaK 200 for sotorasib OS (jointly fitted generalised Gamma from CAS RWE in CS base-case) and crossover-adjusted HR from CodeBreaK 200 for docetaxel OS (jointly fitted generalised Gamma from CAS RWE in CS base-case)								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£84,188	-0.71	-0.40
				1.2	████	£70,157	-0.67	-0.36
				1.7	████	£49,522	-0.56	-0.25
EAG_3 MJ: individually fitted log-logistic from CodeBreaK 200 for sotorasib and docetaxel PFS (jointly fitted generalised Gamma from CAS RWE in CS base-case)								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£43,883	-0.52	-0.20
				1.2	████	£36,569	-0.43	-0.11
				1.7	████	£25,813	-0.21	0.10

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
EAG_4 MJ: HR estimated using PFS and time on treatment from CodeBreaK for sotorasib and docetaxel TTD (individually fitted generalised Gamma from CAS RWE in CS base-case)								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	████	████████	1.0	████	£56,799	-0.80	-0.39
				1.2	████	£47,333	-0.71	-0.30
				1.7	████	£33,411	-0.49	-0.08
EAG_5 MJ: include treatment waning starting at 2 years with gradual decline over 5 years (no treatment waning in CS base-case)								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	████	████████	1.0	████	£47,132	-0.55	-0.23
				1.2	████	£39,276	-0.47	-0.15
				1.7	████	£27,725	-0.27	0.05
EAG_6 MJ: treatment-independent utilities based on MMRM sotorasib utilities for sotorasib and docetaxel (treatment-dependent utilities based on descriptive analysis in CS base-case)								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	████	████████	1.0	████	£53,468	-0.60	-0.28
				1.2	████	£44,557	-0.53	-0.21
				1.7	████	£31,452	-0.35	-0.03
EAG base-case								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	████	████████	1.0	████	£122,395	-0.68	-0.41
				1.2	████	£101,996	-0.65	-0.38
				1.7	████	£71,997	-0.59	-0.32

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Probabilistic								
CS base-case								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	██████	████████	1.0	████	£45,837	-0.56	-0.23
				1.2	████	£38,198	-0.47	-0.14
				1.7	████	£26,963	-0.26	0.07
EAG base-case								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	██████	████████	1.0	████	£131,445	-0.69	-0.42
				1.2	████	£109,537	-0.67	-0.40
				1.7	████	£77,321	-0.61	-0.33
CAS = Cancer Analysis System; CS = company submission; EAG = External Assessment Group; FV = fixing violation; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MMRM = mixed models for repeated measures; MJ = matter of judgement; 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; WWT = willingness-to-pay								

2. Critique of company's definition of decision problem (DP)

Table 2.1: Statement of the DP (as presented by the company)

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the NICE final scope	EAG comment
Population	Adults with previously treated KRAS G12C-mutated, locally advanced or metastatic NSCLC	Adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy	In line with (conditional) marketing authorisation	No comment.
Intervention	Sotorasib	Sotorasib	-	The intervention is in line with the NICE scope
Comparator(s)	- Docetaxel - Docetaxel with nintedanib - Adagrasib (subject to NICE appraisal)	Docetaxel	Docetaxel is considered the only relevant comparator for this submission. RWE from the CAS database shows that from 1 January 2017 to 31 January 2024, across all lines of therapy, only ~5% of patients with KRAS-mutated NSCLC who received chemotherapy (monotherapy or combination) in 2L+ received docetaxel + nintedanib, with fewer than nine recorded patients in 2. While RCT data from the LUME-Lung 1 trial suggested an OS and PFS benefit with the docetaxel + nintedanib combination in 2L treatment of patients with adenocarcinoma,	Excluding adagrasib is reasonable. The company justification for excluding docetaxel with nintedanib has some merit, but there might still be a small percentage of patients for who this is the treatment of choice.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the NICE final scope	EAG comment
			upon which use on the NHS was approved, more recent RWE found poor OS with the combination, raising questions regarding the applicability of the trial data, patient selection and the benefit of this treatment regime. NICE guidance for adagrasib is not yet available at the time of submission, and therefore it is not considered a relevant comparator.	
Outcomes	• OS • PFS • Response rates • TTD • AEs of treatment • HRQoL	In the CEA TTNT(D) from the CAS RWE study is used as a proxy for PFS. Otherwise, in line with scope.	PFS was not captured in the CAS RWE study. However, in a scenario analysis PFS data from the pivotal CodeBreaK 200 is used and produces consistent results.	The outcomes reported are largely in line with the NICE scope. Use of TTNT(D) seems justifiable and sensitivity analysis also conducted.
Economic analysis	• The reference case stipulates that the CE of treatments should be expressed in terms of incremental cost per QALY. • The reference case stipulates that the time horizon for estimating clinical and CE should be sufficiently long to reflect any differences in costs	NR	N/A	Consistent with the NICE reference case except: • The crosswalk algorithm by Van Hout et al., 2012 was used in the CS to map EQ-5D-5L to EQ-5D-3L, whereas the NICE HTA manual (Section 4.3.16) stipulates the use of the mapping function by the

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the NICE final scope	EAG comment
	or outcomes between the technologies being compared. - Costs will be considered from an NHS and PSS perspective. - The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			Hernandez Alava et al., 2017. A per treated day approach was used to estimate sotorasib acquisition costs in the CS, whereas the NICE process and methods guide states that oral treatments dispensed in tablet packs should be evaluated on a per pack basis.
Subgroups to be considered	If the evidence allows the following subgroups will be considered: - Disease stage - Histology - Previous treatment - Newly diagnosed or recurrent distant metastatic disease	No subgroups included in the economic model.	- For disease stage and histology, there were insufficient patient numbers in the smaller subgroups (locally advanced/ unresectable, and squamous histology) to perform relevant analyses. - Data were not collected with regards to newly diagnosed versus recurrent distant metastatic disease. - CAS RWE data showed that results for subgroups with and without previous anti-PD-L1 treatment are consistent with the overall population results. Therefore, these were not included in the economic analysis.	The company justification for lack of subgroup analysis seems reasonable.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the NICE final scope	EAG comment
Based on Table 1 of the CS² 2L = second line; AE = adverse event; CAS = Cancer Analysis System; CEA = cost-effectiveness analysis; CS = company submission; DP = decision problem; EAG = External Assessment Group; HRQoL = health-related quality of life; KRAS = Kirsten ras sarcoma; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not reported; NSCLC = non-small cell lung cancer; OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life year; RCT = randomised controlled trial; RWE = real-world evidence; TTD = time to treatment discontinuation; TTNT(D) = time to next treatment (or death)				

2.1 Population

The population in the decision problem (DP) is adult patients with Kirsten ras sarcoma (KRAS) G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti Programmed cell death protein 1/Programmed cell death ligand 1 (PD-1/PD-L1) immunotherapy, which contrasts with that in the National Institute for Health and Care Excellence (NICE) scope of adults with previously treated KRAS G12C-mutated, locally advanced or metastatic NSCLC.^{2, 3} The company state that this is in line with the conditional marketing authorisation.

EAG comment: The External Assessment Group (EAG) note that the DP population is also in line with that of the final guidance (FG) issued by NICE for Technology Appraisal (TA) 781 of which this appraisal is a review.⁴

2.2 Intervention

The intervention in both the DP and the NICE scope is sotorasib.^{2, 3}

EAG comment: No comment.

2.3 Comparators

Three comparators are listed in the scope:³

- Docetaxel
- Docetaxel with nintedanib
- Adagrasib (subject to NICE appraisal)

However, docetaxel is the only comparator in the DP, with adagrasib excluded due to not having been recommended.² Docetaxel with nintedanib is excluded for two reasons: lack of use and lack of advantage over docetaxel. As the company state, “... the CAS [Cancer Analysis System] database shows from 1st January 2017 to 31st January 2024, across all lines of therapy, only ~5% of patients with KRAS-mutated NSCLC who received chemotherapy (monotherapy or combination) in 2L+ received docetaxel + nintedanib, with fewer than nine recorded patients in 2L.” They also cited a conference abstract that showed poorer outcomes in a United Kingdom (UK) real-world study than in the pivotal LUME-Lung 1 randomised controlled trial (RCT).^{5, 6}

EAG comment: NICE have confirmed to the EAG that it is reasonable to exclude adagrasib. The EAG consider that it does appear that docetaxel plus nintedanib is little used in the National Health Service (NHS) and asked for further clarification. On the reasons for prescribing docetaxel + nintedanib, the company noted that the Cancer Analysis System (CAS) database does not record clinical rationale for treatment allocation. Therefore, it is not possible to determine why patients received this regimen. The company suggested that patients receiving docetaxel + nintedanib are likely to have NSCLC with adenocarcinoma histology, in line with the treatment’s licensed indication.⁷ On whether the use of docetaxel + nintedanib is declining, the company explained that this cannot be reliably assessed using CAS real-world evidence (RWE). In line with NHS Digital reporting rules, patient counts ≤ 5 are masked to protect anonymity. Fewer than 10 patients (<5%) in the KRAS-mutated NSCLC second-line (2L+) population received docetaxel + nintedanib over the study period, making stratification by year infeasible. The company therefore could not provide data on temporal prescribing trends.⁷ The EAG

therefore concludes that the exclusion of docetaxel + nintedanib as a comparator is reasonable given its very limited use in NHS practice.

In terms of relative efficacy between docetaxel and docetaxel with nintedanib, the study cited by the company has the advantage of being based on UK patients.⁶ However, it is only presented as a conference abstract. Also, the EAG found a full publication of a study by Ljubicic et al., 2023 that showed better outcomes: median overall survival (OS) of 8 (95% confidence interval [CI] 7, 10) instead of 7.4 (95% CI not reported) in Heseltine et al., 2022. Nevertheless, both values are much lower than in the LUME-Lung 1 RCT i.e. 12.6 months. Also, median OS for docetaxel in LUME-Lung 1 also seems very high i.e. 10.3 months,⁵ versus 6.87 (95% CI 6.01, 7.82) from the CAS RWE study.² Also, there appears to be no advantage in progression-free survival (PFS): median PFS of 3.4 for docetaxel with nintedanib from both LUME-Lung 1 and Heseltine et al., 2024 versus 4.47 (95% CI 3.02, 5.68) and 5.62 (95% CI 5.06, 6.18) from CodeBreak 200 and the CAS RWE respectively for docetaxel.^{2, 6}

It therefore appears that there might be no significant advantage to adding nintedanib to docetaxel in clinical practice, and very few patients might be prescribed the combination therapy. However, the EAG requested some clarification as to whether there was a subgroup who were eligible for docetaxel with nintedanib and if there was evidence of declining use, to which the company responded that no information was available in the CAS database on indication for treatment, and too few patients were treated to estimate a trend.⁷ In addition, the EAG clinical expert stated that he agreed with the exclusion of docetaxel with nintedanib as a comparator. Nevertheless, given the statement in the FG that it should be, there remains some uncertainty, which therefore constitutes a key issue.

2.4 Outcomes

The outcomes in the DP are in line with those in the NICE scope, excepting the use of either time to treatment discontinuation (or death) (TTD[D]) or time to next treatment (or death) (TTNT[D]) in the CAS RWE, which the company justified as a proxy for PFS.^{2, 3}

EAG comment: The company make a good case for using proxies given that PFS was not available in the CAS RWE. However, it should be noted that using the CAS RWE led to a larger treatment effect than using PFS from the CodeBreak 200 trial i.e. hazard ratio (HR) of HR: 0.567; 95% CI: 0.485, 0.663; p<0.001) instead of 0.663 (95% CI 0.509, 0.864), and there seems to be little justification for believing that the treatment effect on PFS in the trial would be biased.

2.5 Other relevant factors

None.

EAG comment: No comment.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

Two systematic literature reviews (SLRs) were conducted to identify all available evidence for the clinical effectiveness and safety of treatments in adults with KRAS-mutated locally advanced and unresectable or metastatic NSCLC:⁸

- SLR of RCTs conducted in patients with KRAS-mutated locally advanced and unresectable or metastatic NSCLC who have received at least one prior systemic therapy
- SLR of single-arm trials (SATs) conducted in patients with KRAS-mutated advanced or metastatic NSCLC, irrespective of line of therapy (LoT)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.² The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.⁹ The EAG has presented only the major limitations of each search strategy in the report.

Appendix B of the CS details two SLRs conducted to identify evidence for the clinical effectiveness and safety of treatments in adults with KRAS-mutated locally advanced and unresectable or metastatic NSCLC.⁸

EAG comment:

- Two SLRs were conducted to identify evidence for the clinical effectiveness and safety of treatments in adults with KRAS-mutated locally advanced and unresectable or metastatic NSCLC. The first was an SLR of RCTs conducted in patients with KRAS-mutated locally advanced and unresectable or metastatic NSCLC who have received at least one prior systemic therapy, and the second was a SLR of SATs conducted in patients with KRAS-mutated advanced or metastatic NSCLC, irrespective of LoT.
- The CS, Appendix B and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{2, 7, 8}
- The RCT SLR, based on the published SLR by Schulz et al., 2019¹⁰ was conducted in June 2020 and updated in January 2021, September 2024 and March 2025. The SAT SLR was conducted in July 2019 and updated in March 2021, September 2024 and March 2025.
- For the RCT SLR, the following databases were searched: Embase, MEDLINE (including In Process, Epub ahead of print and MEDLINE Daily), the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL). Four key conferences were manually searched for proceedings between January 2021 and March 2025: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), World Conference on Lung Cancer (WCLC) and American Association of Cancer Research (AACR). Seven clinical trial registries were searched to identify potentially relevant clinical trials, and reference lists were scanned.
- For the SAT SLR, the following databases were searched: Embase, MEDLINE (including In Process, Epub ahead of print and MEDLINE Daily), CDSR, Database of Abstracts of Reviews of Effects (DARE), CENTRAL, Cochrane Methodology Register (CMR), NHS Economic

Evaluations Database (NHS EED), Health Technology Assessment (HTA) Database and the American College of Physicians (ACP) Journal Club. Five key conferences were manually searched for proceedings: ASCO (2017-2024), ESMO (2016-2024), WCLC (2016-2024), European Lung Cancer Congress (ELCC) (2017-2024) and ASCO Gastrointestinal Cancers Symposia (2017-2021). Six clinical trial registries were searched to identify potentially relevant clinical trials, and reference lists were scanned.

- The RCT strategies were limited to a date range of 2015 to date, and the SAT strategies from 2014 to date. No language limit was applied to the RCT searches, and an English language limit was applied to the SAT searches.
- All database strategies searched for a range of terms for NSCLC. For the SAT SLR this was then combined with terms for KRAS mutation. The population facet was then combined with study design filters for either RCTs or SATs. The EAG noted that an RCT filter was applied to searches of CDSR and CENTRAL. These are already pre-filtered databases and therefore the use of a filter could be considered to be overly restrictive.
- Study design filters, where used, were not referenced, so it was unclear whether the filters used were published objectively-derived filters. The filters contained a combination of subject heading terms and free text terms, and the EAG considered them to be appropriate. The EAG noted however, that in the RCT searches Emtree indexing terms were used in the MEDLINE search strategy, rather than the Medical Subject Headings (MeSH) equivalent. Although mapping between indexing terms does take place, it is good practice to use the database-appropriate subject headings to ensure no potentially relevant records are missed.
- All clinical effectiveness searches were well structured, transparent and reproducible, and contained a good range of search terms, synonyms and subject headings. A good range of bibliographic databases, conference proceedings and trials registers were searched.

3.1.2 *Inclusion criteria*

The eligibility criteria used in SLRs for RCTs and SATs is presented in Table 3.1 and 3.2.

EAG comment: The EAG notes that these SLRs were conducted in the context of the company's own RCT, CodeBreaK 200, and the CAS RWE study, both of which provide direct comparative evidence for sotorasib versus the main comparator, docetaxel. Therefore, the only useful evidence that was likely to come from the SLRs would have been of sotorasib versus another comparator, and that comparator versus docetaxel i.e. to inform an indirect treatment comparison (ITC), and the eligibility criteria were sufficiently broad (any therapy) to find such studies.

Table 3.1: Eligibility criteria used in search strategy for RCT evidence

Criteria	Include	Exclude
Population	Adults (≥ 18 years) with <i>KRAS</i>-mutated locally advanced and unresectable or metastatic (stage IIIB-IV) NSCLC who had received at least one prior systemic therapy. Studies with non-adult participants if information specific to adults was reported separately. Subgroups of particular interest including but not limited to: - PD-L1 expression - Prior PD-(L)1 therapies - Early versus late progressors	Paediatric and adolescent (< 18 years) patients. Patients with cancers other than NSCLC. Early-stage NSCLC patients (Stage $< \text{IIIB}$). Trials studying safety and efficacy of treatment administered in adjuvant setting. Treatment naïve patients.
Intervention/comparator	Any therapies licensed in the US or EU for the second or later line treatment of patients with NSCLC. <i>Retreatment with Immuno-oncology therapies will be considered as is in scope even if not a specified retreatment post progression on an anti PD-(L)1</i>	Treatments specifically targeting <i>EGFR/ALK/ROS1</i> or other targetable mutation.
Outcomes	Efficacy - OS[§] - PFS[§] - Progression after next LoT[§] - TTP[§] - TTNT - EFS[§] - ORR - PR - CR - OR for response rates - DOR - Disease control rate or clinical benefit rate - Treatment duration and dosing (median duration, mean duration, mean number of doses, cumulative doses, etc.) Safety and tolerability: - All-grade TEAEs - Treatment related Grade 3 or 4 AEs - Treatment related SAEs - Tolerability: dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs)	Non-clinical outcomes
Study design/setting	Phase II–IV RCTs	Trials with a Phase 1 component only. Non-randomised clinical trials. Studies with < 10 participants.

Criteria	Include	Exclude
Language of publication	English language publications (English language abstracts of foreign language publications will be considered for inclusion)	Non-English language publications without an English abstract.
Date of publication	Original SLR/2021 update: Full papers published during or after 2015[‡] Conference abstracts published during or after 2017[‡] 2024 update: 1 January 2021 - 19 September 2024 full papers and conference abstracts published since 2021. 2025 update: 19 September 2024 - 3 March 2025 full papers and conference abstracts published since September 2024.	Studies published prior to 2015[‡] Conference abstracts published prior to 2017.
Countries	No restriction.	-

Based on Table 13, Appendices⁸
 AEs = adverse events; ALK = anaplastic lymphoma kinase; CI = confidence interval; CR = complete response; DOR = duration of response; EFS = event-free survival; EGFR = epidermal growth factor receptor; EU = European Union; HR = hazard ratio; KRAS = Kirsten ras sarcoma; LoT = line of therapy; NSCLC = non-small cell lung cancer; OR = odds ratio; ORR = objective response rate; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free response; PR = partial response; RCT = randomised controlled trial; ROS = proto-oncogene tyrosine-protein kinase; SAE = serious adverse events; SLR = systematic literature review; TEAEs = treatment-emergency adverse event; TTNT = time to next treatment; TTP = time to progression; US = United States
[†] Studies were included even if the investigational dose was not the approved treatment.
[‡] Studies published prior to 2017 were identified in a previous SLR by Schulz et al., 2019 and were automatically included in the current review.
[§] For time to event endpoints, data were to be captured as median, HRs with 95% CIs and as rates at landmark timepoints (12, 24, 36, 48, 60 months).

Table 3.2: Eligibility criteria used in search strategy for SAT evidence

Eligibility criterion	Inclusion criteria	Exclusion criteria
Population	Patients with NSCLC (any stage, any line of treatment) carrying a <i>KRAS G12C</i> mutation or any other <i>KRAS</i> mutation (<i>KRASm</i>)	Tumour types other than NSCLC.
Interventions	Any anticancer drugs, any line of treatment or no treatment.	Radiotherapy or surgery (unless a relevant comparator arm).
Comparator	Any or none.	N/A
Outcomes	Outcome reported by <i>KRASm</i> status Clinical evidence OS PFS AEs ORR TTR DOR HRQoL evidence	N/A

Eligibility criterion	Inclusion criteria	Exclusion criteria
	Note: search strings were limited by outcomes and do not include HRQoL terms. However, if HRQoL data from SAT studies were identified in the NSCLC SLR Update and SLR Rescreen, data will be included.	
Study design	Only single-arm trials (experimental/interventional, not observational).	Exclude animal/in vitro studies, case studies, and case reports.
Date restrictions	Original SLR: 2014 to July 2019 Update 1 (2021): 2019 to March 2021 Rescreen (as part of update 1): Published from 2014 to 2019 (covering <i>KRASm</i>) Update 2 (2024): Published from 1 March 2021 – 19 September 2024 (covering <i>KRASm</i>) Update 3 (2025): Published from 19 September 2024 – 3 March 2025 (covering <i>KRASm</i>)	Studies published prior to 2014
Language restrictions	English language.	Non-English language publications without an abstract published in English.
Publication type	All publication types, except editorials and reviews, but including systematic reviews.	N/A
Country	Not restricted.	N/A
Based on Table 31, Appendices. ⁸ AEs = adverse events; DOR = duration of response; HRQoL = health-related quality of life; KRAS = Kirsten ras sarcoma; <i>KRASm</i> = Kirsten ras sarcoma mutation; N/A = not applicable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; SAT = single-arm trial; TTR = time to response		

3.1.3 Critique of data extraction

The extraction process was performed by one reviewer and independently checked for errors against the original study report by a second reviewer. Any discrepancies were resolved through discussion or through the intervention of a third reviewer.

EAG comment: This is an acceptable process.

3.1.4 Quality assessment

Quality assessment was performed using the Risk of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool for CodeBreaK 100.

EAG comment: This is an acceptable instrument.

3.1.5 *Evidence synthesis*

Not applicable.

EAG comment: None.

3.2 **Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)**

Two studies formed the mainstay of the comparative clinical effectiveness evidence of sotorasib versus docetaxel, one an RCT, CodeBreaK 200, and the other UK RWE, the CAS RWE study, neither of which had been available in TA781.^{2, 4} In addition, there was SAT of sotorasib, CodeBreaK 100, with longer term follow-up than had been available in TA781.^{2, 4}

3.2.1 *Methodology*

3.2.1.1 *CodeBreaK 200*

3.2.1.1.1 *Data-cut*

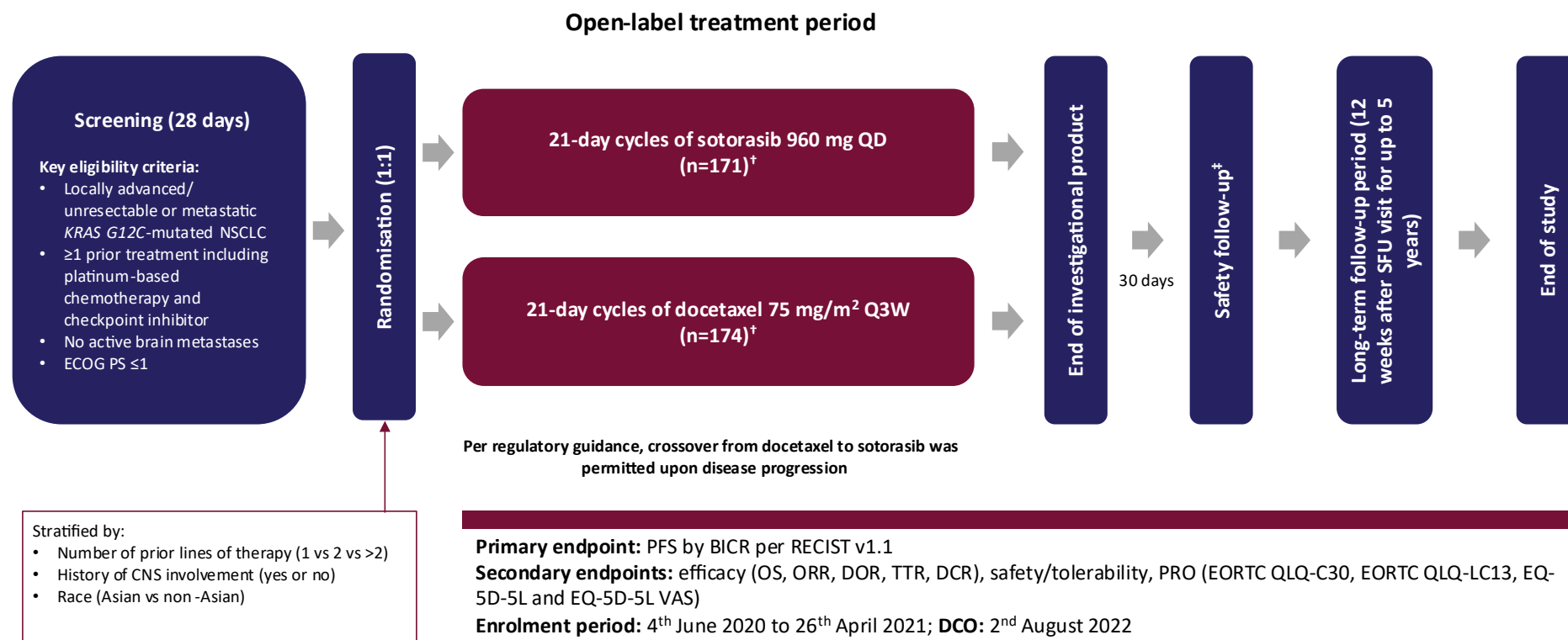
CodeBreaK 200 was initiated on 4 June 2020 and is currently ongoing; the data presented with a database cut-off date of 2 August 2022 and a database snapshot date of 23 August 2022.²

3.2.1.1.2 *Study locations*

The study is being conducted at 149 centres in Europe (including the UK), North America, Asia, Australia, and South America.²

3.2.1.1.3 *Design, including method of randomisation*

Patients meeting the eligibility criteria were randomised 1:1 to receive sotorasib or docetaxel. Further details can be found in Figure 3.1 below.

Figure 3.1: Overview of CodeBreakK 200 trial design

Based on Figure 2 of the CS²

BICR = blinded independent central review; CNS = central nervous system; CS = company submission; DCO = data cut-off; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-5L = European Quality of Life-5 Dimensions 5 Levels; *KRAS* = Kirsten ras sarcoma; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; QD = once daily; QLQ-C30 = Quality of Life Questionnaire 30-Item Core Module; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer Module; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SFU = safety follow-up; TTR = time to response; VAS = visual analogue scale

[†] Treatment with investigational product continues until independent central confirmation of progression, intolerance of treatment, initiation of another anticancer therapy, withdrawal of consent, or death. Subjects that consent to treatment beyond progression or consent to crossover, from docetaxel to sotorasib, will continue to receive investigational product after independent central confirmation of progression at the time of first progressive disease. [‡] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed 30 days (±7 days) after the end of the last dosing interval of investigational product.

The randomisation was performed by interactive response technology, and the randomisation number was provided to the study centre by the interactive response technology system. Randomisation was stratified by number of prior lines of therapy in advanced disease (1 versus 2 versus >2), race (Asian versus non-Asian), and history of central nervous system (CNS) involvement (present or absent).²

3.2.1.1.4 Eligibility criteria

- Were ≥ 18 years of age.
- Had histologically or pathologically documented locally advanced and unresectable or metastatic NSCLC with KRAS G12C mutation and no other known oncogenic driver mutation (e.g. epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK]) for which there is an approved targeted therapy according to local standard of care or guidelines.
- Must have received and progressed or experienced disease recurrence on or after receiving at least one prior systemic therapy for advanced disease, including a platinum-based doublet chemotherapy and a checkpoint inhibitor, either as one line or individual lines of therapy, unless there was a contraindication to those therapies.
- Must have had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1 , and no active brain metastases.

3.2.1.1.5 Crossover

Once subjects in the docetaxel group were determined to have radiological progression according to RECIST v1.1 by the investigator and progressive disease confirmed by independent central imaging review, they had the opportunity to crossover and receive sotorasib.²

3.2.1.1.6 Protocol amendments

The company mentioned that “*The protocol for this study (originally dated 19th November 2019) was amended four times. Each protocol amendment included a number of changes.*”²

Key changes are described below:

- The study began in November 2019, and its timeframe included the period during which the COVID-19 pandemic was occurring globally. The study was at the stage of recruitment when the pandemic occurred. Contingency measures were implemented to manage study conduct during the COVID-19 pandemic.
- Following regulatory feedback from the United States (US) Food and Drug Administration (FDA), a substantial change in study conduct was the reduction of the sample size in amendment 3 from 650 subjects (powered for the secondary endpoint of OS) to 330 subjects (powered for the primary endpoint of PFS). This change was brought forth following data that became available at the time from the primary analysis of CodeBreak 100, which demonstrated a rapid and durable response and a high disease control rate (DCR), providing evidence that sotorasib offers a benefit over docetaxel. Sotorasib became the first KRAS G12C inhibitor to show PFS (median of 6.8 months) in a Phase 2 study. As a result of this change, the study was no longer powered to detect an OS benefit.
- Another noteworthy change in study conduct following FDA feedback was to allow subjects randomised to the docetaxel group to crossover to the sotorasib group, to maximise the number of patients who received sotorasib due to the positive data from CodeBreak 100. With the option for

crossover, investigators could consider if allowing their subjects in the docetaxel group to crossover to sotorasib would be beneficial with regard to disease-related symptoms and quality of life (QoL) relative to docetaxel. Additionally, crossover would have been considered if, at the time of PFS interim analysis, efficacy (statistically significant and clinically meaningful) was noted by the independent Data Monitoring Committee (DMC) regardless of the progression status.

EAG comment: The CodeBreakK 200 trial presents results based on a relatively early data cut-off (2 August 2022), despite the study being ongoing. Interim analyses are a common practice in oncology trials; however, in this case, the early cut-off, combined with the reduced sample size following protocol amendment 3 (from 650 to 330 participants), may limit the statistical power and maturity of key secondary endpoints, particularly OS. OS generally requires extended follow-up to capture a sufficient number of events.

3.2.1.2 CodeBreak 100

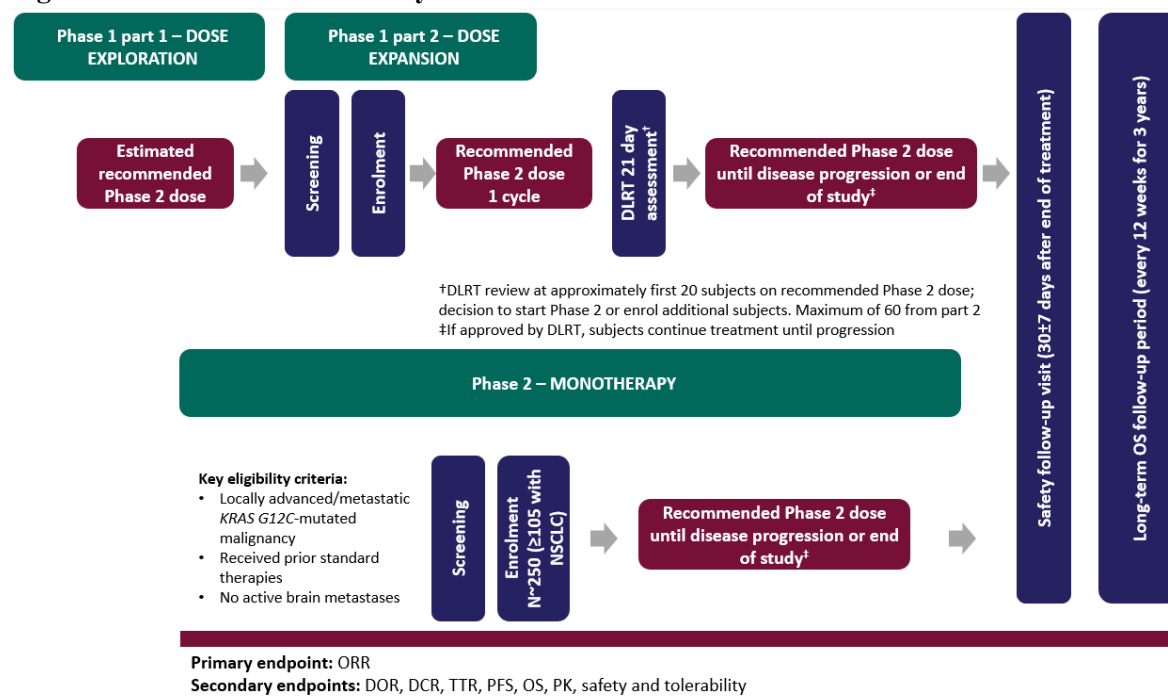
3.2.1.2.1 Study locations

The study is being conducted in Australia, Austria, Brazil, Canada, France, Germany, Greece, Hungary, Japan, Korea, Portugal, Romania, Spain, Switzerland, United States.

3.2.1.2.2 Design, including method of randomisation

CodeBreakK 100 is an ongoing, single-arm open-label Phase 1/2 trial of sotorasib in patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC after progression on prior therapies.² Further details can be found in Figure 3.2 below.

Figure 3.2: CodeBreakK 100 study schematic



Based on Figure 3 of the CS²

CS = company submission; DCR = disease control rate; DLRT = dose level review team; DOR = duration of response; *KRAS* = Kirsten ras sarcoma; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; TTR = time to response

3.2.1.2.3 *Eligibility criteria*

- Adult subjects (≥ 18 years of age) with advanced *KRAS G12C*-mutated solid tumours as assessed by molecular testing and confirmed by central testing.
- Subjects must have had:
 - ≥ 1 prior line of systemic anticancer therapy
 - Progression on prior LoT
 - Measurable disease per RECIST 1.1 criteria
 - ECOG PS of ≤ 1
 - No active brain metastases (but patients with treated and stable brain metastases could enrol)
 - QTc ≤ 470 msec (based on average of screening triplicates)
 - Ability to take oral medications
 - Adequate haematological, renal, hepatic, and coagulation laboratory assessments

EAG comment: No comment.

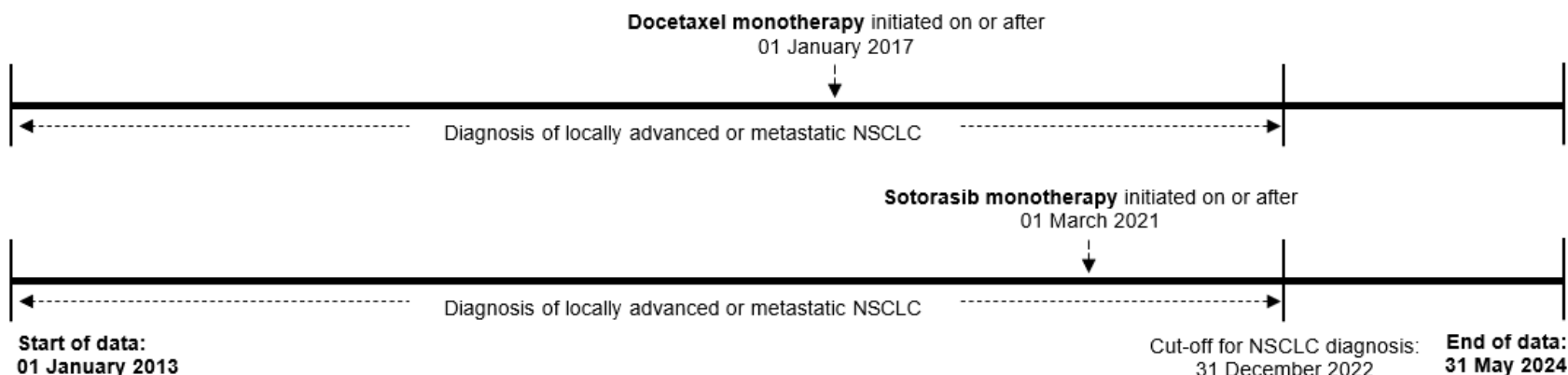
3.2.1.3 *CAS RWE Study*

3.2.1.3.1 *Study design*

This was a comparative, retrospective, new-user cohort study using the CAS database in England to generate evidence on the comparative effectiveness of sotorasib monotherapy in 2L+ patients with locally advanced or metastatic NSCLC who have previously been treated with platinum-doublet chemotherapy and/or PD 1/PD-L1 targeted immunotherapy. Eligible patients with *KRAS G12C*-mutated NSCLC who initiated sotorasib monotherapy were compared against patients with NSCLC who initiated docetaxel monotherapy. Patients who initiated docetaxel monotherapy were included irrespective of *KRAS* mutation status (i.e. with mutated, wild type, or unknown *KRAS* status), as an initial pilot study in the CAS database found that there were few eligible patients with any *KRAS* mutation or specific G12C mutation due to limited testing for *KRAS* mutations prior to the introduction of *KRAS* inhibitors.² Further details can be found in Figure 3.3 below.

Figure 3.3: Overview of CAS RWE study design

- Baseline period to assess demographics, clinical characteristics, tumour characteristics, and prior therapies for advanced NSCLC from 01 January 2013 until initiation of either sotorasib or docetaxel monotherapy (index date). Molecular characteristics to be assessed from any point in patient records.
- Follow-up period to assess clinical study outcomes from start of either sotorasib or docetaxel monotherapy (index date) to the earliest date of death, loss to follow-up, 31 May 2024, or 39 months post-index date.



Data source: Study data were collected from the Cancer Analysis System (CAS) database, which contains data on nearly all cancer patients treated in National Health Service hospitals in England. Patients were included if they are aged ≥ 18 years and had a diagnosis of advanced NSCLC between 1 January 2013 and up to 31 December 2022. Patients who initiated docetaxel monotherapy in 2L+ between 01 January 2017 and 31 May 2024 were part of the docetaxel cohort, while patients who initiated sotorasib monotherapy in 2L+ between 01 March 2021 and 31 May 2024 were part of the sotorasib cohort. Index date for assessing clinical study outcomes was the date of treatment initiation of sotorasib or docetaxel monotherapy.

Patient-level characteristics collected:

- Demographics (e.g., age, ethnicity, gender)
- Clinical and tumour characteristics (e.g., staging, histology, performance status, comorbidities)
- Treatments received in the advanced setting
- Molecular profile (e.g., *KRAS*, *EGFR*, *ALK*, *PD-L1*, *ROS1*, *BRAF*, *RET*, *NTRK*, *MET*, *STK11*, *TP53*)

Clinical study outcomes:

- Overall survival (OS)
- Time to next treatment or death (TTNTD)
- Time to treatment discontinuation or death (TTDD)

Based on Figure 4 of the CS²

CAS = Cancer Analysis System; CS = company submission; NSCLC = non-small cell lung cancer; RWE = real-world evidence

3.2.1.3.2 *Setting and study populations*

Patients with locally advanced or metastatic NSCLC were identified in the CAS database, which includes diagnosis, treatment, tumour, molecular, and survival data relating to nearly all patients diagnosed with cancer in England. Diagnoses of NSCLC were identified according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes and International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) codes.²

3.2.1.3.3 *Study period*

The overall study period ran from 1 January 2013 to 31 May 2024, based on most recent data availability in the CAS database at the time of analysis.²

3.2.1.3.4 *Eligibility criteria*

Staging in CAS is only recorded at initial diagnosis, and treatment intent (i.e. curative versus palliative) is not reliably captured. Consequently, the study population for all main analyses was restricted to patients with de novo stage III or stage IV NSCLC. Sensitivity analyses were conducted in an expanded study population which includes patients who received sotorasib but were initially diagnosed with stage I or stage II NSCLC.

To ensure comparability of the two cohorts, study eligibility criteria were based on the key eligibility criteria for the use of sotorasib in the Cancer Drugs Fund (CDF). Further details can be found in Table 3.3 below.

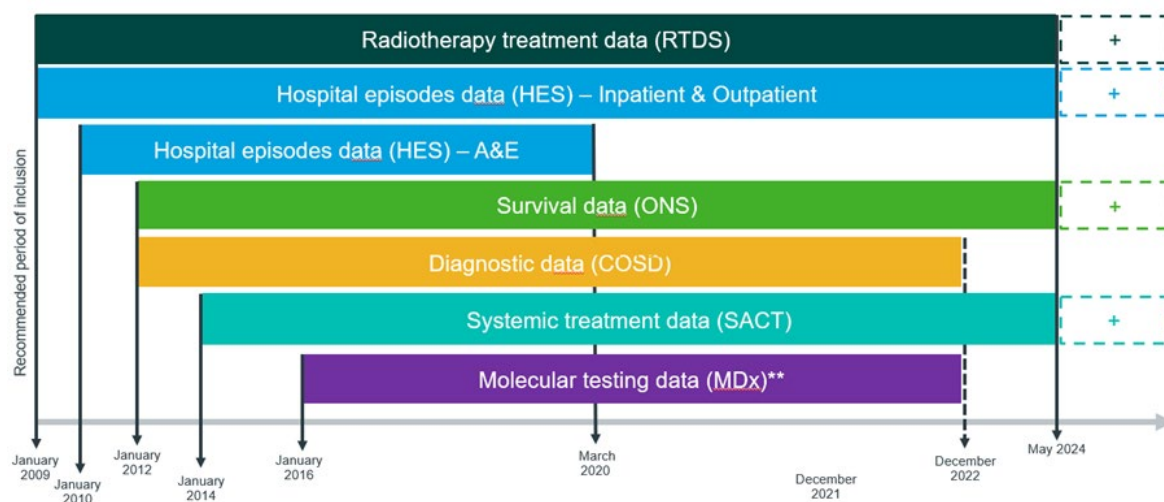
Table 3.3: Summary of key eligibility criteria for sotorasib treatment through the CDF and applicability to CAS RWE study cohorts

Eligibility criterion in Managed Access Agreement for sotorasib[†]	Applicability to sotorasib cohort	Applicability to docetaxel cohort
Patient has locally advanced or metastatic NSCLC	Assumed to apply, but main study population restricted to de novo stage III and stage IV NSCLC due to limitations of CAS database and use of algorithm for classifying LoTs	Main study population restricted to de novo stage III and stage IV NSCLC due to limitations of CAS database and use of algorithm for classifying LoTs
Patient has a histologically confirmed diagnosis of NSCLC that has been shown to exhibit a KRAS G12C mutation at any point prior to index date	Assumed to apply	Not applied to main study population due to sample size limitations but applied in descriptive sensitivity analyses; measurements at any point in patient records allowed to preserve sample size
Patient has been treated with platinum doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy at any point prior to index date	Assumed to apply	Applied directly as inclusion criterion

Eligibility criterion in Managed Access Agreement for sotorasib [†]	Applicability to sotorasib cohort	Applicability to docetaxel cohort
Patient has an ECOG PS score of 0 or 1 at index date	Assumed to apply; confirmed during data extraction that all patients have an ECOG PS score of 0, 1, or 2 [‡] (or missing) within ± 7 days of index date [§]	Applied directly as exclusion criterion (i.e. ECOG PS score $> 2^{\ddagger}$); measurements within ± 7 days of index date allowed to preserve sample size [§]
Patient either has no known brain metastases or is symptomatically stable if he/she does have brain metastases at index date	Assumed to apply	Unable to apply due to limitations of metastasis and symptom recording in CAS
Based on Table 13 of the CS² [†] There are not expected to be major differences in eligibility for patients who received sotorasib via the Early Access to Medicines Scheme versus the CDF, and the proportion of patients who received sotorasib via the Early Access to Medicines Scheme is expected to be low. [‡] Although the eligibility criterion for the Managed Access Agreement specified sotorasib patients should have an ECOG PS ≤ 1, patients with ECOG 2 were identified in the CAS database. Accordingly, to ensure comparability an exclusion criteria of ECOG > 2 was applied to the docetaxel cohort. [§] To allow for variations in the measurement timings in real-world data, values of ECOG score within ± 7 days of index date were allowed to preserve sample size. To quantify the potential magnitude of any immortal time bias due post-index date selection criteria, the timing of ECOG measurement at index date was reported descriptively as part of study outputs. CAS = Cancer Analysis System; CDF = Cancer Drugs Fund; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LoT = line of therapy; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; RWE = real-world evidence		

3.2.1.3.5 Data sources

NHS Digital collects, stores, and analyses data through the National Disease Registration Service (NDRS). An important component of NDRS is the National Cancer Registration and Analysis Service (NCRAS) which maintains the datasets that comprises CAS. The CAS database comprises several distinct datasets. For the purposes of this study, the Cancer Outcomes and Services Dataset (COSD), Systemic Anti-Cancer Therapy (SACT), and Molecular Diagnostics (MDx) datasets were used, containing detailed patient-level information about tumours, therapies, somatic mutations, and mortality, as well as other linked datasets. Due to data quality assurance processes, there is a time lag from data collection to data being available for research on each of the datasets that form CAS. Further details can be found in Figure 3.4 below.

Figure 3.4: Data availability in CAS

Based on Figure 5 of the CS²

**PD-L1/MMR biomarker data availability: January 2019 to December 2022.

A&E = Accident & Emergency; CAS = Cancer Analysis System; COSD = Cancer Outcomes and Services Dataset; CS = company submission; HES = Hospital Episode Statistics; MDx = Molecular Diagnostics; NHS = National Health Service; ONS = Office for National Statistics; RTDS = Radiotherapy Data Set; SACT = Systemic Anti-Cancer Therapy

3.2.1.3.6 Variables (Exposure, outcome and covariates assessment)

The primary exposure of interest was sotorasib monotherapy, and the comparator exposure of interest was docetaxel monotherapy. Both exposures must be delivered after at least one prior LoT in the advanced setting (i.e. in 2L+). No restrictions on dose or duration of therapy were applied.²

The following outcomes were evaluated²:

- OS: defined as the time from index date to the date of death due to any cause; patients who did not experience death were censored at the earliest date of loss to follow-up, end of study period, or 39 months post-index date
- TTNT(D): defined as the time from index date to the earliest date of start of next LoT or date of death due to any cause; patients who did not experience a next LoT or death were censored at the earliest date of loss to follow-up, end of study period, or 39 months post-index date
- TTD(D): defined as the time from index date to the earliest date of discontinuation of the current LoT or date of death due to any cause; patients who did not experience treatment discontinuation or death were censored at the earliest date of loss to follow-up, end of study period, or 39 months post index date

Date of death was obtained from the COSD (a component of CAS). Mortality data in COSD is updated regularly using data from the Office for National Statistics (ONS).²

LoTs were derived from systemic treatments which are recorded in the SACT database. The end date of the current LoT and the start date of next LoT were derived from treatment data which are recorded in the SACT database.²

The following variables relating to study follow-up were also described for all patients:²

- Time (in months) from index date to end of follow-up
- Treatment switching after index date (i.e. from sotorasib to docetaxel, and vice versa)
- Subsequent LoT initiated after index date

A summary of key covariates of interest is provided in Table 3.4 below, including parameterisation and data source(s).

Table 3.4: Key covariates describing baseline characteristics

Variable	Parameterisation	Data Source(s)
Year of diagnosis	Categorical (2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021)*	COSD
Age at diagnosis	Continuous; and Categorical (<65, 65-74, 75-84, ≥85)	COSD
Sex	Categorical (Male, Female, Missing/Unknown)	COSD
Ethnicity	Categorical (White, Black, Asian, Chinese, Mixed, Other, Missing/Unknown)	COSD
Stage at diagnosis	Categorical (stage Ia, stage Ib, stage IIa, stage IIb, stage IIIa, stage IIIb, stage IIIc, stage IV)	COSD
Histologic type at diagnosis	Categorical (squamous cell carcinoma, non-squamous cell carcinoma, Missing/Unknown)	COSD
Tumour size at diagnosis	Continuous	COSD
ECOG PS score at diagnosis	Categorical (0, 1, 2, 3, 4, Missing/Unknown)	SACT
Year of index date	Categorical (2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024)	SACT
Age at index date	Continuous; and Categorical (<65, 65-74, 75-84, ≥85)	COSD
ECOG PS score at index date	Categorical (0, 1, Missing/Unknown)	SACT
LoT number at index date	Categorical (2, 3, 4, ≥5)*	SACT
Diagnosis of brain metastasis prior to index date	Categorical (Yes, No Record)	HES
Record of brain metastasis prior to index date	Categorical (Yes, No Record)	HES
Diagnosis of liver metastasis prior to index date	Categorical (Yes, No Record)	HES
Record of any metastasis prior to index date	Categorical (Yes, No Record)	HES
Prior treatment with PD-1/PD-L1 targeted immunotherapy	Categorical (Yes, No)	SACT
KRAS mutation status	Categorical (Mutated, Borderline, Normal, Missing/Unknown, No Record of Test)	MDx

Variable	Parameterisation	Data Source(s)
KRAS G12C mutation status	Categorical (Mutated, Missing/Unknown, No Record of Test)	MDx
Presence of any actionable non-KRAS gene alteration or rearrangement (i.e. EGFR, ALK, ROS1, BRAF, RET, NTRK, MET, STK11, TP53)	Categorical (Yes, No, No Record of Any Test)	MDx
PD-L1 expression	Categorical (<1%, 1-49%, ≥50%, Missing/Unknown, No Record of Test)	MDx
Treatment switching after index date	Categorical (Yes, No)	SACT
Time (in months) from diagnosis to index date	Continuous	COSD, SACT
Time (in months) from 1L initiation to index date	Continuous	SACT
Time (in months) from end of previous LoT to index date	Continuous	SACT
Time (in months) from index date to end of follow-up	Continuous	SACT, ONS
Based on Table 15 of the CS² 1L = first-line; ALK = anaplastic lymphoma kinase; COSD = Cancer Outcomes and Services Dataset; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; HES = Hospital Episode Statistics; KRAS = Kirsten ras sarcoma; LoT = line of therapy; MDx = Molecular Diagnostics; ONS = Office for National Statistics; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; SACT = Systemic Anti-Cancer Therapy		

EAG comment:

- The EAG reviewed the CAS RWE study, which used the CAS database in England to generate comparative evidence on sotorasib versus docetaxel in 2L+ NSCLC. The EAG requested completion of the QuEENS checklist (priority question A4). In response, the company highlighted its critical appraisal in Section 2.5 of the CS and reported that the study design was informed by the target trial emulation framework, consistent with NICE Technical Support Document (TSD) 17.⁷
¹¹ The EAG agrees that target trial emulation represents a best-practice methodological approach, and that use of a comprehensive national database is a strength. However, the EAG notes that the company did not have access to patient-level data, relying instead on outputs from the original CAS analysis. This lack of direct access limits transparency, reproducibility, and the ability to test alternative modelling assumptions (e.g. uncensored follow-up, different parametric forms), thereby increasing uncertainty around the reliability of the comparative effectiveness estimates.
- The EAG also raised concerns regarding censoring of follow-up at 39 months for the docetaxel cohort (priority question A5). The company stated that this was applied to avoid bias arising from unequal follow-up, but indicated that sensitivity analyses without censoring could not be conducted because the analyses were pre-specified and patient-level data were not available.⁷ This restricts the ability to fully assess the robustness of the comparative effectiveness estimates used in the economic model.
- The EAG sought clarification on the apparent inconsistency in reporting of data availability (priority question A6). The CS suggested no patient-level data were available, whereas

the technical report described use of weighted Kaplan-Meier (KM) analyses and Cox regression. The company explained that while the original CAS study team had access to patient-level data, the company itself did not, and therefore had to digitise KM curves to generate pseudo-patient data for parametric modelling.⁷ The EAG acknowledges this explanation, but highlights that reliance on digitised outputs rather than raw data increases uncertainty, particularly for extrapolation of OS, TTNT(D), and TTD(D).

In conclusion, the fact the CAS RWE study is not a RCT, and lack of access to patient-level data raise doubts as to its validity in estimating the effectiveness of sotorasib versus docetaxel, which indicates a key issue.

3.2.2 Statistical analysis

3.2.2.1 CodeBreaK 200

There were several analysis sets, including the intention-to-treat (ITT)/full analysis set (FAS), for which efficacy outcomes are reported below. In addition, given the high proportion of crossover from docetaxel to sotorasib, three methods of adjustment for crossover were considered. Among these three methods, two-stage estimation (TSE), inverse probability of censoring weighting (IPCW), and rank preserving structural failure time (RPSFT), only the TSE is considered appropriate due to the trial design and the covariates considered for adjustment.²

3.2.2.1.1 TSE

The TSE adjusted for crossover effect by estimating the relative treatment effect of OS that would have been observed in the docetaxel group in the absence of crossover, based on the adjusted survival time fitted, by means of an accelerated failure time (AFT) model on post-progression subjects in the docetaxel group.

The TSE has been developed for trials designed exactly as CodeBreaK 200 was designed. The TSE assumes there is a “secondary baseline” before which crossover is not allowed. Furthermore, crossover should occur close to this secondary baseline. In the context of CodeBreaK 200, this secondary baseline is disease progression (i.e. the date of the first scan determined to exhibit progressive disease by investigator which underwent independent central confirmation). Once subjects of the docetaxel arm progressed, their decision to crossover is analysed as in the context of an observational study. The post-progression crossover effect, adjusted for confounders, is used to re-adjust the observation times. For the TSE, the key limitation is the assumption of “no unmeasured confounders.” Based on a structured interview of experienced NSCLC physicians, multiple confounders in CodeBreaK 200 were identified and pre-specified for adjustment. The remaining bias should therefore be small.²

3.2.2.1.2 IPCW

Per pre-specification, the same confounders were defined for the IPCW method as for the TSE. However, for IPCW, time-dependent covariates need to be measured continuously, which in the context of CodeBreaK 200, has high levels of missing data, particularly for later intervals. In such cases, the weights were imputed, introducing potentially substantial bias. Furthermore, the progression status was not accounted for in time varying covariates. Not capturing this key confounder is a major miss. 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 disfavour of sotorasib. Conducting an IPCW ad hoc analysis addressing this issue is challenging for the following reasons:

- If certain patient characteristics are very strong predictors of switching, extreme weights can be obtained. In these circumstances the IPCW becomes prone to error (88).
- Per European Medicines Agency (EMA) Guidance (89): “Furthermore, sufficient heterogeneity in the crossover pattern should be present in the sense that baseline and time-dependent covariates should not be (close to) perfectly predicting crossover; for if they do, the weights used in IPCW would be (close to) infinity, and the method would break down.”
- Finally, even if the progression status would have been included as a time varying covariate, and the instability and bias issue above would have overcome, the issue would remain that also the time since progression could be a relevant predictor. As the timing of disease progression between crossover and non-crossover subjects differs, it would be about impossible to find similar subjects for appropriate weight assignment.

In conclusion, the IPCW method is not appropriate for CodeBreak 200.²

3.2.2.1.3 *RPSFT*

The RPSFT model is incompatible with the CodeBreak 200 trial design. The key limitation of the RPSFT model is the assumption of a ‘common treatment effect’. More specifically, the treatment effect is assumed to be the same in the intervention arm and for subjects after crossover. This simple assumption in the context of the CodeBreak 200 trial, however, is heavily breached for three reasons:

- First, treatment switching is only permitted after disease progression; therefore, crossover subjects have more advanced disease.
- Second, the comparator in CodeBreak 200 is not placebo; rather, it is an active treatment that prolongs survival. This situation was identified by Latimer & Abrams et al., 2014 as an important biasing factor. This is because the RPSFT counterfactual survival model requires that patients are either ‘on’ or ‘off’ at any one time. If patients in the control group receive an active treatment followed by supportive care upon treatment failure, the ‘off’ treatment category represents more than one type of treatment, and the counterfactual survival model is not appropriate.
- Third, in CodeBreak 200, the RPSFT model does not consider whether a subject is still actively taking the drug or has already discontinued the drug. Subjects in the sotorasib treatment arm are always considered to be on treatment. Correspondingly, crossover subjects are considered to be on treatment after crossover. This assumption does not reflect reality as the proportion of those “on” versus “off” active treatment may substantially differ between the intervention arm and the crossover subjects.

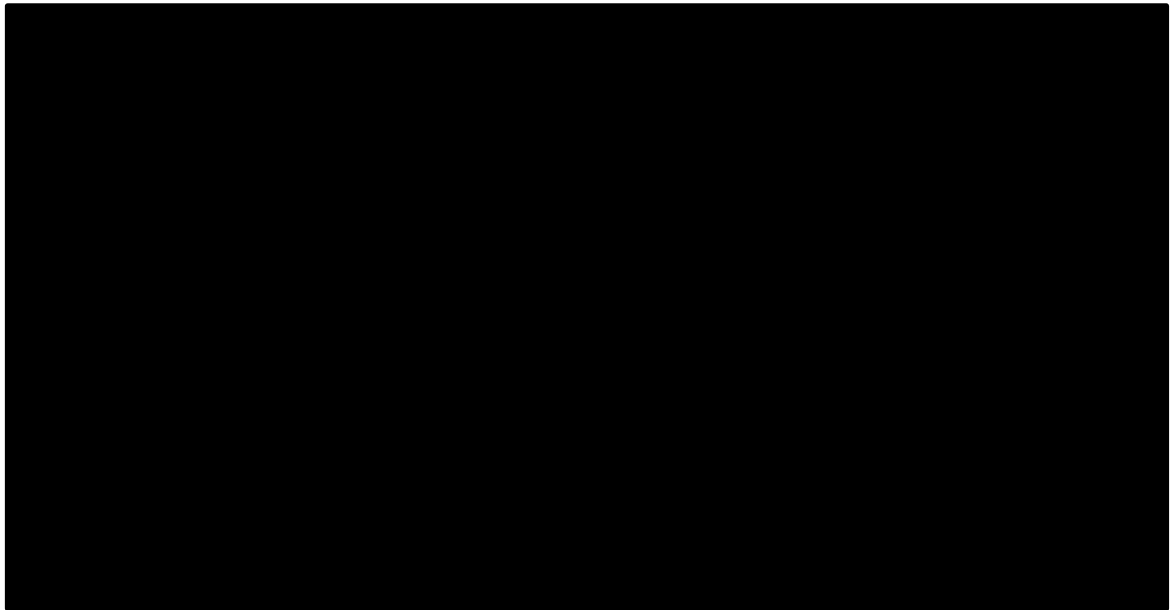
EAG comment: The EAG reviewed the company’s approach to adjusting for crossover in CodeBreak 200. Given the high proportion of patients switching from docetaxel to sotorasib, the company considered three standard methods: TSE, IPCW, and RPSFT. The company justified selection of the TSE method on the basis that it aligns with the trial design, allows disease progression to act as the secondary baseline, and accounts for prespecified confounders. The EAG agrees that TSE is the most appropriate method in this context, given the limitations of IPCW (missing time-dependent data,

instability of weights, and inability to adjust for progression adequately) and RPSFT (violation of common treatment effect assumptions and incompatibility with an active comparator). Nevertheless, the EAG notes that the validity of TSE depends on the assumption of no unmeasured confounding at progression, which cannot be fully verified. This residual uncertainty should be considered when interpreting the adjusted OS results.

The EAG noted that the similarity in OS between the two arms is the crossover to sotorasib from docetaxel and the possibility of the result might indicate an advantage to treating with docetaxel before treating with sotorasib. The company argued that the ITT analysis showed numerically longer OS for patients randomised to sotorasib, which makes the hypothesis that sequencing docetaxel before sotorasib might be advantageous highly unlikely.⁷ The EAG is puzzled that the company make this claim because in the CS the main analysis set for all outcomes was the ITT population, and there was actually a numerical advantage to docetaxel, albeit small (see Table 3.11). The plausibility of the EAG hypothesis is therefore not undermined by this and could be tested to some extent by comparing the outcomes after crossover with starting on sotorasib, albeit acknowledging the potential for bias. Therefore, the EAG also requested the company to present OS data separately for those who crossed over to sotorasib and those who did not cross over. Treatment durations, response to treatment and OS outcomes for patients who crossed over to sotorasib per protocol are provided by the company in Figure 3.5 below. The key baseline characteristics of these patients were shown in Table 3.5 below.⁷ The EAG noted from Table 3.5 that baseline characteristics of crossover and non-crossover patients show broadly similar distributions of age, ECOG PS, smoking history, and comorbidities, though some imbalances are evident. For example, a higher proportion of early crossover patients had received two prior lines of therapy compared with non-crossover patients. While OS following crossover appears favourable, the EAG highlights that these data are based on a small subgroup (n=46) and are therefore it is no surprise that median OS has not been reached.

In conclusion, the EAG acknowledges that there is insufficient evidence to test the hypothesis of and advantage to docetaxel followed by sotorasib. The EAG was also puzzled by the division of crossover patients into those where crossover occurred ‘early’ and those where it occurred after blinded independent central review (BICR)-confirmed progression, given that the CS stated that only the latter is possible (see Section 3.2.1.1.5). The EAG checked the clinical study report (CSR) and confirmed that this appears to be the case:¹² *“During the study, 46 subjects who were randomized to docetaxel crossed over to sotorasib treatment following confirmed progressive disease.”* (Section 9.1)

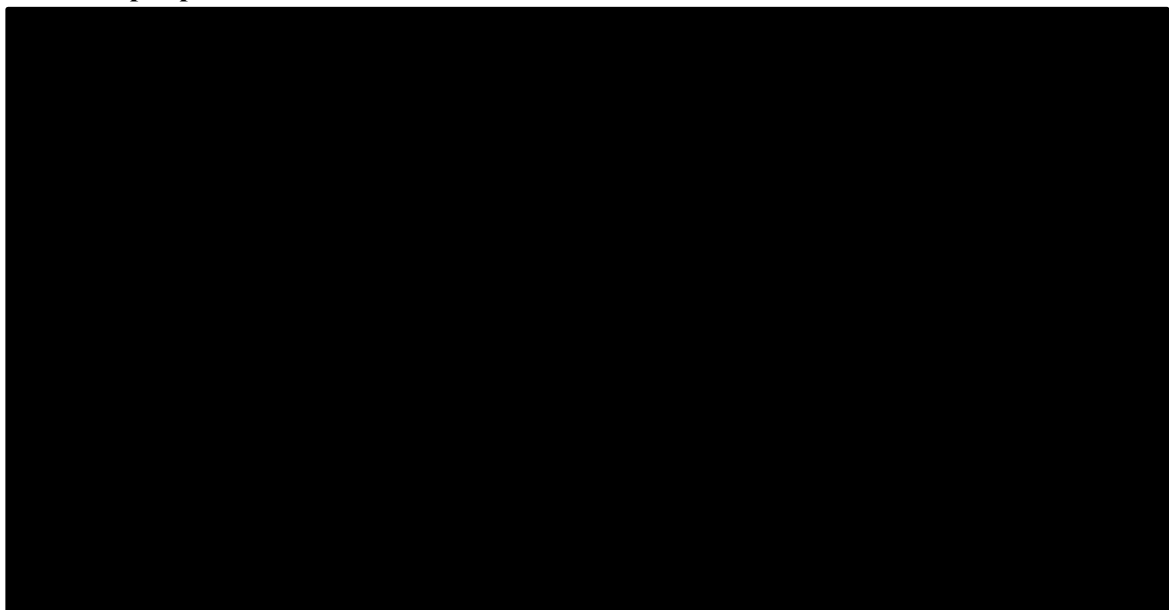
Figure 3.5: Outcomes for patients in docetaxel arm who crossed over to sotorasib per protocol



Based on clarification letter response⁷

CI = confidence interval; DCR = disease control rate; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival

Table 3.5: Key baseline characteristics of patients from docetaxel arm who crossed over to sotorasib per protocol



Based on clarification letter response⁷

BICR = blinded independent central review; CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; PD = progressive disease; SLD = sum of longest diameter

3.2.2.2 CAS RWE

3.2.2.2.1 Missing or incomplete data

Missing baseline data for all variables were reported descriptively (N, %), with no imputation performed. To preserve sample size in propensity score (PS) modelling, key covariates like ECOG PS and body mass index (BMI) included a “missing” category. Endpoint missingness was expected to be minimal.²

3.2.2.2.2 PS weighting

For all study objectives, PS weighting was used to balance treatment groups with respect to important baseline covariates. The R WeightIt package was used for PS estimation and weighting, and the cobalt package was used for evaluation of covariate balance.²

The average treatment effect in the treated (ATT) was considered the most appropriate estimand for all main analyses. Standardised mortality ratio weighting (SMRW) was used, such that the analysis set is re-weighted so that the distribution of covariates in both treatment groups matches the distribution of covariates in the sotorasib treatment group. Standardised mortality ratio weights were derived according to the following formulae:

$$SMRW_j = 1, \text{ for patients in the sotorasib treatment group}$$

$$SMRW_j = \frac{PS_j}{1-PS_j}, \text{ for patients in the docetaxel treatment group}$$

The weightit function in the R WeightIt package was used, with the argument estimand = "ATT" specified.⁸

3.2.2.2.3 Survival analysis (KM and Cox regression)

For all study objectives, the KM method was used to graphically depict the survival functions according to treatment group. In adjusted analyses, the KM analysis was performed using a weighted analysis set to account for baseline confounding; in unadjusted analyses, the KM analysis was performed using an unweighted analysis set. For all analyses, a two-sided log-rank test with a significance level of 0.05 was performed to compare treatment groups. The number of patients still at risk at discrete time points (e.g. every 3 months post-index date, up to 36 months) was tabulated below the curves. Median survival time and two-sided 95% CIs were reported for each outcome, along with the first and third quartiles (Q1 and Q3). The probability of not experiencing the event of interest at each selected time point was estimated and reported along with the corresponding two-sided 95% CIs.²

For all study objectives, the effect of sotorasib monotherapy versus docetaxel monotherapy was estimated using a Cox PH regression model. In adjusted analyses, the Cox model was fitted in the weighted analysis set to account for baseline confounding. Baseline confounders which remained imbalanced (i.e. standardised mean difference [SMD] ≥ 0.1) following weighting were included as covariates in the Cox model. An adjusted HR with associated 95% CI was reported as an estimate of the treatment effect. In unadjusted analyses, the Cox model was fitted in the unweighted analysis set without any confounders included as covariates, and an unadjusted HR with associated 95% CI was reported.

The PH assumption was assessed using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals, using the plot.cox.zph function in the same package. If the PH assumption is violated for the exposure, an interaction between the exposure and time (either continuous or categorical)

was introduced to account for non-PH by allowing the HR to vary over time. If imbalanced variables were included as adjustment into the Cox model, these variables were removed and adjusted for through stratification. This was implemented in order to allow the baseline hazard to vary across levels of the stratifying variable(s), as direct inclusion of such variables could violate the assumption of correct model specification.²

PS weighting generates a pseudo-population in which some individuals contribute more to the analysis than others, depending on their assigned weights. This process can impact the effective sample size (ESS) and introduce correlation within the data, as observations are no longer equally weighted. As a result, standard error (SE) estimates based on traditional methods may be biased. To account for this, robust SEs were used to calculate CIs for treatment effect estimates using the argument `robust = TRUE` in the `coxph` function. This approach adjusts for the variability introduced by the weighting process and provides more reliable estimates of statistical uncertainty.²

The use of robust estimator methods for estimating CIs increases the variance in estimated effects (i.e. the ESS is reduced). For each analysis, the ESS which resulted from the use of treatment weighting to adjust for baseline confounding was reported based on the formula:

$$ESS = \frac{(\sum_{j=1}^n w_j)^2}{\sum_{j=1}^n w_j^2}$$

where w_j is the weight for individual j . ESS was calculated using the ESS function in the `WeightIt` package.²

EAG comment: The EAG reviewed the company's statistical analysis of the CAS RWE study. The overall approach, including use of PS weighting (SMRW with ATT estimand), weighted Cox regression, robust standard errors, and reporting of ESS, is in line with best practice for handling baseline imbalances in observational data.

However, the EAG highlights several limitations. Missing baseline data for key variables such as ECOG PS and BMI were handled by creating a "missing" category, with no imputation performed. This pragmatic approach preserves sample size but may introduce bias if the missingness is informative. Furthermore, while PS weighting can balance observed covariates, the risk of residual confounding due to unmeasured factors remains. The reliance on weighting also reduces the ESS, which can limit statistical power and increase uncertainty in effect estimates.

Overall, while the company's analysis is technically sound and consistent with NICE TSD 17 guidance on RWE,¹¹ the EAG considers that the findings should be interpreted with caution due to potential bias from missing data and unmeasured confounding. This therefore raises doubts as to the validity of the CAS RWE study, which need to be considered alongside the pros and cons of the CodeBreak 200 RCT, which is part of the key issue regarding the most appropriate source of comparative evidence.

3.2.3 Baseline characteristics

3.2.3.1 CodeBreak 200

The majority of subjects in the study were men (204 subjects [59.1%]), white (286 subjects [82.9%]) or Asian (43 subjects [12.5%]), and not Hispanic/Latino (328 subjects [95.1%]). The median age was 64.0 (range: 32 to 88) years, and approximately half of the subjects were <65 years (186 subjects [53.9%]). The majority of subjects were from Europe (252 subjects [73.0%]),

followed by the rest of world (51 subjects [14.8%] in Asia, Australia, and South America), and North America (42 subjects [12.2%]).²

Most subjects had non-squamous (334 subjects [96.8%]), metastatic disease (328 subjects [95.1%]). All 345 subjects had a first prior LoT, 197 subjects (57.1%) had a 2L of therapy, 56 subjects (16.2%) had a third line (3L) of therapy, and 118 subjects (34.2%) were on maintenance therapy. The majority of subjects had no history of CNS involvement (227 subjects [65.8%]) and had an ECOG PS of 1 at screening (227 subjects [65.8%]). PD-L1 protein expression was <1% for 112 subjects (32.5%), ≥1% to <50% for 116 subjects (33.6%), and ≥50% for 100 subjects (29.0%). Other co-mutations at baseline included TP53 (10 subjects [2.9%]), STK11 (8 subjects [2.3%]), MET and KEAP1 (3 subjects [0.9%] each), BRAF (2 subjects [0.6%]), and EGFR, ALK, and ROS1 (1 subject [0.3%] each).²

The company concluded that “no noteworthy differences in baseline demographics or characteristics were observed between the treatment groups.”² Further details can be found in Table 3.6 below.

Table 3.6: Key baseline characteristics of participants in CodeBreaK 200

	Docetaxel (N=174)	Sotorasib (N=171)
Age at randomisation, years		
N	174	171
Mean	63.6	63.4
Median	64.0	64.0
Min, max	35, 87	32, 88
<65 years, n (%)	95 (54.6)	91 (53.2)
≥65 years, n (%)	79 (45.4)	80 (46.8)
Sex, n (%)		
Male	95 (54.6)	109 (63.7)
Female	79 (45.4)	62 (36.3)
Ethnicity, n (%)		
Hispanic/Latino	9 (5.2)	5 (2.9)
Not Hispanic/Latino	163 (93.7)	165 (96.5)
Unknown	2 (1.1)	1 (0.6)
Race, n (%)		
American Indian or Alaska Native	0 (0.0)	0 (0.0)
Asian	22 (12.6)	21 (12.3)
Black or African American	0 (0.0)	2 (1.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
White	144 (82.8)	142 (83.0)
Multiple	0 (0.0)	1 (0.6)
Other	7 (4.0)	4 (2.3)
Unknown	1 (0.6)	1 (0.6)
ECOG PS at screening, n (%)		
0	59 (33.9)	59 (34.5)
1	115 (66.1)	112 (65.5)

	Docetaxel (N=174)	Sotorasib (N=171)
ECOG PS at Cycle 1 Day 1, n (%)		
0	46 (26.4)	66 (38.6)
1	105 (60.3)	100 (58.5)
2	1 (0.6)	1 (0.6)
3	1 (0.6)	0 (0.0)
Missing	21 (12.1)	4 (2.3)
Prior line of therapy, n (%)[†]		
First	174 (100.0)	171 (100.0)
Second	100 (57.5)	97 (56.7)
Third	27 (15.5)	29 (17.0)
Fourth	6 (3.4)	6 (3.5)
Fifth	2 (1.1)	2 (1.2)
Sixth	1 (0.6)	0 (0.0)
Seventh	0 (0.0)	0 (0.0)
Maintenance	56 (32.2)	62 (36.3)
Other	2 (1.1)	2 (1.2)
History of CNS involvement, n (%)		
Yes	60 (34.5)	58 (33.9)
No	114 (65.5)	113 (66.1)
Liver metastasis, n (%)		
Yes	35 (20.1)	30 (17.5)
No	139 (79.9)	141 (82.5)
Smoking history – tobacco, n (%)		
Never	8 (4.6)	5 (2.9)
Current	35 (20.1)	32 (18.7)
Former	131 (75.3)	134 (78.4)
Histology, n (%)		
Squamous	7 (4.0)	1 (0.6)
Non-squamous	165 (94.8)	169 (98.8)
Other	2 (1.1)	1 (0.6)
Disease stage, n (%)		
Locally advanced and unresectable	8 (4.6)	9 (5.3)
Metastatic	166 (95.4)	162 (94.7)
Other	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)
Best response on prior therapy, n (%)		
Primary refractory (progression on first scan)	57 (32.8)	67 (39.2)
Suboptimal response (stable disease)	53 (30.5)	50 (29.2)

	Docetaxel (N=174)	Sotorasib (N=171)
Recurrent (initial response with subsequent growth)	47 (27.0)	35 (20.5)
Not evaluable	11 (6.3)	10 (5.8)
Non-PD/non-CR	6 (3.4)	9 (5.3)
Time from initial diagnosis to randomisation, months		
N	161	162
Mean	24.47	23.33
Median	16.92	16.21
Min, max	1.5, 227.3	2.3, 132.3
PD-L1 protein expression, n (%)		
<1%	55 (31.6)	57 (33.3)
≥1 to <50%	70 (40.2)	46 (26.9)
≥50%	40 (23.0)	60 (35.1)
Based on Table 10 of the CS ² † Same subject can be counted under multiple categories. CNS = central nervous system; CR = complete response; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; PD = progressive disease; PD-L1 = programmed cell death ligand 1		

3.2.3.2 CodeBreak 100

As of 22 February 2022, 174 patients (Phase 1, N=48; Phase 2, N=126) received sotorasib. Median treatment duration was 5.6 months (range, 0.2–35.9); 13 patients remained on treatment at cut-off. Median prior lines of therapy was 2.0 (range, 0–4+). Prior therapies included anti-PD-(L)1 (157 [90%]) and platinum-based chemotherapy plus anti-PD-(L)1 (144 [83%]).² Further details can be found in Table 3.7 below.

Table 3.7: Patient demographics and baseline characteristics in CodeBreak 100

	Phase 1 (N=48)	Phase 2 (N=126)	Total (N=174)
Age, years, median (range)	68.5 (49-86)	63.5 (37-80)	65.0 (37-86)
Female, n (%)	28 (58)	63 (50)	91 (52)
Race, n (%)			
White	38 (79)	103 (82)	141 (81)
Asian	6 (13)	19 (15)	25 (14)
Black	2 (4)	2 (2)	4 (2)
Other	2 (4)	2 (2)	4 (2)
ECOG PS at baseline, n (%)			
0	11 (23)	38 (30)	49 (28)
1	37 (77)	88 (70)	125 (72)
Metastatic sites, n (%)			
Bone	20 (42)	61 (48)	81 (47)
Brain	14 (29)	26 (21)	40 (23)

	Phase 1 (N=48)	Phase 2 (N=126)	Total (N=174)
Liver	12 (25)	26 (21)	38 (22)
Disease stage at screening, n (%)			
III	1 (2)	5 (4)	6 (3)
IV	47 (98)	121 (96)	168 (97)
PD-L1 protein expression, n (%)[†]			
<1%	13 (27)	33 (26)	46 (26)
≥1 to 49%	12 (25)	30 (24)	42 (24)
≥50%	9 (19)	35 (28)	44 (25)
Unknown	14 (29)	28 (22)	42 (24)
Prior lines of therapy, n (%)			
0	2 (4)	0	2 (1)
1	17 (35)	54 (43)	71 (41)
2	14 (29)	44 (35)	58 (33)
≥3	15 (31)	28 (22)	43 (25)
Type of prior therapy, n (%)[‡]			
Platinum-based chemotherapy	48 (100)	113 (90)	161 (93)
Anti-PD-(L)1	41 (85)	116 (92)	157 (90)
Platinum-based chemotherapy and anti-PD-(L)1	41 (85)	103 (82)	144 (83)
Anti-VEGF biological therapy	10 (21)	26 (21)	36 (21)
Targeted small molecules	10 (21)	9 (7)	19 (11)
Best response to last prior line of therapy, n (%)			
Complete response	0	1 (1)	1 (1)
Partial response	2 (4)	12 (10)	14 (8)
Stable disease	11 (23)	33 (26)	44 (25)
Progressive disease	24 (50)	48 (38)	72 (41)
Unevaluable/unknown/missing	9 (19)	32 (25)	41 (24)
Duration of sotorasib treatment, months, median (range)	6.0 (0.2-35.9)	5.5 (0.2-26.9)	5.6 (0.2-35.9)
Based on Table 12 of the CS ² [†] Determined locally [‡] Each patient may have had more than one prior therapy CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; VEGF = vascular endothelial growth factor			

3.2.3.3 CAS RWE

In the sotorasib cohort (N=394), ■ patients (■%) were female and ■ (■%) were of White ethnicity. The median age at diagnosis was ■ years (Q1-Q3: ■), and ■ (■%) patients were diagnosed with stage IV NSCLC, whilst ■ (■%) tumours were non-squamous cell carcinomas. There was no record of any *KRAS* test in ■ patients (■%). Though not all patients had record of any *KRAS* test, ■ (■%) had a record of *KRAS G12C* mutation.

In the docetaxel cohort (N=1,271), [REDACTED] patients ([REDACTED]%) were female and [REDACTED] ([REDACTED]%) were of white ethnicity. The median age at diagnosis was [REDACTED] years (Q1-Q3: [REDACTED]), and [REDACTED] ([REDACTED]%) patients were diagnosed with stage IV NSCLC, whilst [REDACTED] ([REDACTED]%) were non-squamous cell carcinomas. There was no record of any KRAS test in [REDACTED] patients ([REDACTED]%); record of *KRAS G12C* mutation was reported in [REDACTED] patients ([REDACTED]%).² Further details can be found in Table 3.8 below.

Table 3.8: Characteristics of participants in CAS RWE

	Docetaxel (N=1,271)	Sotorasib (N=394)
Age at diagnosis, years		
N	1,271	394
Mean (SD)	[REDACTED]	[REDACTED]
Median (Q1, Q3)	[REDACTED]	[REDACTED]
Sex, n (%)		
Male	[REDACTED]	[REDACTED]
Female	[REDACTED]	[REDACTED]
Ethnicity, n (%)		
White	[REDACTED]	[REDACTED]
Asian	[REDACTED]	[REDACTED]
Black	[REDACTED]	[REDACTED]
Chinese/Other	[REDACTED]	[REDACTED]
Mixed	[REDACTED]	[REDACTED]
Missing	[REDACTED]	[REDACTED]
Stage at diagnosis, n (%)		
I	[REDACTED]	[REDACTED]
II	[REDACTED]	[REDACTED]
III	[REDACTED]	[REDACTED]
IV	[REDACTED]	[REDACTED]
Histology, n (%)		
Squamous	[REDACTED]	[REDACTED]
Non-squamous	[REDACTED]	[REDACTED]
Unspecified carcinoma	[REDACTED]	[REDACTED]
Other and unspecified types of cancer	[REDACTED]	[REDACTED]
Age at index, years		
N	[REDACTED]	[REDACTED]
Mean (SD)	[REDACTED]	[REDACTED]
Median (Q1, Q3)	[REDACTED]	[REDACTED]
ECOG PS at index, n (%)		
0	[REDACTED]	[REDACTED]
1	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]
3	[REDACTED]	[REDACTED]

	Docetaxel (N=1,271)	Sotorasib (N=394)
4	██████	██████
Missing	██████	██████
Line of therapy number at index, n (%)		
2	██████	██████
3	██████	██████
4	██████	██████
≥5	██████	██████
Diagnosis of brain metastasis prior to index date, n (%)		
Yes	██████	██████
No record	██████	██████
Record of any metastasis prior to index date, n (%)		
Yes	██████	██████
No record	██████	██████
Prior treatment with PD-1/PD-L1 targeted immunotherapy, n (%)		
Yes	██████	██████
No	██████	██████
KRAS mutation status, n (%)		
Mutated	██████	██████
Borderline	██████	██████
Normal	██████	██████
No record of test	██████	██████
Missing/unknown	██████	██████
KRAS G12C mutation status, n (%)		
Mutated	██████	██████
Not mutated	██████	██████
No record of test	██████	██████
Time from initial diagnosis to index date, months		
N	████	██
Mean (SD)	██████	██████
Median (Q1, Q3)	██████	██████
Based on Table 16 of the CS ²		
* Numbers from 1-5 may be masked, in accordance with NHS England policy to minimise the risk of patient identification.		
** Numbers are masked to prevent back-calculation of masked values.		
CAS = Cancer Analysis System; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; KRAS = Kirsten ras sarcoma; NHS = National Health Service; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; Q1 = first quartile; Q3 = third quartile; RWE = real-world evidence; SD = standard deviation		

3.2.4 Efficacy results

3.2.4.1 CodeBreak 200

3.2.4.1.1 Primary efficacy outcome: PFS

In total, 223 PFS events were reported by the data cut-off date for this analysis, including 122 subjects (71.3%) in the sotorasib group and 101 subjects (58.0%) in the docetaxel group. The median PFS was 5.62 months (95% CI: 4.27, 7.75) in the sotorasib group compared with 4.47 months (95% CI: 3.02, 5.68) in the docetaxel group. The HR for disease progression or death following treatment with sotorasib versus docetaxel was 0.663 (95% CI: 0.509, 0.864; $p=0.002$), demonstrating a statistically significant benefit in PFS and a 34% reduction in the risk of progression or death with sotorasib versus docetaxel. Results of the primary analysis of PFS are summarised in Table 3.9.

Table 3.9: Primary analysis of PFS as assessed by BICR (FAS)

	Docetaxel (N=174)	Sotorasib (N=171)
PFS events, n (%)	101 (58.0)	122 (71.3)
Progressive disease	68 (39.1)	100 (58.5)
Death	33 (19.0)	22 (12.9)
Censored, n (%)	73 (42.0)	49 (28.7)
Hazard ratio (95% CI) [†]	0.663 (0.509, 0.864)	
p-value (1-sided) [†]	0.002	
PFS, months [‡]		
n	174	171
Median (95% CI)	4.47 (3.02, 5.68)	5.62 (4.27, 7.75)
Min, Max (+ for censored)	0.0+, 21.6+	0.0+, 23.7+
Based on Table 25, CS ²		
† HRs and 95% CIs are estimated using a stratified Cox PH model. A HR <1.0 indicates a lower average event rate and a longer PFS for sotorasib relative to docetaxel. P-value is calculated using a stratified log-rank test.		
‡ Medians and percentiles are estimated using the KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.		
§ Medians and percentiles of follow-up time are estimated using the reverse KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.		
BICR = blinded independent central review; CI = confidence interval; CS = company submission; FAS = full analysis set; HRs = hazard ratios; KM = Kaplan-Meier; PFS = progression-free survival; PH = proportional hazards		

The KM estimated PFS rates were 46.49% and 39.06% at 6 months and 24.84% and 10.12% at 12 months, for sotorasib versus docetaxel, respectively.²

Results from the sensitivity analyses of PFS as assessed by BICR are shown in Table 3.10.

Table 3.10: Sensitivity analyses of PFS

	HR (95% CI)	p-value
Unstratified analysis	0.692 (0.528, 0.908)	0.003
Initiation of new anticancer therapy treated as PFS event	0.599 (0.474, 0.757)	<0.001
LTFU/withdrawal of consent treated as PFS event	0.651 (0.501, 0.846)	<0.001

	HR (95% CI)	p-value
Per protocol population	0.686 (0.520, 0.905)	0.005
Scheduled assessment dates instead of actual assessment dates	0.658 (0.506, 0.855)	0.001
PFS assessed by investigators	0.645 (0.504, 0.824)	<0.001
Based on Table 26, CS ² CI = confidence interval; CS = company submission; HR = hazard ratio; LTFU = long-term follow-up; PFS = progression-free survival		

3.2.4.1.2 Secondary efficacy outcome: OS

A total of 203 deaths were reported by the data cut-off date, including 109 subjects (63.7%) in the sotorasib group and 94 subjects (54.0%) in the docetaxel group. The median OS was 10.64 months (95% CI: 8.94, 13.96) in the sotorasib group versus 11.30 months (95% CI: 9.00, 14.85) in the docetaxel group. The HR for OS following treatment with sotorasib versus docetaxel was 1.010 (95% CI: 0.766, 1.331; p=0.53).

Results from the sensitivity analyses of OS were consistent with that of the primary analysis for the unstratified analysis (HR: 1.009, 95% CI: 0.766, 1.331; p=0.53), and the per protocol population (HR: 1.048, 95% CI: 0.785, 1.399; p=0.62), but differed for the initiation of new anticancer therapy treated as PFS event, where a significant difference in favour of sotorasib was observed (HR: 0.642, 95% CI: 0.500, 0.823; p<0.001). The OS sensitivity analysis based on the two-stage approach adjusting only for per-protocol crossover resulted in a HR of 0.885 (0.172, 1.328). A post-hoc two-stage analysis adjusting for all crossover (i.e. per-protocol crossover and off-protocol crossover to commercial sotorasib) yielded an OS HR of 0.820 (95% CI: 0.315, 1.309).

Results of the OS analysis are shown in Table 3.11.

Table 3.11: Analysis of OS (FAS)

	Docetaxel (N=174)	Sotorasib (N=171)
Death, n (%)	94 (54.0)	109 (63.7)
Censored, n (%)	80 (46.0)	62 (36.3)
Hazard ratio (95% CI) [†]	1.010 (0.766, 1.331)	
p-value (1-sided) [†]	0.53	
OS, months [‡]		
n	174	171
Median (95% CI)	11.30 (9.00, 14.85)	10.64 (8.94, 13.96)
Min, max (+ for censored)	0.0+, 24.1+	0.8, 24.0+
Follow-up time, months [§]	16.33 (16.07, 17.08)	17.71 (16.95, 19.15)
Based on Table 27, CS ²		
† HRs and 95% CIs are estimated using a stratified Cox PH model. A HR <1.0 indicates a lower average death rate and a longer OS for sotorasib relative to docetaxel. P-value is calculated using a stratified log-rank test.		
‡ Medians and percentiles are estimated using the KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.		
§ Medians and percentiles of follow-up time are estimated using the reverse KM method. 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.		
CIs = confidence intervals; CNS = central nervous system; CS = company submission; FAS = full analysis set; HRs = hazard ratios; KM = Kaplan-Meier; OS = overall survival; PH = proportional hazards		

3.2.4.1.3 Secondary efficacy outcome: ORR

An objective response was achieved for 48 subjects (complete response [CR] for 2 subjects, partial response [PR] for 46 subjects) in the sotorasib group, and for 23 subjects (all PR) in the docetaxel group. The objective response rate (ORR) was 28.1% (95% CI: 21.5, 35.4) in the sotorasib group compared with 13.2% (95% CI: 8.6, 19.2) in the docetaxel group (odds ratio [OR] of 2.600; 95% CI: 1.483, 4.557; $p < 0.001$).

Results from the sensitivity analyses of ORR were consistent with those of the primary analysis: response as assessed by the investigator (OR of 2.299; 95% CI: 1.323, 3.997; $p = 0.001$), and in the per protocol set (PPS) response as assessed by BICR (OR of 2.504; 95% CI: 1.416, 4.427; $p < 0.001$).

3.2.4.1.4 Secondary efficacy outcome: DOR

Forty-eight subjects (28.1%) in the sotorasib group and 23 subjects (13.2%) had a confirmed best overall response of CR or PR. The median (95% CI) duration of response (DOR) was 8.64 (7.06, 17.97) months in the sotorasib group compared with 6.80 (4.27, 8.28) months in the docetaxel group.

Results from the sensitivity analyses for DOR were consistent with that of the main analysis: for the response as assessed by the investigator, the median (95% CI) DOR was 8.34 (7.13, 10.35) months in the sotorasib group and 4.27 (2.96, 11.53) in the docetaxel group; and for the response as assessed by BICR using the PPS, the DOR was 8.64 (6.93, 12.25) months in the sotorasib group and 6.80 (4.27, 8.28) in the docetaxel group.

3.2.4.1.5 Secondary efficacy outcome: TTR

Among the 48 responders (2 CR, 46 PR) in the sotorasib group, the median (range) time to response (TTR) was 1.41 (1.2, 8.3) months. Among the 23 responders (all PR) in the docetaxel group, the median (range) TTR was 2.76 (1.3, 11.3) months.

Results from the sensitivity analyses for TTR were consistent with that of the main analysis: for the response as assessed by the investigator, the median (range) TTR was 1.48 (1.2, 11.0) months in the sotorasib group and 2.76 (1.3, 9.4) in the docetaxel group; and for the response as assessed by BICR using the PPS, the TTR was 1.41 (1.2, 8.3) months in the sotorasib group and 2.76 (1.3, 11.3) in the docetaxel group.

3.2.4.1.6 Secondary efficacy outcome: DCR

In total, 141 subjects in the sotorasib group and 105 subjects in the docetaxel group achieved disease control. CR was reported for 2 subjects (1.2%) in the sotorasib group and 0 subjects in the docetaxel group, PR for 46 subjects (26.9%) and 23 subjects (13.2%), respectively, and stable disease for 93 subjects (54.4%) and 82 subjects (47.1%), respectively. The DCR (95% CI) was 82.5% (75.9, 87.8) in the sotorasib group compared with 60.3% (52.7, 67.7) in the docetaxel group (OR of 3.077, 95% CI: 1.862, 5.085; $p < 0.001$).

Results from the sensitivity analyses for DCR were consistent with that of the main analysis: for the response as assessed by the investigator, the DCR was 81.3% (74.6, 86.8) in the sotorasib group and 54.6% (46.9, 62.1) in the docetaxel group (OR of 3.695, 95% CI: 2.240, 6.094; $p < 0.001$); and for the response as assessed by BICR using the PPS, the DCR was 81.8% (74.9, 87.4) in the sotorasib group and 61.3% (53.4, 68.9) in the docetaxel group (OR of 2.803, 95% CI: 1.670, 4.704; $p < 0.001$).

3.2.4.1.7 Key patient reported outcomes (PROs)

The key PROs were change from baseline (Cycle 1 Day 1) to Week 12 in:

- Global health status and physical functioning as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-Item Core Module (EORTC QLQ-C30)
- Dyspnoea as measured by a four-item dyspnoea domain from EORTC QLQ-C30 and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module (EORTC QLQ-LC13)
- Cough and chest pain as measured by EORTC QLQ-LC13

The key PRO endpoints were not statistically tested, because the hierarchical testing was stopped at the non-statistically significant OS endpoint. The results on PRO endpoints are considered descriptive in nature.

The key PRO endpoints were stabilised for subjects in the sotorasib group, whereas there was clinically meaningful worsening in the docetaxel group.

For global health status and physical functioning (for which negative results equate to worsening) and dyspnoea (for which positive results equate to worsening), within group least squares (LS) mean (SE) changes from baseline to Week 12 were:

- 0.03 (1.45) versus -6.90 (1.58) for global health status/QoL
- 0.10 (1.48) versus -8.68 (1.62) for physical functioning
- -0.57 (1.41) versus 9.52 (1.58) for dyspnoea (composite)

These correspond to LS mean change differences from baseline to Week 12 (mixed model for repeated measurement [MMRM] analyses) which were all in favour of sotorasib, with corresponding p-values unadjusted for multiplicity below 0.001:

- 6.93 (95% CI: 3.66, 10.19) for global health status
- 8.78 (95% CI: 5.39, 12.17) for physical functioning
- -10.09 (95% CI: -13.39, -6.78) for dyspnoea (composite)

The generalised estimating equations (GEE) analysis for cough suggests a likelihood of having improved symptoms at Week 12 (OR of sotorasib versus docetaxel 3.21; 95% CI: 1.55, 6.65; $p=0.002$). Numerical improvements (not statistically significant) in chest pain symptoms were also observed for sotorasib versus docetaxel (OR 1.56; 95% CI: 0.82, 2.96; $p=0.18$).

3.2.4.1.8 Secondary PRO outcomes

Secondary PRO measures included:

- Time to deterioration for the subscales for EORTC QLQ-C30 and EORTC QLQ-LC13
- Summary scores at each assessment and changes from baseline of visual analogue scale (VAS) scores as measured by the European Quality of Life-5 Dimensions 5 Levels (EQ-5D-5L)
- Change from baseline to Week 12 for the remaining subscales for 29 EORTC QLQ-C30 and EORTC QLQ-LC13

Time to deterioration

Overall, sotorasib showed a clinically meaningful difference compared with docetaxel in delaying time to deterioration in global health status (HR: 0.694, 95% CI: 0.530, 0.909), physical functioning (HR: 0.692, 95% CI: 0.521, 0.920), dyspnoea (composite) (HR: 0.629, 95% CI: 0.479, 0.825), and cough (HR: 0.553, 95% CI: 0.381, 0.803). Furthermore, a trend was observed for chest pain (HR: 0.839, 95% CI: 0.595, 1.183).

In terms of weeks to deterioration, the median time was increased with sotorasib compared with docetaxel for global health status from 6.55 to 9.25 weeks, for physical functioning from 9.40 to 15.09 weeks, for dyspnoea (composite) from 6.55 to 12.10 weeks, for cough from 15.23 to 49.26 weeks, and for chest pain from 27.33 to 34.88 weeks.

EQ-5D-5L VAS

QoL as measured by the VAS of the EQ-5D-5L questionnaire was comparable at baseline in both treatment groups. Mean (SD) was 67.6 (19.9) in the sotorasib group and 68.3 (20.3) in the docetaxel group. Overall, VAS changes were favourable for sotorasib when compared with docetaxel. Immediately after administration of investigational product, i.e. at Day 5, mean (SD) change from baseline in EQ-5D-5L VAS scores were 1.5 (15.9) in the sotorasib group compared with -8.4 (20.8) in the docetaxel group. Also, long term, i.e. all follow-up Cycles up to Week 12, noteworthy changes were observed; at Week 12, mean (SD) changes from baseline in VAS scores were 2.2 (15.6) in the sotorasib group compared with -5.8 (18.2) in the docetaxel group.

Change from baseline to Week 12 in EORTC QLQ-C30 and EORTC QLQ-LC13 subscales

Change from baseline to Week 12 in the EORTC QLQ-C30 and EORTC QLQ-LC13 subscales were broadly consistent with the changes from baseline to Week 12 in the key secondary endpoints, as outlined in Section 3.2.4.1.7.

3.2.4.1.9 Exploratory PRO outcomes

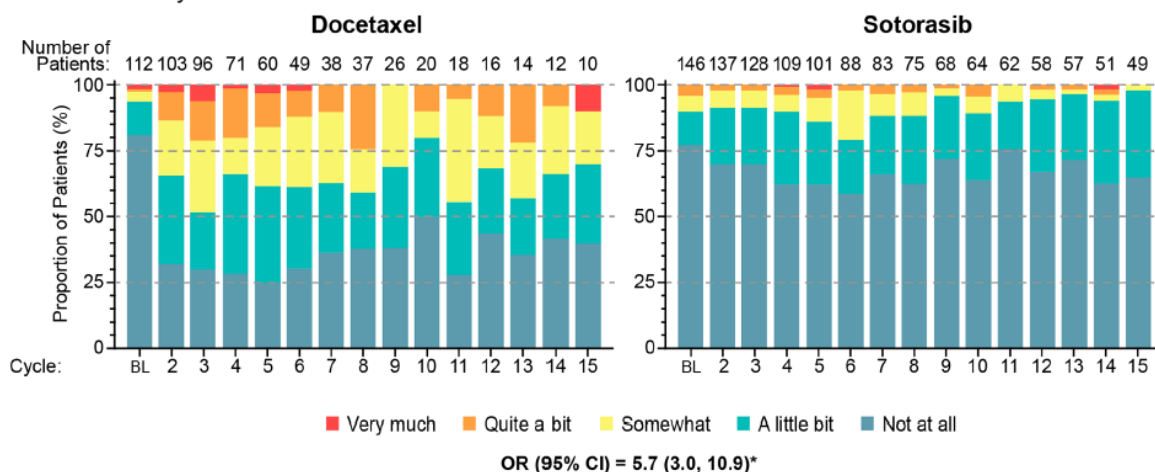
The Functional Assessment of Cancer Therapy-General, item 5 (FACT-G GP5) scale was used to assess bother from side effects of treatment, and Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) scores were collected to assess the severity, frequency, and interference of treatment-related symptoms.

FACT-G GP5

Patients treated with sotorasib compared with those treated with docetaxel were less bothered by the side effects of treatment. The Functional Assessment of cancer Therapy-General, Item 5 (FACT-G GP5) score suggested that sotorasib was better tolerated compared with docetaxel, with the OR at Week 12 (Cycle 5, Day 1) of selecting a superior category while being treated with sotorasib at 5.7 (95% CI: 3.0, 10.9; $p < 0.001$) (Figure 3.6). The OR corresponds to the likelihood of patients selecting a more favourable response category. Similar results were observed at other cycles and overall.

Figure 3.6: Treatment side effects over time by FACT-G GP5**FACT-G GP5**

"I am bothered by side effects of treatment"



Based on Figure 10, CS²

Patients completed the FACT-G GP5 on Day 1 (administered by tablet in the clinic) of each Cycle and at the safety follow-up.

* OR of change from baseline to Week 12, based on GEE model.

BL = baseline; CI = confidence interval; CS = company submission; FACT-G GP5 = Functional Assessment of Cancer Therapy Tool General Form, single item "I am bothered by side effects of treatment", rated on a 5-point Likert scale; GEE = generalised estimating equation; OR = odds ratio

PRO-CTCAE

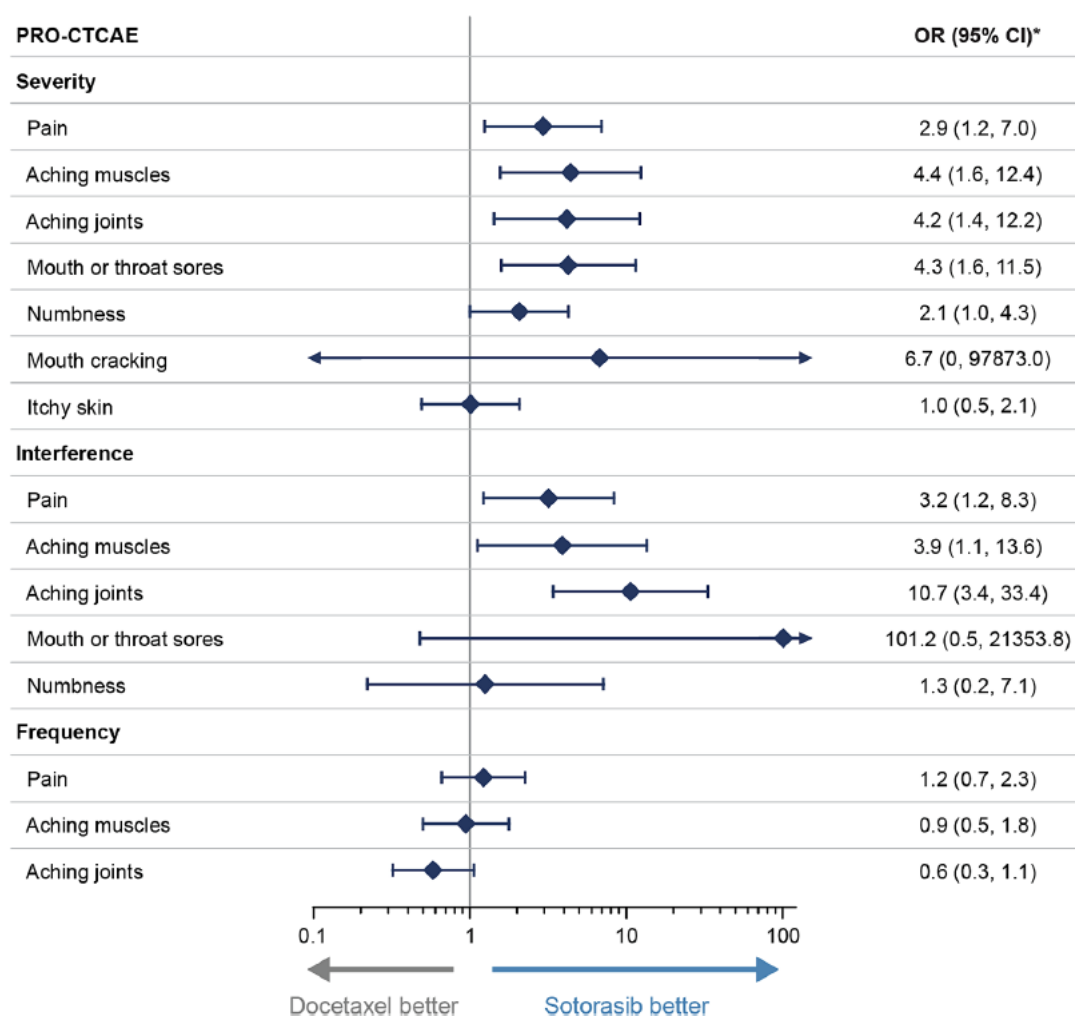
Overall, PRO-CTCAE scores suggested that sotorasib was better tolerated compared with docetaxel (Figure 3.7). In particular, for docetaxel, the symptoms showed a higher severity and stronger interference with daily/usual activities. However, in terms of frequency of symptoms, both trial groups were similar.

Severity: The impact of treatment on severity of symptoms suggested better outcomes with sotorasib compared with docetaxel. At Week 12 (Cycle 5, Day 1), compared with docetaxel, sotorasib improved the severity of pain (OR: 2.9, 95% CI: 1.2, 7.0; $p=0.014$), aching muscles (OR: 4.4, 95% CI: 1.6, 12.4; $p=0.005$), aching joints (OR: 4.2, 95% CI: 1.4, 12.2; $p=0.009$), mouth or throat sores (OR: 4.3, 95% CI: 1.6, 11.5; $p=0.004$), numbness (OR: 2.1, 95% CI: 1.0, 4.3; $p=0.050$), and mouth cracking (OR: 6.7, 95% CI: 0.0, 97873.0; $p=0.700$). In addition, based on Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), sotorasib patients were less likely to lose fingernails (OR: 0.13, 95% CI: 0.07, 0.25), have bumps on the nails (OR: 0.16, 95% CI: 0.08, 0.30), or have a change in nail colour (OR: 0.06, 95% CI: 0.03, 0.12). The severity of itchy skin was similar between sotorasib and docetaxel treatment groups (OR: 1.0, 95% CI: 0.5, 2.1; $p=0.990$) at Week 12, with similar results observed at other cycles and overall.

Interference: Patients treated with sotorasib reported less interference in daily/usual activities for pain (OR: 3.2, 95% CI: 1.2, 8.3; $p=0.018$), aching muscles (OR: 3.9, 95% CI: 1.1, 13.6; $p=0.033$), aching joints (OR: 10.7, 95% CI: 3.4, 33.4; $p<0.001$), mouth or throat sores (OR: 101.2, 95% CI: 0.5, 21353.8; $p=0.091$), and numbness (OR: 1.3, 95% CI: 0.2, 7.1; $p=0.80$) at Week 12. Similar results were observed at other cycles and overall.

Frequency: The frequency of pain (OR: 1.2, 95% CI: 0.7, 2.3; $p=0.520$), aching muscles (OR: 0.9, 95% CI: 0.5, 1.8; $p=0.850$), and aching joints (OR: 0.6, 95% CI: 0.3, 1.1; $p=0.760$) were similar between treatment groups. Generally similar results were observed in other cycles and overall.

Figure 3.7: Impact of treatment on symptoms by PRO-CTCAE (including severity, interference, and frequency) after 12 weeks of treatment



Based on Figure 11, CS²

The analysis set included all randomised patients with a non-missing baseline measurement and ≥ 1 non-missing post-baseline measurements (sotorasib, $n=48$; docetaxel, $n=113$). The displayed PRO-CTCAE list is comprehensive: there were no further assessments on severity, interference, or frequency of symptoms beyond the list presented here.

* OR and 95% CIs were estimated using a generalised estimating equations model. Arrows indicate continuation of 95% CI past the OR graph range. An OR >1.0 indicates higher improvement in symptom scale for sotorasib relative to docetaxel.

CI = confidence interval; CS = company submission; OR = odds ratio; PRO-CTCAE = Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events

EAG comment: The primary efficacy result from the RCT of PFS suggests a statistically significant difference in PFS between the two groups, with the sotorasib group experiencing a longer duration of 5.62 months compared with the docetaxel group reporting a PFS of 4.47 months. Additionally, there was a reduction in the risk of progression or death by 34% in the sotorasib group versus docetaxel (HR: 0.66 [95% CI: 0.51, 0.86], $p=0.002$), corresponding to a 1.1-month improvement in median PFS. This

was also reflected in an increase in 1-year PFS (24.8% for sotorasib versus 10.1% for docetaxel). The sensitivity analyses also show a similar HR.

In addition, ORR, DOR, TTR, and DCR were improved for sotorasib versus docetaxel.

In the primary analysis, OS was not significantly different between the sotorasib group (median 10.6 months) and the docetaxel group (median 11.3 months). However, crossover-adjusted analyses resulted in an OS HR of 0.820 (95% CI: 0.315, 1.309). The EAG notes that the lack of statistical significance might be a result of insufficient power (see Section 3.2.2).

Treatment with sotorasib demonstrated better QoL and reduced symptom burden compared with docetaxel.

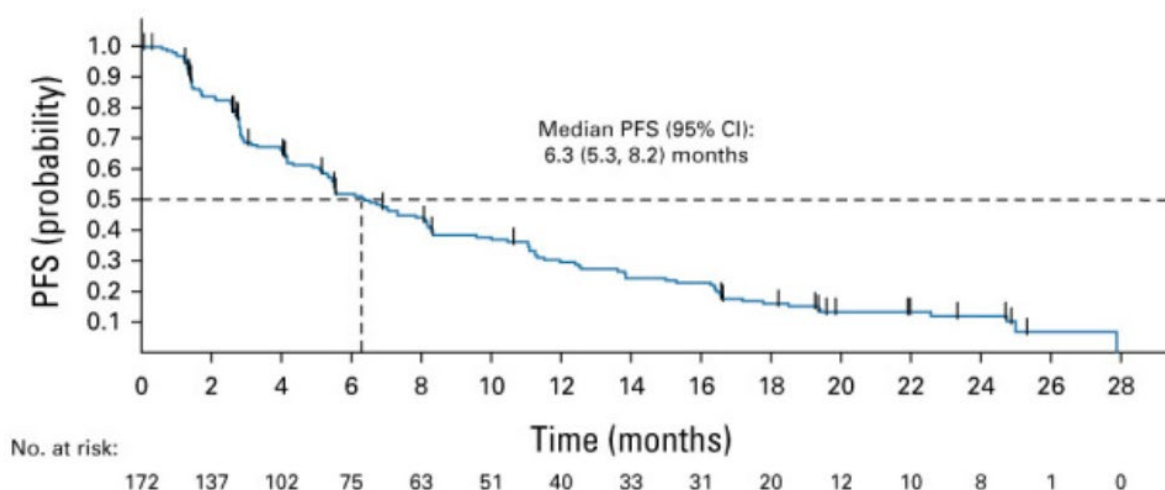
The probable lack of power accompanied by crossover, albeit adjusted for, implies some uncertainty as to the validity of the OS results from CodeBreak 200, which therefore forms part of the key issue regarding the most valid source of data for estimating the treatment effect of sotorasib versus docetaxel. Note that the EAG consider that CodeBreak 200 is probably the best source of comparative evidence for the other outcomes, including PFS, notwithstanding the potential UK applicability of the CAS RWE study.

3.2.4.2 CodeBreak 100 (long term follow-up)

As of 22 February 2022, of the 174 patients treated with sotorasib, ORR in CodeBreak 100 was 41% (95% CI: 33.3, 48.4). Of patients with confirmed response, an estimated 72.8% (95% CI: 60.0, 82.2) and 50.6% (37.4, 62.4) remained in response at 6 and 12 months, respectively. Median DOR was 12.3 months (95% CI: 7.1, 15.0).

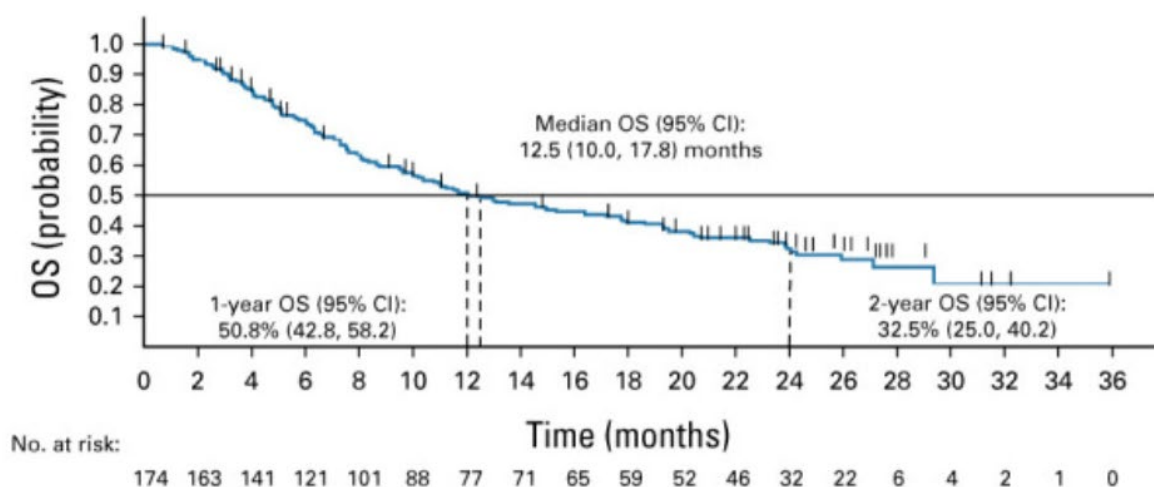
Median PFS was 6.3 months (95% CI: 5.3, 8.2; Figure 3.8), while median OS was 12.5 months (10.0, 17.8). The KM OS estimates were 51% (95% CI: 42.8, 58.2) and 33% (95% CI: 25.0, 40.2) at 12 and 24 months, respectively (Figure 3.9). At data cut-off, nine of 70 (13%) patients with response remained on study without progression, including five receiving sotorasib for ≥ 2 years with continued response.

Figure 3.8: KM plot of PFS from long-term CodeBreak 100 follow-up



Based on Figure 12, CS²

CI = confidence interval; CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival

Figure 3.9: KM plot of OS from long-term CodeBreakK 100 follow-up

Based on Figure 13, CS²

CI = confidence interval; CS = company submission; KM = Kaplan-Meier; OS = overall survival

3.2.4.3 CAS RWE

The median follow-up time from index date was 8.62 months (Q1-Q3: 4.47-13.90) for the sotorasib cohort and 6.11 months (Q1-Q3: 3.22-10.87) for the docetaxel cohort. Prior to SMRW, large differences in the PS distributions were observed between treatment groups, and the following covariates were imbalanced: sex, BMI, stage at diagnosis, histology, ECOG PS score at index date, LoT number 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, 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). The ESS was 394 patients in the sotorasib treatment group and 392 patients in the docetaxel treatment group.

3.2.4.3.1 Primary efficacy outcome: OS

Prior to SMRW, unadjusted median OS in the 2L+ analysis set was [REDACTED] months (95% CI: [REDACTED]) in the sotorasib treatment group and [REDACTED] months (95% CI: [REDACTED]) in the docetaxel treatment group (p=[REDACTED]). Treatment with sotorasib was associated with a [REDACTED]% decreased risk of death (HR: [REDACTED]; 95% CI: [REDACTED]; p<[REDACTED]) compared with docetaxel monotherapy. Full unadjusted results can be found in Appendix K.⁸

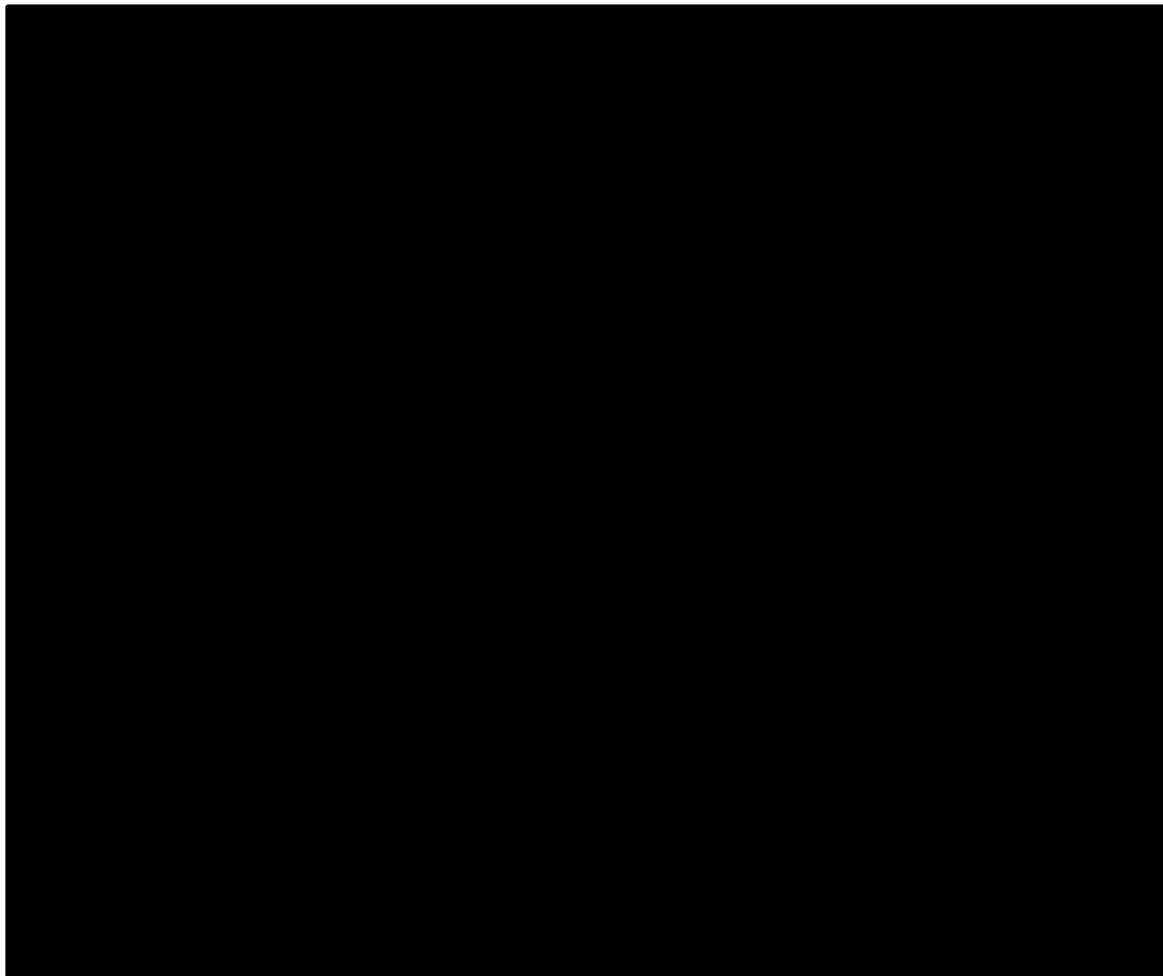
Following SMRW, adjusted median OS in the 2L+ analysis set was 10.18 months (95% CI: 9.10, 12.02) in the sotorasib treatment group and 6.87 months (95% CI: 6.01, 7.82) in the docetaxel treatment group (p<0.001) (Table 3.12). The weighted KM plot for OS in the 2L+ analysis set is provided in Figure 3.10. Treatment with sotorasib was associated with a 36.7% decreased risk of death (HR: 0.633; 95% CI: 0.536, 0.749; p<0.001) compared with docetaxel monotherapy.

Table 3.12: KM results for OS in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)

		Docetaxel (N=363)	Sotorasib (N=394)
Total	Number of patients, n	363	394
	Number of events, n	[REDACTED]	[REDACTED]

		Docetaxel (N=363)	Sotorasib (N=394)
	Number of censored patients, n	■	■
	Median (95% CI)	6.87 (6.01, 7.82)	10.18 (9.10, 12.02)
	Q1-Q3	■	■
3 months	Number of patients	■	■
	Probability (95% CI)	■	■
6 months	Number of patients	■	■
	Probability (95% CI)	■	■
9 months	Number of patients	■	■
	Probability (95% CI)	■	■
12 months	Number of patients	■	■
	Probability (95% CI)	■	■
24 months	Number of patients	■	■
	Probability (95% CI)	■	■
36 months	Number of patients	■	■
	Probability (95% CI)	■	■
Hazard ratio (95% CI) [†]		0.633 (0.536, 0.749)	
p-value		<0.001	
Based on Table 28, CS ²			
† Based on Cox regression analysis. Adjusted for confounding using SMRW or IPTW (as applicable). If other covariates may be unbalanced that were not considered in the propensity score model, these will be adjusted for in the Cox model. CIs for the treatment effect estimate calculated using robust standard errors.			
* Numbers from 1-5 are masked, in accordance with NHS England policy to minimise the risk of patient identification.			
2L = second-line; ATT = average treatment effect in the treated; CI = confidence interval; CS = company submission; IPTW = inverse probability of treatment weighting; KM = Kaplan-Meier; NHS = National Health Service; OS = overall survival; Q1 = first quartile; Q3 = third quartile; SMRW = standardised mortality ratio weighting			

Figure 3.10: KM plot for OS in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)



Based on Figure 14, CS²

ATT = average treatment effect in the treated; CS = company submission; KM = Kaplan-Meier; OS = overall survival; 2L = second-line; SMRW = standardised mortality ratio weighting

3.2.4.3.2 Secondary efficacy outcome: TTNT(D)

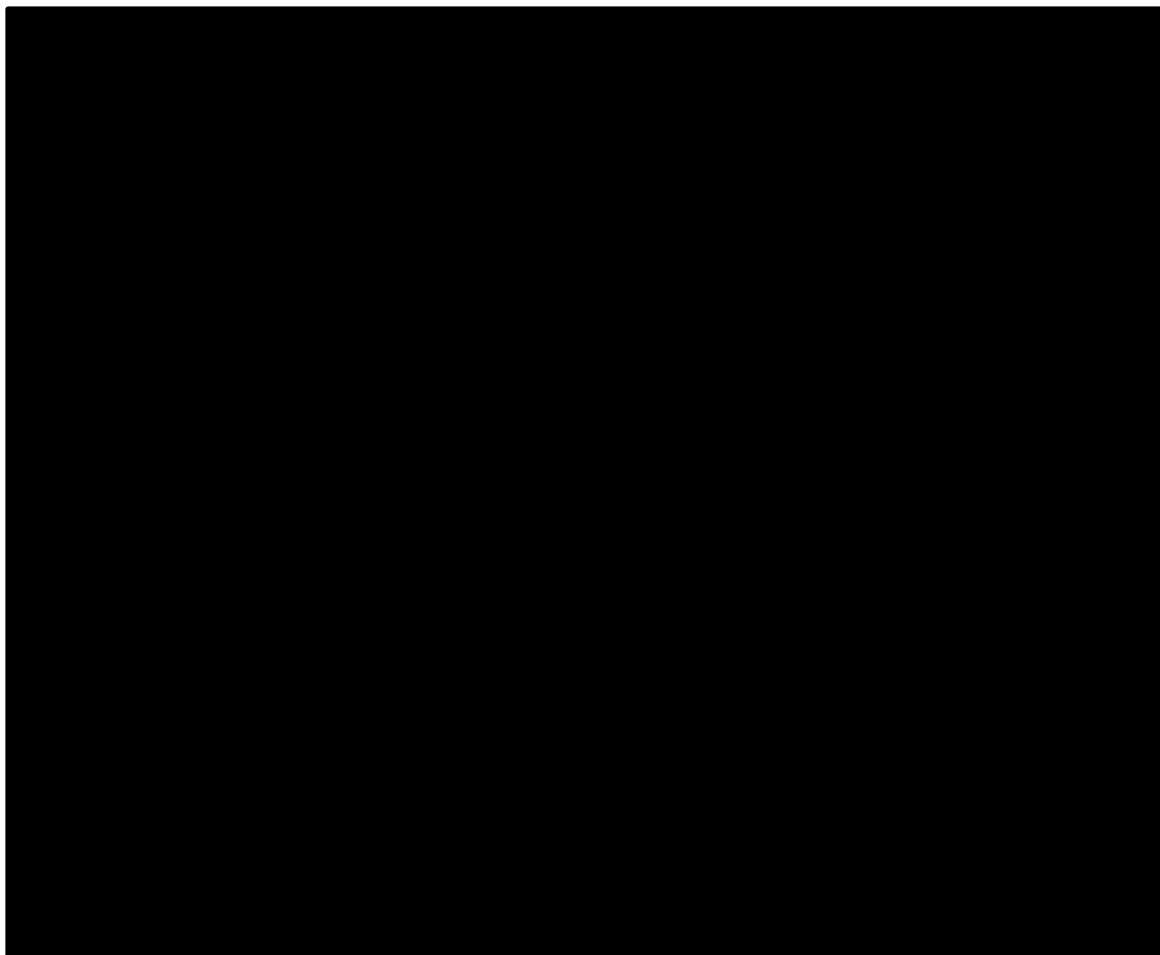
Prior to SMRW, the unadjusted median TTNT(D) in the 2L+ analysis set was [REDACTED] months (95% CI: [REDACTED]) for the sotorasib group and [REDACTED] months (95% CI: [REDACTED]) for the docetaxel group (p [REDACTED]). Treatment with sotorasib was associated with a [REDACTED]% decreased risk of initiation of a new LoT or death (HR: [REDACTED]; 95% CI: [REDACTED]; p [REDACTED]) compared with docetaxel monotherapy. Full unadjusted results can be found in Appendix K.⁸

Following SMRW, the adjusted median TTNT(D) in the 2L+ analysis set was 8.51 months (95% CI: 7.33, 9.43) for the sotorasib group and 5.62 months (95% CI: 5.06, 6.18) for the docetaxel group (p<0.001) (Table 3.13). The weighted KM survival plot for TTNT(D) in the 2L+ analysis set is provided in Figure 3.11. Treatment with sotorasib was associated with a 43.3% decreased risk of initiation of a new LoT or death (HR: 0.567; 95% CI: 0.485, 0.663; p<0.001) compared with docetaxel monotherapy.

Table 3.13: KM results for TTNT(D) in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)

		Docetaxel (N=363)	Sotorasib (N=394)
Total	Number of patients, n	363	394
	Number of events, n	■	■
	Number of censored patients, n	■	■
	Median (95% CI)	5.62 (5.06, 6.18)	8.51 (7.33, 9.43)
	Q1-Q3	■	■
3 months	Number of patients	■	■
	Probability (95% CI)	■	■
6 months	Number of patients	■	■
	Probability (95% CI)	■	■
9 months	Number of patients	■	■
	Probability (95% CI)	■	■
12 months	Number of patients	■	■
	Probability (95% CI)	■	■
24 months	Number of patients	■	■
	Probability (95% CI)	■	■
36 months	Number of patients	■	■
	Probability (95% CI)	■	■
Hazard ratio (95% CI) [†]		0.567 (0.485, 0.663)	
p-value		<0.001	
Based on Table 29, CS. ²			
† Based on Cox regression analysis. Adjusted for confounding using SMRW or IPTW (as applicable). If other covariates may be unbalanced that were not considered in the PS model, these will be adjusted for in the Cox model. CIs for the treatment effect estimate calculated using robust SEs.			
* Numbers from 1-5 are masked, in accordance with NHS England policy to minimise the risk of patient identification.			
2L = second-line; ATT = average treatment effect in the treated; CI = confidence interval; CS = company submission; IPTW = inverse probability of treatment weighting; KM = Kaplan-Meier; NHS = National Health Service; PS = propensity score; SEs = standard errors; SMRW = standardised mortality ratio weighting; TTNT(D) = time to next treatment (or death)			

Figure 3.11: KM plot for TTNT(D) in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)



Based on Figure 15, CS²

2L = second-line; ATT = average treatment effect in the treated; KM = Kaplan-Meier; SMRW = standardised mortality ratio weighting; TTNT(D) = time to next treatment (or death)

3.2.4.3.3 Exploratory outcome: TTD(D)

Prior to SMRW, unadjusted median TTD(D) in the 2L+ analysis set was [REDACTED] months (95% CI: [REDACTED]) in the sotorasib treatment group and [REDACTED] months (95% CI: [REDACTED]) in the docetaxel treatment group (p[REDACTED]). Treatment with sotorasib was associated with a [REDACTED]% decreased risk of treatment discontinuation or death (HR: [REDACTED]; 95% CI: [REDACTED]; p[REDACTED]) compared with docetaxel monotherapy. Full unadjusted results can be found in Appendix K.⁸

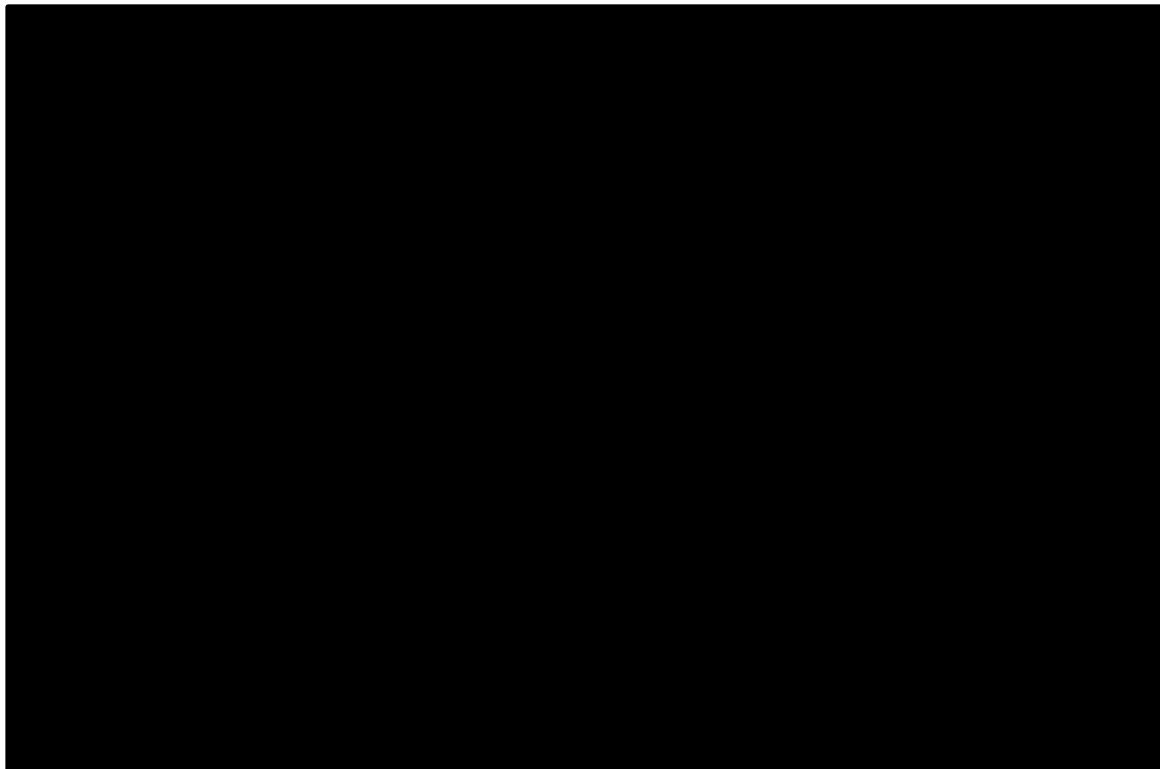
Following SMRW, adjusted median TTD(D) in the 2L+ analysis set was 5.06 months (95% CI: 4.34, 6.11) in the sotorasib treatment group and 2.30 months (95% CI: 2.07, 2.76) in the docetaxel treatment group (p<0.001) (Table 3.14). The weighted KM survival plot for TTD(D) in the 2L+ analysis set is given in Figure 3.12. Treatment with sotorasib was associated with a 74.8% decreased risk of treatment

discontinuation or death (HR: 0.252; 95% CI: 0.212, 0.300; $p < 0.001$) compared with docetaxel monotherapy.

Table 3.14: KM results for TTD(D) in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)

		Docetaxel (N=363)	Sotorasib (N=394)
Total	Number of patients, n	363	394
	Number of events, n	■	■
	Number of censored patients, n	■	■
	Median (95% CI)	2.30 (2.07, 2.76)	5.06 (4.34, 6.11)
	Q1-Q3	■	■
3 months	Number of patients	■	■
	Probability (95% CI)	■	■
6 months	Number of patients	■	■
	Probability (95% CI)	■	■
9 months	Number of patients	■	■
	Probability (95% CI)	■	■
12 months	Number of patients	■	■
	Probability (95% CI)	■	■
24 months	Number of patients	■	■
	Probability (95% CI)	■	■
36 months	Number of patients	■	■
	Probability (95% CI)	■	■
Hazard ratio (95% CI) [†]		0.252 (0.212, 0.300)	
p-value		<0.001	
Based on Table 30, CS ²			
† Based on Cox regression analysis. Adjusted for confounding using SMRW or IPTW (as applicable). If other covariates may be unbalanced that were not considered in the PS model, these will be adjusted for in the Cox model. CIs for the treatment effect estimate calculated using robust SEs.			
* Numbers from 1-5 are masked, in accordance with NHS England policy to minimise the risk of patient identification.			
2L = second-line; ATT = average treatment effect in the treated; CI = confidence interval; CS = company submission; IPTW = inverse probability of treatment weighting; KM = Kaplan-Meier; N/A = not applicable; NHS = National Health Service; PS = propensity score; SEs = standard errors; SMRW = standardised mortality ratio weighting; TTNT(D) = time to next treatment (or death)			

Figure 3.12: KM plot for TTD(D) in the 2L+ analysis set (sotorasib versus docetaxel monotherapy), after SMRW (ATT estimand)



Based on Figure 15, CS²

2L = second-line; ATT = average treatment effect in the treated; KM = Kaplan-Meier; SMRW = standardised mortality ratio weighting; TTNT(D) = time to next treatment (or death)

3.2.4.3.4 Sensitivity analyses

A summary of key sensitivity analyses for the comparison of sotorasib versus docetaxel monotherapy for all study outcomes is provided in Appendix K:⁸

OS: Across all adjusted sensitivity analyses performed, median OS ranged from [REDACTED] to [REDACTED] months in the sotorasib treatment group and from [REDACTED] to [REDACTED] months in the docetaxel treatment group, while the HR ranged from [REDACTED] to [REDACTED].

TTNT(D): Adjusted TTNT(D) ranged from [REDACTED] to [REDACTED] months in the sotorasib treatment group and from [REDACTED] to [REDACTED] months in the docetaxel treatment group, while the HR ranged from [REDACTED] to [REDACTED].

TTD(D): Adjusted TTD(D) ranged from [REDACTED] to [REDACTED] months in the sotorasib treatment group and was [REDACTED] in the docetaxel treatment group, while the HR ranged from [REDACTED] to [REDACTED].

EAG comment: Sotorasib was significantly more effective than docetaxel in 2L+ by prolonging

- OS (36.7% lower risk of death, median OS increased by approximately 3.25 months)
- TTNT(D) (43.3% lower risk of death or new LoT initiation, median TTNT(D) increased by approximately 3 months)

- and TTD(D) (74.8% lower risk of death or treatment discontinuation, median TTD(D) increased by 2.75 months)

3.2.5 Subgroup analyses

3.2.5.1 CodeBreak 200

The PFS benefit observed in the sotorasib group versus the docetaxel group was consistent across all relevant subgroups, including history of CNS involvement and liver metastasis at baseline. Likewise, results from the subgroup analyses of OS and ORR were generally consistent with those of the primary analyses. Key subgroup analyses of PFS are provided in Table 3.15, with further results in Appendix C,⁸ including subgroup analyses for OS and ORR.

Table 3.15: Key subgroup analyses of PFS

Subgroup	Number of patients		HR for disease progression or death (95% CI)
	Docetaxel	Sotorasib	
All randomised subjects	174	171	0.663 (0.509, 0.864)
Europe	126	126	0.675 (0.497, 0.916)
History of CNS involvement	60	58	0.530 (0.342, 0.821)
No history of CNS involvement	114	113	0.735 (0.528, 1.025)
History of liver metastasis	35	30	0.471 (0.260, 0.853)
No history of liver metastasis	139	141	0.667 (0.493, 0.902)
One prior line of therapy in advanced disease	78	77	0.695 (0.466, 1.036)
Two prior lines of therapy in advanced disease	69	65	0.608 (0.399, 0.924)
More than two prior lines of therapy in advanced disease	27	29	0.740 (0.374, 1.463)
Based on Table 32, CS ² CI = confidence interval; CNS = central nervous system; CS = company submission; PFS = progression-free survival			

3.2.5.2 CAS RWE study

Compared with docetaxel monotherapy, treatment with sotorasib decreased the risk of death by:

- ███% (HR: ███; 95% CI: ███; p ███) among patients who received prior PD-1/PD-L1 targeted immunotherapy
- ███% (HR: ███; 95% CI: ███; p ███) among patients who did not receive prior PD-1/PD-L1 targeted immunotherapy
- ███% (HR: ███; 95% CI: ███; p ███) among patients with a prior record of brain metastasis
- ███% (HR: ███; 95% CI: ███; p ███) among patients without a prior record of brain metastasis.

3.2.6 Safety results

The CAS RWE study did not collect any safety data. Adverse reactions from CodeBreak 200 and CodeBreak 100 long term follow-up are presented in the Sections below.

3.2.6.1 CodeBreak 200

Unless otherwise stated, all adverse events (AEs) summarised in text are treatment-emergent, defined as events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if subjects crossed over from docetaxel to sotorasib, whichever occurred earlier. Safety analyses were conducted using the safety analysis set (SAS) (N=169 sotorasib, N=151 docetaxel).

3.2.6.1.1 Extent of exposure

In the sotorasib group (median [range]), the duration of treatment was 19.86 (0.4, 101.3) weeks administered over 7.0 (1, 34) cycles, and the relative dose intensity (RDI) was 100% (23.7, 100.0). In the docetaxel group (median [range]), the duration of treatment was 12.0 (3.0, 101.0) weeks administered over 4.0 (1, 33) cycles, and the RDI was 94.8% (48.9, 105.6).

3.2.6.1.2 Overall treatment-emergent adverse events (TEAEs)

A summary of AEs is provided in Table 3.16. A total of 166 subjects (98.2%) in the sotorasib group and 148 subjects (98.0%) in the docetaxel group had at least one AE; of these subjects, 119 subjects (70.4%) in the sotorasib group and 130 subjects (86.1%) in the docetaxel group had AEs that were considered treatment related by the investigator.

Grade ≥ 3 AEs were reported for 121 subjects (71.6%) in the sotorasib group (treatment related for 56 subjects [33.1%]) and for 91 subjects (60.3%) in the docetaxel group (treatment related for 61 subjects [40.4%]). AEs that led to the discontinuation of investigational product occurred in 28 subjects (16.6%) in the sotorasib group and 24 subjects (15.9%) in the docetaxel group, of which 16 subjects (9.5%) in the sotorasib group and 17 subjects (11.3%) in the docetaxel group had AEs that were considered treatment related.

Serious adverse events (SAEs) were reported in 91 subjects (53.8%) in the sotorasib group and 67 subjects (44.4%) in the docetaxel group, of which 18 subjects (10.7%) in the sotorasib group and 34 subjects (22.5%) in the docetaxel group had SAEs that were considered treatment related. Fatal AEs occurred in 37 subjects (21.9%) in the sotorasib group and 18 subjects (11.9%) in the docetaxel group; for 1 subject (0.6%) in the sotorasib group and 2 subjects (1.3%) in the docetaxel group, the fatal event was considered treatment related.

Table 3.16: Summary of TEAEs (SAS)

	Docetaxel (N=151), n (%)	Sotorasib (N=169), n (%)
All TEAEs	148 (98.0)	166 (98.2)
Grade ≥ 2	136 (90.1)	152 (89.9)
Grade ≥ 3	91 (60.3)	121 (71.6)
Grade ≥ 4	35 (23.2)	48 (28.4)
SAEs	67 (44.4)	91 (53.8)
Leading to discontinuation of IP	24 (15.9)	28 (16.6)
Leading to dose reduction	43 (28.5)	26 (15.4)
Leading to dose interruption	42 (27.8)	86 (50.9)
Fatal AEs	18 (11.9)	37 (21.9)
Treatment-related TEAEs	130 (86.1)	119 (70.4)

	Docetaxel (N=151), n (%)	Sotorasib (N=169), n (%)
Grade ≥ 2	114 (75.5)	89 (52.7)
Grade ≥ 3	61 (40.4)	56 (33.1)
Grade ≥ 4	19 (12.6)	10 (5.9)
SAEs	34 (22.5)	18 (10.7)
Leading to discontinuation of IP	17 (11.3)	16 (9.5)
Leading to dose reduction	40 (26.5)	26 (15.4)
Leading to dose interruption	23 (15.2)	60 (35.5)
Fatal AEs	2 (1.3)	1 (0.6)
Based on Table 33, CS² AEs coded using MedDRA (version 25.0) and graded using CTCAE (version 5.0). TEAEs in this table are events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if subjects crossed over from docetaxel to sotorasib, whichever occurred earlier. For subjects with multiple events under the same category, only the worst grade was reported. Grade 5 fatal AEs may have started before data cut-off and resulted in death after data cut-off. These events are summarised in this table, but deaths after data cut-off are not included in analysis. † TRAEs are AEs considered related to at least one investigational product by the investigator. AE = adverse event; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SAS = safety analysis set; TEAE = treatment-emergent adverse event; TRAEs = treatment-related adverse events		

3.2.6.1.3 Most common AEs, any Grade

The most frequently reported AEs (>20% of subjects in either group), were diarrhoea (70 subjects [41.4%]), nausea (44 subjects [26.0%]), and decreased appetite (39 subjects [23.1%]) in the sotorasib group; and fatigue (45 subjects [29.8%]), diarrhoea (39 subjects [25.8%]), nausea (37 subjects [24.5%]), anaemia (35 subjects [23.2%]), and alopecia (35 subjects [23.2%]) in the docetaxel group.

3.2.6.1.4 TRAEs

The most common TRAEs (>10% of subjects in either group) were diarrhoea (57 subjects [33.7%]), nausea (24 subjects [14.2%]), decreased appetite (18 subjects [10.7%]), and alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased (17 subjects [10.1%] each) in the sotorasib group; and fatigue (38 [25.2%]), alopecia (31 subjects [20.5%]), nausea (30 subjects [19.9%]), diarrhoea (28 subjects [18.5%]), anaemia (27 subjects [17.9%]), decreased appetite (21 [13.9%]), stomatitis (17 subjects [11.3%]), and asthenia and constipation (16 subjects [10.6%] each) in the docetaxel group.

3.2.6.1.5 Grade ≥ 3 AEs

The most frequently reported grade ≥ 3 AEs (>5% in either group) were diarrhoea (23 subjects [13.6%]), NSCLC (17 subjects [10.1%]), ALT increased (14 subjects [8.3%]), and AST increased (10 subjects [5.9%]) in the sotorasib group; and neutropenia (13 subjects [8.6%]), anaemia (10 subjects [6.6%]), fatigue and pneumonia (9 subjects [6.0%] each), and febrile neutropenia (8 subjects [5.3%]) in the docetaxel group (Table 3.17).

Table 3.17: Grade ≥ 3 AEs by preferred term reported for $\geq 3\%$ of subjects in either treatment group (SAS)

	Docetaxel (N=151) n (%)	Sotorasib (N=169) n (%)
Number of subjects reporting treatment-emergent Grade 3 or higher AEs	91 (60.3)	121 (71.6)
Diarrhoea	4 (2.6)	23 (13.6)
Non-small cell lung cancer	5 (3.3)	17 (10.1)
Alanine aminotransferase increased	0 (0.0)	14 (8.3)
Aspartate aminotransferase increased	0 (0.0)	10 (5.9)
Anaemia	10 (6.6)	8 (4.7)
Dyspnoea	5 (3.3)	8 (4.7)
Blood alkaline phosphatase increased	0 (0.0)	6 (3.6)
Decreased appetite	0 (0.0)	6 (3.6)
Abdominal pain	2 (1.3)	5 (3.0)
Hypokalaemia	1 (0.7)	5 (3.0)
Fatigue	9 (6.0)	4 (2.4)
Asthenia	6 (4.0)	4 (2.4)
Pneumonia	9 (6.0)	1 (0.6)
Neutropenia	13 (8.6)	0 (0.0)
Febrile neutropenia	8 (5.3)	0 (0.0)
Neutrophil count decreased	5 (3.3)	0 (0.0)
Number of subjects reporting treatment-emergent treatment-related Grade 3 or higher AEs	61 (40.4)	56 (33.1)
Diarrhoea	3 (2.0)	20 (11.8)
Alanine aminotransferase increased	0 (0.0)	13 (7.7)
Aspartate aminotransferase increased	0 (0.0)	9 (5.3)
Blood alkaline phosphatase increased	0 (0.0)	5 (3.0)
Neutropenia	13 (8.6)	0 (0.0)
Fatigue	9 (6.0)	1 (0.6)
Febrile neutropenia	8 (5.3)	0 (0.0)
Anaemia	5 (3.3)	1 (0.6)
Neutrophil count decreased	5 (3.3)	0 (0.0)
Pneumonia	5 (3.3)	0 (0.0)
Based on Table 34, CS ²		
AE = adverse event; CS = company submission; SAS = safety analysis set		

3.2.6.1.6 Withdrawals due to AEs

In total, 28 subjects (16.6%) in the sotorasib group and 24 subjects (15.9%) in the docetaxel group had an AE that led to discontinuation of investigational product, and the exposure-adjusted event rates were 26.8 and 48.9, respectively.

AEs that led to discontinuation of investigational product (reported for ≥ 3 subjects in either group) were ALT increased (6 subjects [3.6%] in sotorasib group versus 0 [0.0%] in docetaxel group), NSCLC (5 subjects [3.0%] versus 2 [1.3%]), and blood bilirubin increased (4 subjects [2.4%] versus 0 [0.0%]) and fatigue (0 subjects [0.0%] versus 3 [2.0%]).

3.2.6.1.7 SAEs

SAEs were reported for 91 subjects (53.8%) in the sotorasib group and 67 subjects (44.4%) in the docetaxel group, and the exposure-adjusted event rates were 102.2 and 169.9, respectively. The most common SAEs (≥ 3 subjects in either group) were NSCLC (18 subjects [10.7%] in sotorasib group

versus 5 [3.3%] in docetaxel group), diarrhoea (5 subjects [3.0%] versus 2 [1.3%]), pyrexia (3 subjects [1.8%] versus 2 [1.3%]), abdominal pain (3 subjects [1.8%] versus 1 [0.7%]), chest pain (3 subjects [1.8%] versus 0 [0.0%]), pneumonia (1 subject [0.6%] versus 10 [6.6%]), febrile neutropenia (0 subjects [0.0%] versus 7 [4.6%]), anaemia (1 subject [0.6%] versus 5 [3.3%]), dyspnoea (2 subjects [1.2%] versus 4 [2.6%]) and respiratory failure (1 subject [0.6%] versus 4 [2.6%]), and sepsis (0 subjects [0.0%] versus 3 [2.0%]).

Treatment-related SAEs were reported for 18 subjects (10.7%) in the sotorasib and 34 subjects (22.5%) in the docetaxel group, and the exposure-adjusted event rates were 17.9 and 77.3, respectively.

The most frequently reported treatment-related SAEs (≥ 2 subjects in either group) were diarrhoea (3 subjects [1.8%]), drug-induced liver injury and hypertransaminasaemia (2 subjects [1.2%] each) in the sotorasib group; and febrile neutropenia (7 subjects [4.6%]), pneumonia (5 subjects [3.3%]), anaemia (3 subjects [2.0%]), and diarrhoea, fatigue, malaise, pneumonitis, sepsis, and stomatitis (2 subjects [1.3%] each) in the docetaxel group.

3.2.6.1.8 Fatal AEs

Fatal AEs were reported for 37 subjects (21.9%) in the sotorasib group and 18 subjects (11.9%) in the docetaxel group, and the exposure-adjusted event rates were 35.4 and 36.0, respectively.

The most frequently reported fatal AEs in both groups were related to disease progression and included NSCLC (17 subjects [10.1%]), and lung adenocarcinoma, lung neoplasm malignant (2 subjects [1.2%]), and NSCLC metastatic (2 subjects [1.2%]) in the sotorasib group; and NSCLC (5 subjects [3.3%]) and respiratory failure (2 subjects [1.3%]) in the docetaxel group.

Treatment-related fatal AEs were interstitial lung disease (1 subject [0.6%]) in the sotorasib group and ileus (1 subject [0.7%]) and multiple organ dysfunction syndrome (1 subject [0.7%]) in the docetaxel group. The exposure-adjusted fatal AE rates were 1.0 and 4.0 in the sotorasib and docetaxel groups, respectively.

3.2.6.1.9 Events of interest (EOI)

Subject incidences for adverse EOIs - hepatotoxicity, pneumonitis, and renal toxicity - were summarised according to the search strategy categories using Standardised MedDRA Queries (SMQs). Preferred terms consistent with hepatic EOIs were identified using hepatic disorders SMQ (broad and narrow) search criteria; pneumonitis EOIs were identified using interstitial lung disease (broad and narrow) search criteria; and renal EOIs were identified using acute renal failure SMQ (broad and narrow) and chronic kidney disease SMQ (broad and narrow) search criteria.

Using the narrow search strategy, hepatotoxicity EOIs were reported for 41 subjects (24.3%) in the sotorasib group and 7 subjects (4.6%) in the docetaxel group, pneumonitis EOIs for 4 subjects in each group (2.4% and 2.6%, respectively), and renal toxicity EOIs for 10 subjects (5.9%) in the sotorasib group (none in the docetaxel group).

Using the broad search strategy, hepatotoxicity EOIs were reported for 46 subjects (27.2%) in the sotorasib group and 14 subjects (9.3%) in the docetaxel group, pneumonitis EOIs for 4 subjects in each group (2.4% and 2.6%, respectively), and renal toxicity EOIs for 31 subjects (18.3%) in the sotorasib group and 18 subjects (11.9%) in the docetaxel group.

3.2.6.1.10 *Exposure-adjusted event rates*

Given the differences with the longer exposure to sotorasib compared with docetaxel, exposure-adjusted event rates per 100 subject years for AEs were also evaluated in an ad hoc analysis (see Appendix J).⁸ The exposure-adjusted event rate for all AEs was 1,055.4 in the sotorasib group and 2,443.8 in the docetaxel group. Exposure-adjusted event rates in the sotorasib group and docetaxel group were 177.4 and 271.2, respectively, for Grade ≥ 3 AEs; 26.8 and 48.9, respectively, for AEs leading to discontinuation of investigational product; and 102.2 and 169.9, respectively, for SAEs. The exposure-adjusted event rate for fatal AEs was 35.4 in the sotorasib group and 36.0 in the docetaxel group.

The exposure-adjusted event rate for all AEs considered related to investigational product by the investigator was 297.3 in the sotorasib group and 1,327.1 in the docetaxel group. Exposure-adjusted event rates for TRAEs in the sotorasib group and docetaxel group were 71.6 and 160.9, respectively, for Grade ≥ 3 TRAEs; 15.3 and 34.4, respectively, for TRAEs leading to discontinuation of investigational product; and 17.9 and 77.3, respectively, for treatment-related SAEs. The exposure-adjusted event rate for treatment-related fatal AEs was 1.0 in the sotorasib group and 4.0 in the docetaxel group.

3.2.6.2 *CodeBreak 100*

Any-Grade TRAEs were observed in 121 (70%) patients, with Grade 3 in 34 (20%), Grade 4 in 2 (1%), and no fatal TRAEs. TRAEs led to treatment reduction or interruption in 39 (22%) and treatment discontinuation in 11 (6%). The most common TRAEs were diarrhoea (53 [30%]), increased ALT level (31 [18%]), and increased AST level (31 [18%]). Median (range) time to Grade ≥ 3 diarrhoea and hepatotoxicity onset was 6.1 (1.7, 11.1) and 9.1 (3.1, 18.7) weeks. All Grade ≥ 3 (median [range] duration, weeks) diarrhoea resolved (2.9 [0.3, 6.0]); Grade ≥ 3 hepatotoxicity resolved in all but three of 19 (16%; 5.5 [0.4, 39.1]). Trends toward increased hepatotoxicity in patients receiving checkpoint inhibitors $\leq$ versus >3 months before sotorasib initiation were observed.

Of 45 patients who continued sotorasib beyond 1 year, 11 (24%) had any-Grade TRAEs after 1 year on treatment (new-onset TRAEs), without trends in AE type. One Grade 3 new-onset TRAE (2%; haemolytic anaemia) resolved in 5 days (sotorasib discontinued after disease progression). No Grade 4 or 5 new-onset TRAEs occurred. New-onset TRAEs led to dose reduction in one (2%) patient without treatment discontinuation.

EAG comment: Crude rates of Grade ≥ 3 AEs, serious events, and fatal events were higher in the sotorasib group compared with the docetaxel group. However, ad hoc analyses of exposure-adjusted event rates were lower in the sotorasib group for all event categories, except for dose interruption. In addition, long-term follow-up of CodeBreak 100 detected no new safety signals.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No trials were included in an indirect comparison.

EAG comment: No comment.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

None undertaken.

EAG comment: No comment.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None undertaken.

EAG comment: No comment.

3.6 Conclusions of the clinical effectiveness Section

The CS, Appendix B and response to clarification^{2, 7, 8} provided sufficient details for the EAG to appraise the two sets of literature searches conducted to identify relevant clinical evidence on the clinical effectiveness and safety of treatments in adults with KRAS-mutated locally advanced and unresectable or metastatic NSCLC. The RCT SLR was conducted in June 2020 and updated in January 2021, September 2024 and March 2025. The SAT SLR was conducted in July 2019 and updated in March 2021, September 2024 and March 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

Two studies formed the mainstay of the comparative clinical effectiveness evidence of sotorasib versus docetaxel, one an RCT, CodeBreaK 200, and the other UK RWE, the CAS RWE study, neither of which had been available in TA781.^{2, 4} In addition, there was SAT of sotorasib, CodeBreaK 200, with longer term follow-up than had been available in TA781. There are pros and cons to each of CodeBreaK 200 and the CAS RWE study, supplemented by CodeBreaK 100, the results for which have been summarised in Table 3.18. The company also make a comparison with the Flatiron study, which is based on US data. It appears to be the case that there is much similarity between all three evidence sources in OS for sotorasib, with a median of about 10.2 months. There is also much similarity between the CAS RWE and the Flatiron studies in OS for docetaxel, with a median of between about 6 and 7 months. However, OS is higher for docetaxel in CodeBreaK 200 (about 11 months), which is after adjustment for crossover. This could be to some extent due to insufficient power, but this is uncertain. PFS is also higher in CodeBreaK 200 than in the CAS RWE study for both sotorasib and docetaxel, although the treatment effect is larger in the latter study. In conclusion, the estimate of the treatment effect for PFS is probably closer to that estimated from CodeBreaK 200 given that it is an RCT and not subject to any crossover effect. However, it is less clear to which of the study outcomes OS is closest, and the EAG would summarise the factors that need to be considered in making a judgment as:

- CodeBreaK 200 is an RCT, but:
 - there was a high rate of withdrawal from the docetaxel arm of the RCT;
 - there was crossover from docetaxel to sotorasib in the RCT, although there was crossover adjustment in the analyses.
- The CAS RWE study is not an RCT and so subject to selection bias, but:
 - it is UK based,
 - efforts were made to ensure recruitment of most patients who received docetaxel in the same population as who received sotorasib,
 - statistical analyses were conducted to adjust for any remaining differences in prognostic factors/treatment effect modifiers,
 - sensitivity analyses were also applied to address uncertainty in analysis population and statistical adjustment,

- the Flatiron study provides some external validation.

Table 3.18: Summary of clinical evidence base for sotorasib versus docetaxel

Study	Design	Overall survival					Progression-free survival				
		Sotorasib		Docetaxel			Sotorasib		Docetaxel		
		N [†]	OS, months (95% CI)	N [†]	OS, months (95% CI)	HR (95% CI)	N [†]	PFS, months (95% CI)	N [†]	PFS, months (95% CI)	HR (95% CI)
CodeBreaK 200	Phase 3 RCT of sotorasib versus docetaxel	171	10.64 (8.94, 13.96)	174	11.3 (9.00, 14.85)	0.820 (0.315, 1.309) [¶]	171	5.62 (4.27, 7.75)	174	4.47 (3.02, 5.68)	0.663 (0.509, 0.864), p=0.002
CodeBreaK 100	Single-arm Phase 1/2 trial of sotorasib	174	12.5 (10.0, NE)	N/A	N/A	N/A	174	6.8 (5.1, 8.2)	N/A	N/A	N/A
CAS RWE study	Retrospective RWE study of CAS database in England	394	10.18 (9.10, 12.02) [‡]	1,271	6.87 (6.01, 7.82) [‡]	0.633 (0.536, 0.749), p<0.001	394	8.51 (7.33, 9.43) ^{‡, §}	1,271	5.62 (5.06, 6.18) ^{‡, §}	0.567; 95% CI: 0.485, 0.663; p<0.001 ^{§*}
Flatiron US RWE	Retrospective RWE study of Flatiron US EHR dataset	164 ^{††}	10.2 (8.0, 14.6) ^{††}	116 ^{††}	7.2 (5.1, 10.6) ^{††}	0.65 (0.49, 0.87) ^{††}	N/A	N/A	N/A	N/A	N/A
		102 ^{‡‡}	10.2 (7.6, 16.3) ^{‡‡, §§}	58 ^{‡‡}	6.0 (4.2, 11.0) ^{‡‡, §§}	0.62 (0.41, 0.93) ^{‡‡, §§}	N/A	N/A	N/A	N/A	N/A

Based on Table 35, CS²

† Number of patients treated. †† 2L+ setting.

‡ After SMRW. ‡‡ 2L setting.

§ TTNT(D) used as a proxy for PFS. §§ After PS weighting.

¶ Based on two-stage analysis adjusting for all crossover (i.e. per-protocol crossover and off-protocol crossover to commercial sotorasib)... * EAG corrected.

2L = second-line; CAS = Cancer Analysis System; CI = confidence interval; CS = company submission; EHR = electronic health records; HR = hazard ratio; N/A = not applicable; NE = not estimable; OS = overall survival; PFS = progression-free survival; PS = propensity score; RCT = randomised controlled trial; RWE = real-world evidence; SMRW = standardised mortality ratio weighting; TTNT(D), time to next treatment (or death); US = United States

4. Cost effectiveness (CE)

4.1 EAG comment on company's review of CE evidence

This Section pertains mainly to the review of cost-effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to CE presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 *Searches performed for the CE Section*

The following paragraphs contain summaries and critiques of all searches related to CE, health-related quality of life (HRQoL) and cost/healthcare resource use identification presented in the CS.² The CADTH evidence-based checklist for the PRESS, was used to inform this critique.⁹ The EAG has presented only the major limitations of each search strategy in the report.

Appendices E, F and G of the CS provide details of a single set of searches conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in the treatment of patients with metastatic KRAS-mutated NSCLC.⁸ The searches were conducted in February 2020 and updated in January 2021 and March 2025.

EAG comments:

- A single set of searches was undertaken to identify relevant studies on CE, HRQoL and cost/health care resource use in the treatment of patients with metastatic KRAS-mutated NSCLC. The CS, Appendices E, F and G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{2, 7, 8}
- The following databases were searched on 20 February 2020 and updated on 29 January 2021 and 4 March 2025: MEDLINE (including In Process, Epub Ahead of Print and MEDLINE Daily), Embase, CDSR, DARE, CENTRAL, CMR, NHS EED, HTA Database and ACP Journal Club. Four key conferences were manually searched for proceedings: ASCO, ESMO, WCLC and AACR (2017-2020; 2022-2024). Reference lists of relevant SLRs/network meta-analyses (NMAs) were checked for additional studies.
- No publication date limit was applied to the CE or HRQoL searches, and the cost/healthcare resource use searches were limited to a date range of 2009 to date. No language limits were applied to any of the searches.
- The searches contained a population facet for KRAS-mutated NSCLC. This was then combined with study design filters containing terms for costs and economic evaluations, cost/healthcare resource use and HRQoL. None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.
- All searches were well structured, transparent and reproducible and searches contained a good range of search terms, synonyms and subject headings. A good range of databases and conference proceedings were searched.

4.1.2 Inclusion/exclusion criteria

Option 1: The inclusion and exclusion criteria used by the company are presented in Appendices G and H of the CS, Tables 53 and 70.⁸ The EAG considers the inclusion and exclusion criteria suitable to capture all relevant evidence.

Option 2: Inclusion and exclusion criteria for the review on CE studies, utilities and costs and resource use are presented in Table 4.1.

Table 4.1: Eligibility criteria for the SLRs

	Inclusion criteria	Exclusion criteria
Patient population	Patients with NSCLC with KRAS mutation (KRAS G12C of principle interest)	Known KRAS mutation-negative status
Intervention	Any (of primary interest: chemotherapy or a targeted, non-mutation specific treatment [including against PD-1, PD-L1, or CTLA-4])	Drug targeted to either ALK, BRAF, EGFR, NTRK, or ROS1
Comparator	Any or none	N/A
Outcomes(s) 1 (Published economic evaluations)	Economic evaluations Results: QALYs gained, LYs gained	Any other outcomes
Outcomes(s) 2 (HRQoL studies)	HRQoL HSUVs	
Outcomes(s) 3 (HCRU studies)	Treatment cost by stage of disease (e.g. pre- versus post-progression, including HCRU, cost of care, cost of illness)	
Study design 1 (Economic evaluation studies)	Any	Animal/in-vitro studies, case studies, and case reports
Study design 2 (HRQoL studies)	Any	
Study design 3 (HCRU studies)	Any	
Date restrictions	HCRU: 2009 to current HRQoL and economic evaluation: none	
Language restrictions	English language	
Publication type	All primary and systematic reviews	
Country	Not restricted	
Based on CS Appendix E Table 45. ⁸ ALK = anaplastic lymphoma kinase; BRAF = V-Raf murine sarcoma viral oncogene homolog B1; EGFR = epidermal growth factor receptor; HCRU = healthcare costs and resource utilisation; HRQoL = health-related quality of life; HSUV = Health State Utility Value; KRAS = Kirsten rat sarcoma; LY = life year; N/A = not applicable; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death 1; NTRK = neurotrophic tyrosine kinase; PD-L1 = programmed cell death		

	Inclusion criteria	Exclusion criteria
ligand 1; QALY = quality-adjusted life year; ROS1 = proto-oncogene tyrosine-protein kinase; SLR = systematic literature review		

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify CE studies.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Consistent with NICE reference case
Perspective on costs	NHS and PSS	Consistent with NICE reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Consistent with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with NICE reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with NICE reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	The crosswalk algorithm by Van Hout et al., 2012 was used in the CS to map EQ-5D-5L to EQ-5D-3L, whereas the NICE HTA manual (Section 4.3.16) stipulates the use of the mapping function by the Hernandez Alava et al., 2017.
Source of data for measurement of HRQoL	Reported directly by patients, carers or both	Consistent with NICE reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Consistent with NICE reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	Consistent with NICE reference case

Element of HTA	Reference case	EAG comment on CS
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	A per treated day approach was used to estimate sotorasib acquisition costs in the CS, whereas the NICE process and methods guide states that oral treatments dispensed in tablet packs should be evaluated on a per pack basis.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with NICE reference case
CS = company submission; EAG = External Assessment Group; EQ-5D-3L = European Quality of Life-5 Dimensions 3 Levels; EQ-5D-5L = European Quality of Life-5 Dimensions 5 Levels; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALYs = quality-adjusted life years; UK = United Kingdom		

4.2.2 Model structure

A partitioned survival model (PSM) with three distinct health states (progression-free [PF], progressive disease [PD] and dead) was developed in Microsoft Excel®. All patients entered the model in the PF state and were at risk of PD or death, where transitions to death could occur from both PF and PD. This model structure was in line with the original submission (TA781).⁴ The state occupancy of patients for each cycle was estimated using the TTNT(D) data as a proxy for PFS and OS data from the CAS RWE study. Time on treatment was incorporated in the model as the time patients spend receiving treatment while in the PF state. The proportion of patients on treatment was modelled separately and was capped by the PFS curve, so that the proportion of patients on treatment was always equal to or lower than the proportion of patients in PF state. The model used a weekly cycle with a half-cycle correction and a lifetime time horizon of 20 years.

EAG comment: The NICE DSU TSD 19 recommends the use of state transition models (STMs) alongside PSMs to verify the plausibility of PSM extrapolations and explore key clinical uncertainties in the extrapolation period. Moreover, the use of a PSM was considered a key issue in the original TA (TA781). In NICE DSU TSD 19 it is further mentioned that STM has advantages over PSM “*with respect to extrapolation because the changing health state occupancy mix is explicitly modelled, stakeholders should note that the validity of the extrapolation remains dependent upon within trial trends in individual transition rates being representative of post-trial trends*”. Specifically, extrapolated mortality in a PSM model is “*determined by prior trends in mortality rates whereas extrapolated mortality in a state transition model is determined by a structural link between mortality and earlier disease-related events such as cancer progression*”. In the clarification response, the company provided

further insight into the decision to adopt a PSM instead of an STM. The company listed three factors in response to clarification question B3:

- The suitability of the model structure to utilise the available evidence (an STM would not allow for the incorporation of the CAS RWE study as the post-progression survival transitions could not be derived from the aggregate level data available to the company)
- How the limitations of each model structure interact with the available evidence
- Alignment with the work conducted in TA781

The first two bullets relate to data availability; this is inconsistent with best modelling practices where it is stated that:

“Although data are essential to a model, the conceptual structure should be driven by the decision problem or research question and not determined by data availability.” (Best practice II-3 in Roberts et al.,)¹³

Rather best practices describe that:

“Specification of states and transitions should generally reflect the biological/theoretical understanding of the disease or condition being modelled.” (Best practice III-4 in Siebert et al.,)¹⁴

Accordingly, the EAG believes that the company’s PSM approach is not appropriately justified. Moreover, the company acknowledges the limitations of PSM but believes that this is mitigated by the maturity of the evidence (as also stated in NICE DSU TSD 19: *“the extent of differences between predicted and actual outcomes is expected to be less significant as the maturity of the data increases”*). However, as illustrated in CS Figures 8 and 9, follow-up data from CodeBreak 200 beyond 18 months is limited. Furthermore, 58%/54% experienced a PFS/death event in the docetaxel arm while this was 71%/64% for sotorasib (this was 83% and 61% (death events) in CAS RWE). Although more mature data are available compared with the original submission in TA781, the EAG believes that the company’s PSM is not appropriately justified and that this approach could potentially bias the estimated CE. Unfortunately, the company did not develop a STM as part of the evidence submission (as requested in clarification question B3d).

4.2.3 Population

The patient population for the economic analysis is adult patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy. The company stated that this was in line with the final scope of this appraisal, the population in TA781, and the anticipated marketing authorisation as well as with that in the Phase 3 CodeBreak 200 RCT, and the sotorasib arm of the CAS RWE study. Subgroup analyses were not included in the CEA.

EAG comment: The main EAG considerations relate to: a) differences in prior lines of therapy; b) not including subgroup analyses listed in the scope and c) mismatch between the primary source used to inform patient characteristics (CodeBreak 200) and the primary source used to inform treatment effectiveness (CAS RWE).

- a) According to CS Figure 1, sotorasib can be positioned either 2L or 3L for patients with KRAS G12C-mutated NSCLC. Moreover, according to CS Table 70, sotorasib is positioned in 2L+. Consistently, CS Tables 10, 12 and 16 illustrate that patients included in the CodeBreaK 200 and CAS RWE studies typically had 1 () to ≥ 5 prior treatments (in CodeBreaK 100, 2 patients had no prior treatment). Hence, the number of prior treatments might be a source of heterogeneity in terms of differences in (relative) effectiveness but also variations in baseline risks, HRQoL, resource use and cost. Although the final scope listed previous treatment for defining subgroups, the company stated in response to clarification question B4 that it is not possible to re-analyse CAS RWE data for subgroup analyses. The HR for the risk of death in the CAS RWE study was similar for patients with or without prior PD-1/PD-L1 targeted immunotherapy (CS Section 2.8.2.2), as argued by the company. However, the differences in the HR for the risk of disease progression or death in the CodeBreaK 200 study (CS Table 32) were more pronounced when considering prior LoT in advanced disease. Therefore, the EAG believes it would be informative if the company would perform subgroup analyses based on previous treatment, using data from the CodeBreaK 200 study.
- b) In addition to previous treatment, the final scope also mentions disease stage, histology and newly diagnosed or recurrent distant metastatic disease as potential factors to define subgroups. According to the CS *“Subgroup analyses were not included in the cost-effectiveness analysis given there were no subgroups observed with substantially different efficacy to the whole population in CAS RWE”*. The EAG considers the justification provided for not performing subgroup analyses insufficient. As mentioned in clarification question B4, even in the absence of differential efficacy (which is not clearly demonstrated by the company), differences in CE may arise from variations in baseline risks, HRQoL, resource use and cost. In response, the company stated: *“It is not possible to re-analyse the CAS data as requested, as the analyses were pre-specified and the Company does not have access to the patient-level data.”* The EAG believes that the subgroup analyses listed in the final scope are informative and can be explored using the pivotal trial, i.e., CodeBreaK 200 study. Especially given that CS Table 32 indicates that history CNS involvement as well as history of liver metastasis have a substantial impact on relative effectiveness (in CodeBreaK 200). Similarly, CS Section 2.8.2.2 indicates prior record of brain metastasis impacts relative effectiveness (in CAS RWE).
- c) There is currently a mismatch between the primary source used to inform patient characteristics (CodeBreaK 200) and the primary source used to inform treatment effectiveness (CAS RWE) in the company’s base-case. In response to clarification question B5, the company replied that *“Not all of the baseline demographics required to accurately calculate body surface area-based drug dosing (i.e., for docetaxel) were available in CAS RWE – specifically, body weight and body surface area (BSA) were not available. As the baseline demographics of CodeBreaK 200 and CAS RWE are very similar in terms of age and proportion of females (as shown in Table 40 of the CS), the decision was made to use a single source for baseline demographics rather than mixing the sources used to inform age, sex distribution, body weight, and BSA.”* This source of patient characteristics has potential implications for the severity modifier (see Section 5.3 of this report).

4.2.4 *Interventions and comparators*

Sotorasib is a KRAS G12C inhibitor, which is a once-daily (QD) oral therapy (960 mg, administered as eight 120 mg tablets or four 240 mg tablets), that has received a conditional marketing authorisation in the UK by the Medicine and Healthcare products Regulatory Agency (MHRA) since September 2021 as monotherapy for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy, unless contraindicated.¹⁵ Sotorasib is administered until disease progression or until no further clinical benefit is expected, which is aligned with the Phase 3 CodeBreaK 200 trial¹² and the CAS RWE study.¹⁶

The only relevant comparator, according to the company, was docetaxel monotherapy. The other potential comparators were adagrasib and docetaxel + nintedanib combination therapy (only in patients with KRAS-mutated NSCLC). The former was excluded from this analysis as it is currently going through the NICE appraisal process and the latter because it was used by only ~5% (n<5) of patients with KRAS-mutated NSCLC in the 2L+ setting between 2017 and 2021.¹⁶

EAG comment: According to the EAG, excluding nintedanib plus docetaxel is inconsistent with the original submission (TA781). Given that nintedanib plus docetaxel is listed as a comparator in the final scope and continues to be used in UK clinical practice (~5% according to the RWE from the CAS database), its exclusion requires stronger justification as well as potential scenario analyses including nintedanib plus docetaxel (consistent with TA781). Unfortunately, the company did not provide further compelling justification in response to clarification question B6 (it was only stated that docetaxel plus nintedanib is not routinely used in UK clinical practice). Moreover, the company argued that the estimated ICERs for sotorasib compared to docetaxel plus nintedanib would be lower than those calculated for sotorasib compared to docetaxel alone. According to the EAG, the ICERs for sotorasib compared to docetaxel + nintedanib might indeed be lower than for sotorasib compared to docetaxel + nintedanib. Moreover, the clinical expert consulted by the EAG believes that it is reasonable to exclude nintedanib + docetaxel. Additionally, the exclusion of adagrasib as comparator is also considered reasonable by the EAG given the appraisal regarding adagrasib (TA1076) was terminated.

4.2.5 *Treatment effectiveness and extrapolation*

4.2.5.1 *Treatment effectiveness and extrapolation evidence sources*

The company used the non-randomised CAS RWE study as the main source of evidence on treatment effectiveness for both intervention and comparator. As CAS RWE did not capture PFS, TTNT(D) was used as a proxy. The company explored the use of CodeBreaK 200, a Phase 3, multicentre, randomised, open-label, active-controlled clinical trial of sotorasib versus docetaxel in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with centrally confirmed KRAS G12C mutation, as well as Flatiron US RWE in scenario analyses. In CodeBreaK 200, docetaxel patients could cross over to sotorasib at progression.

In the original appraisal (TA781), the company base-case comparison constituted sotorasib versus docetaxel.⁴ Sotorasib PFS and OS data were gathered from CodeBreaK100,¹⁷ a single

arm trial. SELECT-1 informed PFS and OS for docetaxel monotherapy in a population of patients with KRAS-mutated NSCLC (including G12C and non-G12C mutations). A matching-adjusted indirect comparison (MAIC) enabled a comparative effectiveness assessment.

Estimation of parametric survival models

Due to not fully mature KM data on OS, PFS (TTNT[D]) and TTD(D), parametric survival models were fitted to meet the lifetime time horizon requirement of the health economic model. These included exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal and Weibull. In line with NICE DSU 14,¹⁸ the following criteria guided the parametric survival model choice:

- Diagnostic assessment
 - Goodness-of-fit statistics based on Akaike information criterion (AIC) and Bayesian information criterion (BIC)
 - Proportional hazards assumption
 - Log-cumulative hazard plots
 - Schoenfeld residual plots
 - Accelerated failure time assumption (assessed in CodeBreak 200)
 - Quantiles-quantiles plots
- Visual inspection of fit based on the KM curves
- Clinical plausibility of long-term projections for OS and TTNT(D)

The selection process to extrapolate OS, PFS (TTNT[D]) and TTD(D) is summarised in Table 4.3.

In TA781, the company used jointly fitted log-normal distributions for PFS and OS.

Table 4.3: Selection procedure to estimate and extrapolate OS, TTNT(D) (PFS) and TTD(D) for sotorasib and docetaxel from CAS RWE

	OS		TTNT(D) (PFS)		TTD(D)	
	Sotorasib	Docetaxel	Sotorasib	Docetaxel	Sotorasib	Docetaxel
General	Median OS: 10.18 months	Median OS: 6.87 months	Median TTNT(D): 8.51 months	Median TTNT(D): 5.62 months	Median TTD(D): 5.06 months	Median TTD(D): 2.30 months
Fit to the observed data based on AIC and BIC	Log-logistic distributions had the best statistical fit for independent as well as joint curve fit, both in terms of AIC/BIC.		Log-logistic distributions had the best statistical fit for independent as well as joint curve fit, both in terms of AIC/BIC. The generalised gamma was second-best.		Independently fitted log-logistic distributions had the lowest AIC/BIC, and log-logistic, log-normal and generalised gamma distributions were considered of similar fit by the company. For joint fit, generalised gamma and log-logistic distributions were considered best-fitting by the company.	Independently fitted gamma distributions had the lowest AIC/BIC, although gamma, generalised gamma, and Weibull distributions were within 3 points according to the company. For joint fit, generalised gamma and log-logistic distributions were considered best-fitting by the company.
PH assumption	The company considered the validity of the PH assumption uncertain but not strongly violated, based on assessment of log cumulative hazards and Schoenfeld residuals.		The company considered the PH assumption as not violated, based on assessment of log cumulative hazards and Schoenfeld residuals.		The company rejected the PH assumption, based on assessment of log cumulative hazards and Schoenfeld residuals.	

	OS		TTNT(D) (PFS)		TTD(D)	
	Sotorasib	Docetaxel	Sotorasib	Docetaxel	Sotorasib	Docetaxel
Fit to the observed data based on visual comparison with the KM curves	The log-logistic distribution had the best visual fit yet was discarded by the company due to inappropriate long tails (likewise for log-normal and Gompertz). The generalised gamma distribution was considered next-best by the company.		The log-logistic distribution had the best visual fit yet was discarded by the company due to inappropriate long tails (likewise for log-normal). The generalised gamma distribution was considered next-best by the company, based on visual inspection.		The company saw little visual difference between the parametric model due to data maturity.	
Comparison with published data	Not provided in CS section 3.3.4.		Not provided in CS section 3.3.5.		Not provided in CS section 3.3.6.	
Clinical plausibility of long-term projections ¹⁹	All seven parametric extrapolations were considered plausible, with expected 5-year OS to be slightly higher than for docetaxel.	All seven parametric extrapolations were considered plausible, with expected 5-year OS to be 1-2%.	All seven parametric extrapolations were considered equally plausible.	All seven parametric extrapolations were considered equally plausible.	No clinical expert opinion provided.	No clinical expert opinion provided.
Base-case approach	The jointly fitted generalised gamma was selected based on statistical goodness-of-fit and visual fit.		The jointly fitted generalised gamma was selected based on statistical goodness-of-fit and visual fit.		The individually fitted generalised gamma was selected based on statistical goodness-of-fit, visual fit and NICE DSU TSD 14.	The individually fitted generalised gamma was selected based on statistical goodness-of-fit, visual fit and NICE DSU TSD 14.
Scenario analysis (selection)	CodeBreaK 200: individually fitted log-normal	CodeBreaK 200: TSE crossover adjusted constant HR	CodeBreaK 200 (IA assessed): jointly fitted log-logistic distribution		CodeBreaK 200: estimate ToT at month 0-1, 1-12, 12+ by a probability of patients remaining on treatment (while in PFS) and	

	OS		TTNT(D) (PFS)		TTD(D)	
	Sotorasib	Docetaxel	Sotorasib	Docetaxel	Sotorasib	Docetaxel
					applying it to the proportion of patients remaining in PFS	
Based on CS Sections 3.3.3, 3.3.4, and 3.3.6 ² AIC = Akaike information criterion; BIC = Bayesian information criterion; CAS = Cancer Analysis System; CS = company submission; DSU = Decision Support Unit; HR = hazard ratio; IA = investigator assessment; KM = Kaplan-Meier; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PH = proportional hazard; RWE = real-world evidence; ToT = time on treatment; TSD = Technical Support Document; TSE = two-stage estimation; TTD(D) = time to treatment discontinuation (or death); TTNT(D) = time to next treatment (or death)						

4.2.5.2 *Waning of relative treatment effect*

Waning of the relative treatment effect was not considered in the current CS ², as the length of patient follow-up in CAS RWE was considered “sufficient to capture any decline in treatment effectiveness.”

EAG comment: The main concerns of the EAG relate to: a) the source to inform the treatment effectiveness of sotorasib and docetaxel, b) incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreaK 200, c) issues related to the modelling of TTD(D), d) waning of the relative treatment effect and e) the company’s selected parametric distributions for OS and TTNT(D) based on observed data from CAS RWE.

- a) The company used the non-randomised CAS RWE study in their base-case to inform treatment effectiveness (i.e., OS and PFS) of sotorasib and docetaxel in the economic model, despite the availability of the CodeBreaK 200 RCT. The company justified its choice in Section 2.13 of the CS and in response to clarification question B7, stating that the CAS RWE study utilises real-world data captured directly by NHS Digital, has a larger sample size and follow-up compared to CodeBreaK 200 and features exclusively patients from England. The EAG, however, is concerned that both the unobserved and observed imbalances (e.g. sex, LoT, prior treatment with PD-1/PD-L1 targeted immunotherapy) between the two treatment groups of the CAS RWE study as reported in CS Table 16 may introduce bias in the estimation of OS and PFS, despite the company’s mitigation efforts (i.e., PS weighting). In addition to these observed imbalances, the EAG is concerned about unobserved imbalances, e.g. the unknown status of important prognostic factors in CAS RWE such as KRAS G12C mutation status (unknown for ████% of docetaxel patients and ████% of sotorasib patients) and brain metastasis status (unknown for ████% of docetaxel patients and ████% of sotorasib patients). Both the Cochrane handbook and the GRADE Working Group explicitly prefer randomised comparisons for causal treatment effects because matched observational analyses can (at best) adjust for observed factors and typically remain at risk for unmeasured confounding.²⁰⁻²² Next to that, the EAG considers the lack of available PFS data in CAS RWE a major limitation and questions the appropriateness of using TTNT(D) as a proxy instead. The company argued that CodeBreaK 200 had several limitations, including a reduced patient enrolment (n=330), fewer UK patients, and the trial design allowing for crossover from docetaxel to sotorasib upon disease progression. According to the company, the ITT analysis of CodeBreaK 200 was therefore underpowered to detect comparative efficacy in terms of OS and high stochastic uncertainty hindered crossover adjustment methods to reliably estimate OS. Although the EAG acknowledges the advantages of CAS RWE in terms of its UK patient population, large sample size and follow-up, it prefers CodeBreaK 200 as the source to inform PFS (directly) and OS (TSE-adjusted for crossover) of sotorasib and docetaxel in its base-case. Despite acknowledging the potential bias in the estimation of OS introduced by patients crossing over from docetaxel to sotorasib, the main arguments for the EAG to use CodeBreaK 200 are primarily its randomised design and secondly, the direct availability of PFS as well as the availability of important prognostic factors (i.e., KRAS G12C mutation and brain metastases status). According to the EAG, the matched observational comparison should be appraised with ROBINS-I (not provided in the CS) and considered as supportive evidence due to residual (including unmeasured) confounding.²³
- b) The company did not provide all relevant information required for parametric survival curve selection as outlined in NICE DSU TSD 14.¹⁸ Although the EAG requested additional information for both CAS RWE and CodeBreaK 200 in clarification question B8,⁷ the company only provided

this for their base-case approach using CAS RWE data. As previously noted, the EAG considers CodeBreaK 200 the preferred source for informing treatment effectiveness of sotorasib and docetaxel and therefore had to select parametric survival curves based on incomplete information. For OS, the EAG was unsure whether the PH assumption was violated but favoured individually fitted curves based on the convergence of cumulative hazards observed in CS Figure 50. The best statistically fitting curves for sotorasib (i.e., log-normal, log-logistic and generalised gamma) resulted in overly optimistic 3-year (approximately 15%) and 5-year (approximately 7%) survival relative to EAG clinical expert estimates (7% and 2%). Consequently, the EAG selected the Gamma curve (3-year and 5-year OS of 7% and 1%) for sotorasib in its base-case. Due to insufficient available information to robustly assess the optimal parametric curve for docetaxel OS, the EAG aligned its base-case with the company's scenario analysis, applying the TSE crossover-adjusted HR (i.e., 1.22) to the sotorasib OS curve. For PFS, hazards appeared non-proportional over time. The EAG therefore selected individually fitted log-logistic curves for both sotorasib and docetaxel in its base-case, as these provided the best statistical fit to the observed data and yielded long-term estimates consistent with EAG expert opinion.

- c) The company modelled TTD(D) based on parametric curves fitted to pseudo patient-level data from CAS RWE to inform treatment costs in its base-case. The EAG questions this approach, as, according to CS Section 2.13, TTD(D) was an exploratory endpoint that was estimated indirectly using a line of treatment algorithm due to a lack of records on treatment end dates. According to the CS, the use of this algorithm could result in misclassification of TTD(D). In response to clarification question B10, the company stated that it preferred to align the source of evidence (i.e., CAS RWE) with the source used to inform OS and TTNT(D) (as a proxy for PFS) and highlighted the advantages of using CAS RWE over CodeBreaK 200 as mentioned in EAG comment 4.2.5 a) above. The extent of misclassification and impact on the estimated TTD(D) from CAS RWE is unclear to the EAG. It alternatively prefers informing TTD(D) based on CodeBreaK 200 as it does not rely on an algorithm and is in line with the EAG's preferred source of informing OS and PFS. In addition, the EAG considers the company's (scenario) analysis of estimating TTD(D) from CodeBreaK 200 using Cox regressions performed on PFS versus TTD(D) to generate time-varying HRs also to be suboptimal. Alternatively, the EAG's preferred approach would be to inform TTD(D) directly by fitting parametric survival curves to the observed TTD(D) data in CodeBreaK 200, which was requested in the clarification letter but not provided by the company (clarification question B10). In response to clarification question B10, the company argued that *"PFS was used directly as this is representative of how patients would be treated in a real-world scenario in line with the marketing authorisations of sotorasib and docetaxel; specifically, treatment until disease progression"*. In absence of this analysis, the EAG uses the time-varying HRs from CodeBreaK 200 to inform the modelling of TTD(D) in its base-case.
- d) Treatment waning was not explicitly modelled by the company in its base-case, stating that the length of patient follow-up in CAS RWE was sufficient to capture any decline in treatment effectiveness. The EAG considers this a strong assumption given the available evidence on (the longevity of) the relative effectiveness of sotorasib versus docetaxel and requested further exploration in clarification question B9. In response, the company provided smoothed hazards plots for the observed OS and TTNT(D) in CAS RWE. It argued that uncertainty was high towards the end of follow-up due to low patients numbers, making any assessment of treatment effect waning highly uncertain. The EAG is critical of any assessment of treatment waning based on CAS RWE due to the limitations of non-randomised study designs. Although requested by the EAG, the

company did not provide additional evidence and justification for CodeBreak 200 due to time constraints. Hence, the assessment of treatment waning for the EAG base-case was based on very limited information. Considering the relatively immature observed CodeBreak 200 data and the converging trend of cumulative hazards for OS as observed in CS Figure 50, the EAG modelled a gradually declining (over 5 years) sotorasib treatment effect starting at 2 years in its base-case. This approach is in line with the ERG's preferred approach in TA781 ²⁴.

- e) In its base-case analysis, the company applied jointly fitted generalised gamma curves to extrapolate OS and TTNT(D) data from CAS RWE. This choice was primarily justified by its more plausible long-term extrapolations compared to the log-logistic model (best statistical fit). The EAG, however, noted that for sotorasib, the modelled long-term estimates (3-year and 5-year OS of ■ and ■, 3-year TTNT(D) of ■) are higher than those estimated by the EAG clinical expert (3-year and 5-year OS of 7% and 4%, 3-year PFS of 3%). For docetaxel, the EAG noted this discrepancy for OS but not for TTNT(D). The EAG noted that despite their worse statistical and visual fit to the observed CAS RWE data, jointly fitted Gamma and Weibull curves yielded long-term OS and TTNT(D) estimates more consistent with EAG expert opinion and may therefore be more suitable for extrapolating OS and TTNT(D) of sotorasib and docetaxel from CAS RWE. While the EAG considers clinical expert input informative, particularly when there is a lack of alternative long-term evidence, its use to validate long-term extrapolations should be taken with caution as there is limited experience with sotorasib in NHS practice and expert opinions may differ.

4.2.6 AEs

In the economic model, treatment emergent, TRAEs with a Grade 3 or 4 incidence $\geq 5.0\%$ (CodeBreak 200) were included. AE disutilities were assumed to be implicitly captured in the CS base-case and were only explicitly included in a scenario analysis. For any costs/disutilities modelled, no differentiation was made between Grade 3 and Grade 4, and all AEs were assumed to be resolved after 4 weeks.

EAG comment: The main concerns of the EAG relate to: a) assuming the same duration for all AEs, b) the exclusion of Grade 1 and 2 AEs and chosen cut off for including Grade 3+ AEs.

- a) The EAG questioned the assumption that all included AEs would last for a duration of 4 weeks, irrespective of Grade (3 versus 4) or type. Upon clarification, the company suggested that this assumption was made for consistency with TA781 and described the approach as pragmatic. The EAG clinical expert suggested that for most AEs, it would not be possible to say whether they would be resolved within 4 weeks. Whilst the EAG would prefer further justification for the assumption, it accepts the difficulty in sourcing a reflective duration for each included AE, assuming no AE duration data was collected in CodeBreak 200.
- b) Grade 1 and 2 AEs, as well as Grade 3 and 4 AEs with an incidence below 5% in both treatment arms, were excluded from the economic model. Following the clarification, the company suggest that provided Grade 1 and 2 are low Grade, they do not anticipate the conclusions of the modelling to change. No comment was made regarding the chosen incidence rate. Further, the requested scenario analyses to include the excluded AEs was not provided. Whilst Grade 1 AE incidence rates were not provided, incidence for Grade 2 treatment-related TEAEs were higher in the comparator arm (CS Table 33, CodeBreak 200), suggesting that the exclusion is likely conservative.

4.2.7 HRQoL

In the CS, utility values were informed by EQ-5D-5L data collected within CodeBreaK 200, mapped to EQ-5D-3L using the van Hout et al., 2012 crosswalk algorithm (UK tariff). Treatment-dependent time-to-death utilities were derived descriptively for four pre-defined periods: more than 6 months to death, between 3 and 6 months to death, between 1 and 3 months to death, last month of life. A scenario analysis was explored with Health State Utility Values (HSUVs), derived descriptively per treatment arm based on progression status.

4.2.7.1 HRQoL data identified in the SLR

Five studies were identified reporting HRQoL for patients with NSCLC with any KRAS mutation. Findings and reasons for exclusion are presented in Table 4.4.

Table 4.4: Reasons for study exclusion in the economic model

Author	Population	Aim	Reason for exclusion
Yang et al., 2016	Advanced NSCLC	Impact of biomarker testing guided therapy	Scale for HRQoL score not reported
Chouaid et al., 2025	Advanced NSCLC with KRAS mutation	RWE: impact of KRAS mutation in 2L or later treatment	Patients in France and Germany
Felip et al., 2024	Advanced NSCLC with KRAS G12C mutation. Previous treatment with platinum-based chemotherapy and anti PD-L1 immunotherapy	Comparing adagrasib and docetaxel (KRYSTAL-12 RCT)	Value set not reported
Zhu et al., 2024	Advanced NSCLC with KRAS G12C mutation	CE of sotorasib as 2L treatment for NSCLC with	Patients from China and US (source for AE disutilities identified here: Nafees et al., 2017)
Waterhouse et al., 2024		Reported PROs from CodeBreaK 200 for sotorasib and docetaxel	No utility values reported for specific populations
Based on Table 2 of the clarification response ⁷ 2L = second-line; AE = adverse event; CE = cost-effectiveness; HRQoL = health-related quality of life; KRAS = Kirsten rat sarcoma virus; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand 1; PRO = patient-reported outcome; RCT = randomised controlled trial; RWE = real-world evidence; US = United States			

4.2.7.2 Time-to-death and HSUVs

EQ-5D-5L data was analysed descriptively for each period/health state. Utility values applied in the base-case and HSUV scenario analysis are presented in Table 4.5.

Table 4.5: HSUVs

Time-to-death period/health state	Mean utility (95% CI): sotorasib	Mean utility (95% CI): docetaxel
Time-to-death approach		
More than 6 months to death		

Time-to-death period/health state	Mean utility (95% CI): sotorasib	Mean utility (95% CI): docetaxel
Between 3 and 6 months to death (versus more than 6 months)		
Between 1 and 3 months to death (versus more than 6 months)		
Last month of life (versus more than 6 months)		
HSUV approach		
Progression free		
Progressed disease		
Based on CS, Table 57 and 58 ² CI = confidence interval; CS = company submission; HSUV = Health State Utility Value		

4.2.7.3 Disutility values

AE disutilities were excluded from the company's base-case as their impact on HRQoL was assumed to be captured in the utility values estimated from CodeBreaK 200. According to the CS, AE disutilities were explored in a scenario for treatment emergent, treatment-related Grade 3 or 4 AEs with a Grade 3/4 incidence of $\geq 5\%$. Duration for all included AEs was assumed to be 4 weeks, irrespective of Grade or type. Disutilities are presented in CS, Table 59.

EAG comment: The main concerns of the EAG relate to: a) time-to-death versus progression-based approach; b) use of treatment-dependent utilities; c) deviation from the crosswalk algorithm to map EQ-5D-5L to EQ-5D-3L stipulated in the NICE HTA manual; d) No age or sex adjustment; e) methodological rigour of the approach to estimating utilities; f) the exclusion of AE disutilities from the CS base-case analyses; and g) use of pre-defined groupings rather than a continuous approach to time-to-death utilities.

a) To derive utility values utilised in the company's base-case, HRQoL data was analysed descriptively by time-to-death (grouped periods). Time-to-death periods were pre-defined in-line with TA781. In the TA guidance for sotorasib (TA781)⁴, the NICE committee recognised the uncertainty surrounding the decision to utilise a time-to-death approach to model utilities, with the EAG preferring a progression-based approach to estimating utilities in-line with health states. The EAG preferred the progression-based approach provided that, at the time, research pertaining to the validity of a time-to-death approach was limited. In the present submission, the company highlight Hatswell et al.,²⁵ in CS, Table 1 to further support the decision to maintain a time-to-death approach to estimating utilities in the base-case analyses. The EAG accepts the justification for incorporating time-to-death into the utility calculation. However, the incorporation of time-to-death should complement a health-state, progression-based approach (not supplement it). Here, separate utilities would be adopted for PF and progressed-disease health states, with utilities also being lower over time (i.e., closer to death). The EAG requested a scenario analysis informing HSUVs with a full model (i.e., mixed effects model) including (but not limited to) treatment arm, disease progression, and time-to-death. Here, a progression-based approach can incorporate a disutility penalty based on time-to-death weighted at each cycle. The company did not provide the analyses, suggesting that the requested analyses was not possible within the timeframe for response to the EAG clarification questions. The EAG reiterates that it would like to see the requested analyses.

- b) The EAG questions the use of treatment-dependent utilities. The company utilised a descriptive approach to derive utilities. This was done separately for the sotorasib and docetaxel arms. Clarification question B17 questioned the validity of this. The company recognised that a treatment-independent approach may also be valid and suggested that a scenario analysis was provided utilising a treatment-independent approach. No such analyses could be found in the clarification response documents. Further, the EAG requested a scenario analysis informing utility values using a regression-based approach (mixed effects model) including treatment arm as a covariate. Such analysis would have provided clarity regarding whether or not treatment-dependent utilities are valid in the present submission. The company did provide results for a MMRM approach, however here, no covariates were included, leading to outstanding uncertainty regarding treatment-dependent utilities. Given that sufficient justification for treatment-dependent utilities was not provided, the EAG utilised MMRM utilities for sotorasib both treatment arms (i.e., treatment-independent) in its base-case.
- c) The CS utilises the crosswalk algorithm by Van Hout et al.,²⁶ to map EQ-5D-5L outcomes to EQ-5D-3L. The latest version of the NICE HTA manual (Section 4.3.16) stipulates that the mapping function developed by the DSU, using the EEPRU dataset, should be used for the reference-case analysis.²⁷ Clarification question B16 requested this update to be provided, given that the current approach is not aligned with the current manual, and to subsequently update the QALY shortfall analysis. The request is outstanding as the company suggested the request could not be fulfilled in the timeframe given for EAG clarification question responses.
- d) No age or sex adjustment was applied to utility calculations in the time-to-death utility approach (base-case) nor the progression-based approach (scenario). In response to clarification question B15 d), the company suggest that whilst no separate adjustment was performed, the time-to-death approach incorporates patient age. No further explanation is provided. The company further state that the impact of incorporating (Ara and Brazier et. al.²⁸) age and sex adjustment in the previously submitted model had a minor impact on the ICER, and that the same would be true for this analysis. It is unclear to the EAG why age and sex adjustment was no longer considered relevant compared to the original submission. The EAG requested that such adjustment was explored but the requested analysis was not provided. With reference to Section 4.3.7 of NICE health technology evaluations: the manual, further evidence to suggest that age and sex utility adjustment is not relevant to this case, or the provision of such adjustment, remains desirable to the EAG.
- e) The EAG questions the methodological rigour of the current approach to deriving utilities included in the economic model. These pertain to the handling of missing data and the use of a descriptive approach:
 - i. No missing data imputation was performed, with a complete case analysis approach utilised. In the company's response to clarification question B15, the EAG noticed that (exception of baseline) the presented questionnaire completion rates for the combined group is consistently higher than the presented individual completion rate for either treatment arm. Provided that clarification response Table 3 does not provide the number of questionnaires distributed at each time point, the reason for this discrepancy remains unclear. Further, the company conclude that the missing-at-random assumption holds (based on clarification response Figure 17). However, the figure shows that baseline utility is lower for those with missingness at the following timepoint. If the difference between those with/without subsequent missingness is significant, this could suggest that utilities are overestimated. The EAG would like to see further justification or the use of missing data imputation. Further, even if the missing at random assumption holds, the

- results may be biased when not accounting for observed variables (predictors of missingness).
- ii. The descriptive approach to estimating utilities does not account for repeated measures within patients and questioned why a regression-based analysis was not provided. The selection of a descriptive approach was based on “ease of interpretation of methods” and considered appropriate to capture “key trends in HRQoL without overfitting the data.” Results of an MMRM analysis were provided, however seemingly without the inclusion of any covariates (i.e., univariate analysis). The EAG does not find the justification for utilising a descriptive approach to be sufficient and would prefer the inclusion of a fully fitted model, exploring the inclusion of covariates as requested in clarification question B15.
- f) The impact of AEs on HRQoL was assumed to be implicitly captured within the collected HRQoL data. That is, AE disutilities were not included in the CS base-case analysis. Clarification question B12 c) requested justification and supporting evidence to support the assumption. The company suggest that the impact of AEs on HRQoL is captured through the use of time-to-death utilities. However, irrespective of the approach taken (time-to-death versus progression-based) to estimate utilities, if the frequency of EQ-5D questionnaires is not sufficient to capture the (full) impact of AEs on HRQoL, then the assumption does not hold. Further, if, as clarification response Figure 17 potentially suggests, patients with lower HRQoL are less likely to complete questionnaires, then the assumption that the impact of AEs is implicitly captured would not hold. The company report (clarification response Scenario 6) the impact of including AE disutilities in conjunction with using progression-based utilities. The sole impact of incorporating AE disutilities (clarification response model, Grade 3/4 occurring in $\geq 5\%$ patients in either treatment arm) reduced the CS base-case deterministic ICER by £244 to £26,032.
- g) When utilising the time-to-death approach in the CS base-case, groupings based on predefined periods (i.e., grouping observations as discrete time periods) in-line with TA781 were utilised. In the present submission, the company highlight Hatswell et al.,²⁵ in CS Table 1 to further support the decision to maintain a time-to-death approach to estimating utilities in the base-case analyses. This study found the use of continuous models (in advanced NSCLC) to provide a statistically better fit than time-to-death groupings, without needing to make arbitrary assumptions regarding groupings. Clarification question B15 b) therefore requested a scenario analysis utilising a continuous time-to-death approach to derive utility values. In response, the company suggested that the requested analysis could not be performed in the timeframe for responses to EAG clarification questions. The EAG would prefer a continuous approach to incorporating time-to-death into utility functions.

4.2.8 Resources and costs

The cost categories included in the model were medical costs (drug acquisition costs, administration costs, subsequent treatment costs), health state unit costs and resource use, costs of managing AEs and terminal care costs.

According to the company, none of the studies identified in the SLR were relevant for this appraisal; they did not report UK relevant resource use and cost information.

4.2.8.1 Drug acquisition costs

Unit prices were based on the NHS reference prices 23/24,²⁹ electronic market information tool (eMIT),³⁰ British National Formulary (BNF),³¹ and the Personal Social Services Research Unit (PSSRU).³² This is in line with the previous submission (TA781),⁴ except that the unit costs were inflated.

Drug wastage was not discussed as such in the CS but from the economic model it was apparent that the base-case assumption was zero wastage for both sotorasib and docetaxel. The primary therapies in the company's economic model were costed per treatment day and consistent with the license and dosing regimen in CAS RWE study and CodeBreak 200. Acquisition costs were sourced from the TA guidance for sotorasib (TA781),⁴ and eMIT³⁰ for docetaxel. A Patient Access Scheme (PAS) discount of ■ was used for sotorasib. To account for temporary treatment interruptions, dose reductions, and/or missed doses, the acquisition costs of sotorasib and docetaxel were adjusted based on RDI³³ from CodeBreak 200 CSR using the SAS. RDIs in the company's base-case were 86.42% for sotorasib and 90.40% for docetaxel.

Table 4.6: Drug acquisition costs

Drug	Unit	Unit cost (£)	Reference	Dose	RDI	Cost per month (£) [‡]
Sotorasib	240 x 120 mg (or 120 x 240 mg) tablets	6,907.35	TA781	960 mg per day	86.42% [†]	2,129.76
Docetaxel	160 mg per vial	19.70	eMIT	75 mg/m ² on day of treatment	90.40% [†]	21.90 [§]

Based on CS Table 60²
 CS = company submission; eMIT = electronic market access tool; NSCLC = non-small cell lung cancer; RDI = relative dose intensity; TA = Technology Appraisal. [†] CodeBreak 200 phase 3 NSCLC cohort, safety analysis set Table 14-5.1.1
[‡] Calculated from the cost-effectiveness model. [§] Docetaxel cycle cost is based on cost per mg x dose per administration (75 mg/m²) x body surface area (1.81 m²)

4.2.8.2 Administration costs

No administration costs were applied for sotorasib, as the treatment is administered orally. For docetaxel and subsequent treatments associated with intravenous (IV) delivery, the administration costs were obtained from standard NHS England reference cost sources by using code SB12Z: Deliver simple parenteral chemotherapy (£394.17, in line with TA781).²⁹

4.2.8.3 Subsequent treatment costs

The costs of subsequent treatments were included in the economic model as a one-off cost at disease progression (Table 4.7). Detailed costs used to derive subsequent treatments were sourced from eMIT.³⁰ Best supportive care (BSC) was assumed to have no cost in the model. The distribution of subsequent treatments for patients who progress on sotorasib were informed by UK clinical experts during the original submission for sotorasib (TA781).⁴ The distribution of subsequent treatments for patients who progress on docetaxel were informed by NICE TA347.³⁴ For both sotorasib and docetaxel, the duration of subsequent treatments was modelled as 3.3 months, in line with previous assumptions used in NICE TA347³⁴ on nintedanib and TA428³⁵ on pembrolizumab. The schedule used for platinum doublet chemotherapy is consistent with UK clinical practice.³⁶ The dosing regimen for docetaxel as subsequent treatment is similar to the dosing regimen for docetaxel as the main comparator and in line with CodeBreak 200. The RDI for platinum doublet chemotherapy was assumed 100% (see CS Appendix I

for more information on subsequent treatment costs calculation⁸). This is in line with the previous submission (TA781⁴) except that subsequent treatments for docetaxel in combination with nintedanib were included as well.

Table 4.7: Subsequent treatment costs

Subsequent treatment	BSC	Platinum-based chemotherapy	Docetaxel	Source
Sotorasib (%)	50%	10%	40%	Assumption based on clinical expert feedback obtained for TA781
Docetaxel (%)	70%	30%	0%	NICE TA347 – assumption
Cost of subsequent treatment (£)	0	3,641.21	1,957.58	Calculation (Appendix I of CS)
Based on CS Table 64 ² BSC = best supportive care; CS = company submission; NICE = National Institute for Health and Care Excellence; TA = Technology Appraisal				

4.2.8.4 Health state costs

Disease monitoring and management costs were sourced from TA781.⁴ Apart from a per-cycle cost per health state (PF and PD), a one-off disease management cost was applied at treatment initiation and at progression. All costs were sourced from the latest available NHS reference costs 2023/24²⁹ or PSSRU 2024.³² This is in line with the previous submission (TA781⁴) except that the costs are slightly higher now due to inflation.

Table 4.8: Health state costs

	Cost per model cycle (£)	Source
Health state		
Progression-free	77.53	NHS reference costs 2023/2024 ²⁹ ; NICE TA347 ³⁴
Post progression	41.89	
One-off disease management		
At treatment initiation	881.58	NHS reference costs 2023/2024; ²⁹ NICE TA347 ³⁴
At progression	157.62	
Based on CS Table 62 ² CS = company submission; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; TA = Technology Appraisal		

4.2.8.5 AE costs

Unit costs of Grade 3 or 4 TEAEs with incidence $\geq 5.0\%$ (obtained from CodeBreak 200) were included as a one-off cost in the first cycle of the economic model. The unit costs for these AEs were sourced from NHS reference costs 2023/24³⁵ using all complications and comorbidities (CCs), see Table 4.9. This deviates from the previous submission (TA781⁴) which used the NICE Multiple Technology Appraisal (MTA) for erlotinib and gefitinib to inform AE costs.³⁷

Table 4.9: AE costs

AE	Cost per AE (£)	Incidence for sotorasib (%)	AE cost for sotorasib arm (£)	Incidence for docetaxel (%)	AE cost for docetaxel arm (£)
Anaemia	2,292.02	0.00	0.00	0.00	0.00
Decreased neutrophils	159.94	0.00	0.00	0.00	0.00
Decreased white blood cell count	159.94	0.00	0.00	0.00	0.00
Diarrhoea	4,787.87	11.83	566.41	1.99	95.28
Dyspnoea	3,531.54	0.00	0.00	0.00	0.00
Fatigue	2,292.02	0.59	13.52	5.69	130.42
Febrile neutropenia	5,343.40	0.00	0.00	5.30	283.20
Increased ALT	159.94	7.69	12.30	0.00	0.00
Increased AST	159.94	5.33	8.52	0.00	0.00
Neutropenia	1,534.73	0.00	0.00	8.61	132.14
Pneumonia	4,983.35	0.00	0.00	0.00	0.00
Total one-off AE cost			£600.99		£646.96
Based on CS Table 63 and economic model 'Model parameters sheet'. ² AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CS = company submission					

4.2.8.6 Terminal care costs

A one-off end-of-life care cost (£4,489.57) was assigned to each patient upon death (CS Table 65). Resource use was based on the data presented in TA428³⁵ originally sourced from TA374.³⁷ Unit costs were sourced from PSSRU 2024³² or based on the values from original submission (TA781⁴) for year 2014/2015 and inflated to the 2023/24 cost year using the PSSRU 2024³² inflation indices. This deviates from the previous submission (TA781⁴), in which values from the previous NICE MTA for erlotinib and gefitinib were used.³⁷

EAG comment: The main concerns of the EAG relate to: a) the approach for the modelling of acquisition costs, b) the modelling of RDIs for sotorasib and docetaxel, c) the sources to inform subsequent treatments costs:

- a) In response to clarification question B19, the company explained that a cost per treatment day approach was used in their base-case to estimate drug acquisition costs for sotorasib and docetaxel. This involved modelling an average cost per model cycle. However, according to the NICE statement on oral drugs, these should be costed based on a per pack costing approach.³⁸ The EAG noted that this option was also available in the company's model, but it was not possible to select different approaches for sotorasib (oral administration) and docetaxel (IV infusion). Nevertheless, the EAG considers it reasonable to also use the per pack approach for docetaxel, i.e., modelling the total drug acquisition cost per treatment cycle on every first day of that treatment cycle. Hence, in its base-case the EAG adopted the per pack costing approach for both sotorasib and docetaxel.

- b) The RDIs for sotorasib and docetaxel in the company's base-case are informed by the mean values (i.e., 86.42% for sotorasib and 90.40% for docetaxel) of the CodeBreak 200 SAS. In response to clarification question B18, the company provided details on the definition of RDI and how it was calculated. It also justified the use of different RDIs compared to TA781 (i.e., due to different sources to inform RDI [CodeBreak 100 versus 200]), and provided a scenario analysis assuming equal RDI for sotorasib and docetaxel, as recommended by the EAG in TA781. The clinical expert agreed with the current company base-case values, stating *"This seems plausible based on the known discontinuation rates and dose modification rates for both drugs"*. However, the EAG questions the appropriateness of using the mean RDI values from CodeBreak 200 considering the (left) skewness of the data, and therefore explored using median values instead in a scenario analysis (i.e., 100.00% for sotorasib and 94.80% for docetaxel). The scenario increased the deterministic ICER by £15,965 (+15.65%) compared with the EAG base-case (x1.2 severity modifier). The EAG noted that probabilistic results for this scenario analysis were significantly different to the deterministic results. The EAG considers the probabilistic results to be implausible and notes that this discrepancy is likely to be caused by the RDI for sotorasib being capped at 100%, equal to the median point estimate utilised in this analyses. That is, for each iteration, the value of RDI sotorasib can only be $\leq 100\%$, reducing the aggregated cost of sotorasib, compared with deterministic results. The EAG was unable to adjust the SEs (relevant for probabilistic analyses) accordingly, as the required information to do so seemed unavailable. Hence SEs from the company's base-case mean values (i.e., 1.6% for sotorasib and 1.1% for docetaxel) were applied. The EAG would want to receive further information on the SEs for the median RDI values for sotorasib and docetaxel from CodeBreak 200.
- c) The distribution of subsequent treatments for patients who progress on sotorasib, and docetaxel were informed by TA781 (UK clinical experts) and TA347 in the company's base-case, respectively. The EAG requested further justification for the appropriateness of these sources, to which the company responded that this approach was taken due to a lack of data and to maintain consistency with TA781 and TA1076 (terminated). The EAG requested more details regarding the clinical expert opinion used in TA781, which the company did not provide. The requested scenarios based on CodeBreak 100, CodeBreak 200 and CAS RWE were also not provided, but the company stated that the impact of the distribution of subsequent treatments on the CE estimates is expected to be minimal. The EAG would have liked to see the supporting evidence for this statement. Based on the EAGs clinical expert advice stating, *"The type and distributions of subsequent treatments for patients progressing on sotorasib and docetaxel are reflective of UK clinical practice."*, and the clinical expert advice for TA1076 (terminated) who also agreed with the distribution of subsequent treatments in company's base-case, the EAG considers the values for subsequent treatment appropriate.

5. CE results

Section 5.1 summarises the company's CE results, Section 5.2 presents the EAG's additional work and preferred assumptions, and Section 5.3 explores decision modifiers including the company's and EAG's preferred QALY weighting for severity.

5.1 Company's CE results

All reported results are based on the original CS, prior to EAG clarification phase. The company provided ICER and incremental net monetary benefits (NMBs), but no incremental net health benefits (NHBs).

5.1.1 Company's base-case

The CS base-case deterministic results indicated an incremental QALY gain of [REDACTED] with sotorasib compared to docetaxel (applying a severity modifier of 1.7, see Section 5.3.1) and increased incremental costs of £[REDACTED] (Table 5.1). The corresponding ICER was £26,276. The NMB, at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, were -£4,610 and £2,735, respectively.

Table 5.1: Company's deterministic base-case CE results with and without severity weighting (x1.7)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)	NMB at £20,000 (x1.7 weighting)	NMB at £30,000 (x1.7 weighting)
Docetaxel	11,731	[REDACTED]	-	-	-	-	-
Sotorasib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£44,669* (£26,276)	-10,660* (-4,610)	-6,339* (2,735)

Based on Tables 71 and 72 of the CS²
 CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALYs = quality-adjusted life years
 * Calculated by EAG using the CS health economic model

The CS base-case probabilistic results indicated an incremental QALY gain of [REDACTED] with sotorasib compared to docetaxel and increased incremental costs of £[REDACTED] (Table 5.2), based on a severity modifier of 1.7 (see Section 5.3.1.).

Table 5.2: Company's probabilistic base-case CE results with and without severity weighting (x1.7)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)	NMB at £20,000 (x1.7 weighting)	NMB at £30,000 (x1.7 weighting)
Docetaxel	11,611	[REDACTED]	-	-	-	-	-
Sotorasib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	£45,903* (£27,002)	- £11,190* (-£5,142*)	- £6,870 * (£2,202*)

Based on Table 73 of the CS²
 * Calculated by EAG using the CS health economic model

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)	NMB at £20,000 (x1.7 weighting)	NMB at £30,000 (x1.7 weighting)
CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALYs = quality-adjusted life years							

In TA781, the company reported in the original CS a deterministic ICER of £47,146 and a probabilistic ICER of £46,707.²⁴

5.1.2 Company's sensitivity and scenario analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses (Section 3.9). To ensure replicability of results for the 3,000 simulations, a fixed seed was used. The company found the probabilistic ICER to be consistent with the deterministic analysis (applying a severity modifier of 1.7, see Section 5.3.1). Sotorasib indicated a [REDACTED]% ([REDACTED]%) probability of being cost-effective versus docetaxel considering the £20,000 (£30,000) WTP threshold.

Deterministic one-way sensitivity analyses (DOWSA) varied selected parameters ceteris paribus $\pm 20\%$ for all base-case values when no 95% CI information was available. The company further stated that some parameters, such as parametric survival model parameters, were not considered appropriate for ceteris paribus variation, and thus excluded from the analyses. The DOWSA identified the sotorasib RDI as the most impactful input parameter.

The presented scenario analyses addressed uncertainties with regard to clinical effectiveness (Scenarios 1-5), cost inputs (Scenarios 7, and 8) and the utility approach (TTD versus health state, Scenario 6). The following Scenarios had the largest impact on the ICER:

- Source of clinical data: CodeBreaK 200 with Flatiron analysis OS for docetaxel (Scenario 3), decreased the ICER by 35.7%.
- Inclusion of genetic testing costs¹ (Scenario 7), increased the ICER by 8.3%.
- Inclusion of per progression utilities (Scenario 6), increased the ICER by 5.5%.

In TA781, the DSA identified the HR applied to PFS to model sotorasib treatment duration, the time-to-death utility for >6 months prior to death, and the disease management costs per week in the progression free health state as the most impactful input parameters. Performed scenario analyses can be found in TA781, Table 48.²⁴

EAG comment: The main considerations of the EAG related to: a) the updated health economic model and reporting of probabilistic results in response to the clarification letter, b) the health gains accumulated beyond the observed data, and c) an error in scenario analyses reporting.

- The company provided an updated health economic model in response to the EAG clarification letter. Besides descriptive changes and formulae adjustments, it concerned the standardisation of unknown AE disutility SEs to 20% of the mean, correction of CAS RWE HRs and RDI SEs,³⁹ (Sheet "ModelChangesJuly2025"). The changes affected deterministic results in decimals but were more consequential for probabilistic results (applying a severity modifier of 1.7, see Section 5.3.1). Here, sotorasib was associated with probabilistic incremental QALYs

of [REDACTED] and costs of £[REDACTED], versus docetaxel (Table 5.3). The incremental NMB at a WTP threshold of £20,000 (£30,000) per QALY gained was -£5,111 (£2,229). In addition to NMB reporting, the EAG would have liked to also have NHB estimates readily available as stipulated by NICE.²⁷ At a WTP threshold of £20,000 (£30,000) per QALY gained, the probability of sotorasib being cost-effective versus docetaxel was [REDACTED]% ([REDACTED]%).

Table 5.3: Summary of the updated company base-case probabilistic CE results with and without severity weighting (x1.7)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.7 weighting)	ICER (£/QALY) (x1.7 weighting)	NMB at £20,000 (x1.7 weighting)	NMB at £30,000 (x1.7 weighting)
Docetaxel	11,611	[REDACTED]	-	-	-	-	-
Sotorasib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	45,837* (26,963)	-11,157* (-5,111*)	-6,839* (2,229*)
Based on clarification letter response ⁷ * Calculated by EAG using the CS health economic model CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALYs = quality-adjusted life years							

- b) In response to clarification question B24, the company shared observed and modelled restricted mean outcomes for OS and PFS for base-case results from CAS RWE, truncated at 37 months. For both restricted mean survival time and restricted mean PFS time, a considerable share originates from the modelled time horizon beyond observed data, and more so for sotorasib (OS: 15.6%, PFS: 6.4%) than for docetaxel (OS: 6.4%, PFS: 1.5%). The company relates this to better efficacy of sotorasib, qualifying more patients for outcome extrapolation at the end of follow-up. Although the EAG considers the proportions of health gains accumulated beyond the observed CAS RWE data to be reasonable, it is concerned that these may be substantially higher for CodeBreaK 200 (the EAG's preferred source to inform treatment effectiveness in the economic model), considering its less mature PFS and OS data.
- c) The EAG was able to replicate deterministic and probabilistic base-case analyses as well as most scenario analyses, but not scenario analyses 3 and 4. It appreciates the detailed company response to clarification question B26,⁷ yet noticed a contradiction between the CS² and the health economic model: for both scenarios, for the OS curves for sotorasib, restricted instead of reported, individually fitted log-normal parametric distributions from CodeBreaK 200 were used in the health economic model. The reported findings refer to the former. As a consequence, the company's preferred approach (i.e., restricted or individually fitted) was unclear to the EAG and requires clarification. Whereas requested, the company did not report probabilistic results of the presented scenarios, citing time constraints.

5.1.3 Model validation and face validity check

5.1.3.1 Face validity assessment

The company held two meetings, one advisory board meeting on 11 February 2021 (also submitted in TA781) and another informal call with a clinical expert on 20 June 2025. The 2021 meeting (for TA781) included five external clinical experts and two external health economic experts discussing the

company's proposed UK HTA strategy with five company representatives and one external consultant. The 2025 informal call addressed the clinical validation of the parametric curves.

In TA781, median PFS and OS were compared with reported medians in the MAIC adjusted CodeBreaK100 clinical trial and docetaxel arm of SELECT-1. Clinical experts further assessed the predicted OS landmark results at 1, 5, and 10 years.

5.1.3.2 Technical verification

According to the company, internal and external modelling experts not involved in model development assessed model calculations and Visual Basic for Applications coding. A cost-effectiveness model (CEM) verification checklist was used, which among others included extreme value evaluations and calculation tracing. It seemed to mirror procedures performed in TA781 (Section B.3.9.2.).

5.1.3.3 Comparisons with other technology appraisals

Cross-validation with other TAs besides TA781, produced by the company as well, was not explicitly mentioned in the CS Section B3.11. No cross-validations with other TAs were mentioned in TA781, Section 3.9.

5.1.3.4 Comparison with external data used to develop the economic model

Validation of external data used to develop the economic model was not explicitly mentioned in the CS Section B3.11. Furthermore, no such comparison was mentioned in TA781, Section 3.9.

5.1.3.5 Comparison with external data not used to develop the economic model

Cross-validation with external data not used to develop the economic model was not explicitly mentioned in the CS Section B 3.11. In TA781, the real-world Flatiron Health database was used to assess the robustness of findings.

EAG comment: The main concerns of the EAG relate to: a) transparency issues related to the insufficient responses to the clarification questions posed by the EAG, b) violations of good modelling practice concerning the sensitivity analyses, c) an insufficient technical verification of the CS health economic model, and d) insufficient cross and face validation of the economic model structure, input parameters and outcomes.

- a) During clarification, the company did on multiple occasions not comprehensively address the questions posed by the EAG. Thus, the EAG is concerned that the information made available by the company is insufficient to assess the CS DP and chosen methodology. This applies to further analyses requested from CodeBreaK 200, as an RCT a clinical data source of high relevance. For instance, the company did not provide all HRQoL and subsequent treatment analyses. Moreover, various modelling assumptions in the CS were justified based on expert opinion from an advisory board meeting held in 2021 (part of TA781) and an informal call with one clinical expert. The CS and response to clarification question B31 only included summaries rather than the full minutes of these meetings although requested. The EAG views this a serious transparency issue since it is unable to verify various assumptions made by the company.
- b) For the sensitivity analyses, the EAG noted some deviations from good modelling practice in the CS health economic models both at submission and after clarification. First, in the "Model parameters" sheet, user choices considering DSA and PSA parameter inclusion are not the final

determinant of inclusion but columns N and R which feature if statements. The EAG believes that this hampers model transparency and complicates model feature checks. Second, not all relevant parameters have been included in the DSA and PSA. This applies to KRAS G12C testing, distributions of subsequent treatments across patients, cost estimates, and distribution parameters related to efficacy. For instance, disease management costs per week in PFS were identified as one of the most influential parameters in the DSA by the EAG in TA781²⁴ yet excluded in the current CS. The EAG considers it essential to have these input parameters included in the DSA and PSA for its uncertainty assessment. Third, taking into account the EAG considerations presented in EAG report Section 4.2, in a future health economic model, the EAG would prefer to allow for greater variation of parameter values for which SEs were lacking in sensitivity analyses in the CS base-case, applying $\pm 30\%$ of the mean in its EAG analyses instead of $\pm 20\%$ of the mean as the company did.

- c) The EAG notes that although the CS stated that more than one health economist checked the CS health economic model, in the response and document provided upon EAG clarification question B28⁷ only a single developer respectively validator each were listed. For technical verification, the company used an altered version⁴⁰ of the TECH-VER checklist,⁴¹ lacking some of the original items. Some items were categorised as “not applicable” by the external health economist although of relevance, e.g. addressing scenario analyses and input source checks. Moreover, several question items were left blank both by the external health economist and the company. In four instances, the external health economist noted that performance of tests were not possible, without further action reported and thus supposedly taken. Further, in the sheet “Self QC checks”, “Basic validity checks/pressure tests” were listed which were recommended to be implemented in the health economic model. Upon review, the EAG noted that these tests could not be found in the CS health economic model. Whereas overall external technical verification according to the document submitted upon EAG clarification question B28⁷ seemed to be comprehensive, the EAG noted that there was some lack of consistency making the health economic model prone to flaws. This was confirmed by several modelling errors and deviations from good practice flagged by the EAG; for example, the model parameters sheet not being the origin of input data but the latter being linked to it from several sheets (hindering a comprehensive check of model features). Although requested during the clarification phase, the company stated it did not have sufficient time to turn the “Model parameters” sheet into the primary source of input data.
- d) The EAG criticises insufficient face and cross validation. It can relate to the EAG from TA781 which considered the validation efforts made by the company to be “minimal”.²⁴ TA781⁴ itself was used for cross validation and CS Table 39² contrasted the CS economic modelling features with those of GID-TA11432/TA1076, a by-now terminated appraisal in the same indication.⁴² Further, instead of providing face validation of the current data and CS choices via another advisory board meeting, an informal call with one clinical expert¹⁹ and the 2021 advisory meeting summary related to TA781⁴³ were submitted. The EAG considers the minimal inclusion of expert opinion with regard to the updated evidence as well as face validity assessment of the CE inputs and assumptions as a substantial weakness of the current CS.
- e) Although requested, no further cross validations with other relevant NICE TAs, including but not limited to those focussing on the broader (previously treated) locally advanced or metastatic NSCLC population, were provided, citing time constraints. The company was unable to compare results to published literature, citing non-UK settings and country-specific unit costs.

Acknowledging these valid arguments, the EAG nevertheless would have appreciated to be able to gain a deeper understanding by having access to the identified published literature, despite divergences in scope. This was deemed particularly of relevance as few sources for external validation of the health economic analyses existed, namely the CAS RWE (which the EAG assumes to overall capture UK clinical practice) used for the CS base-case, and CodeBreak 200 commissioned by the company with a data cut-off in 2022. The company confirmed that “direct external validation of final outcomes was limited”.⁷

5.2 EAG’s additional analyses

5.2.1 *Exploratory and sensitivity analyses undertaken by the EAG*

Table 5.4 summarises the key issues related to the CE categorised according to the sources of uncertainty as defined by Grimm et al., 2020:⁴⁴

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the DP and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 5.4 lists suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al., 2016):

- Fixing errors (FE) (correcting the model where the company’s submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

5.2.2 *EAG base-case*

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 5.2. shows how individual adjustments impact the results plus the combined effect of all adjustments simultaneously, resulting in the EAG base-case.

5.2.2.1 Fixing errors

- No fixing errors.

5.2.2.2 Fixing violations

- Modelling of drug acquisition costs (Section 4.2.8).

Use per pack costing instead of per treatment day costing approach for the modelling of sotorasib and docetaxel drug acquisition costs.

5.2.2.3 Matters of judgement

- Modelling of sotorasib and docetaxel OS (Section 4.2.5).

Use individually fitted gamma from CodeBreak 200 instead of jointly fitted generalised gamma from CAS RWE for sotorasib OS, and use crossover-adjusted HR from CodeBreak 200 instead of jointly fitted generalised gamma from CAS RWE for docetaxel OS.

- Modelling of sotorasib and docetaxel PFS (Section 4.2.5).

Use individually fitted log-logistic from CodeBreak 200 instead of jointly fitted generalised gamma from CAS RWE for both sotorasib and docetaxel PFS.

- Modelling of sotorasib and docetaxel TTD(D) (Section 4.2.5).

Use time-varying HRs from CodeBreak 200 estimating TTD(D) from CodeBreak 200 instead of individually fitted generalised gamma from CAS RWE for both sotorasib and docetaxel TTD(D).

- Modelling of treatment waning (Section 4.2.5).

Include treatment waning starting at 2 years with a gradual decline over 5 years.

- Modelling of utility values (Section 4.2.7).

5.2.3 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analysis to explore the impact of alternative assumptions conditional on the EAG base-case.

- Modelling of RDI (Section 4.2.8)

Use median instead of mean RDI from CodeBreak 200 for sotorasib and docetaxel.

5.2.4 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 5.4: Overview of key issues related to the CE

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Missing subgroup analyses	4.2.3	Bias & indirectness	Perform subgroup analyses using available data from CodeBreaK 200	+/-	No	Additional subgroup analyses from CodeBreaK 200 address this key issue
Non-randomised study to inform the treatment effectiveness of sotorasib and docetaxel	4.2.5	Methods, bias & indirectness	Use the CodeBreaK 200 RCT to inform treatment effectiveness	+	Partly	Conduct a risk of bias assessment for the non-randomised study using ROBINS-I to better inform the selection of the source to inform treatment effectiveness in the economic model
Incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreaK 200	4.2.5	Transparency	Details of all criteria from NICE DSU TSD 14 and 21 guidance for OS and PFS for CodeBreaK 200, separately for sotorasib and all relevant comparators	+/-	No	The potential misclassification of TTD(D) in CAS RWE cannot be solved. For the modelling of TTD(D) directly by fitting parametric survival curves to the observed TTD(D) data in CodeBreaK 200, the analyses requested by the EAG in clarification question B10 should be provided
Issues related to the modelling of TTD(D)	4.2.5	Methods, bias & indirectness	Inform TTD(D) directly by fitting parametric survival curves to the observed TTD(D) data in CodeBreaK 200	+	No	The analyses requested by the EAG in clarification question B10 should be provided
Insufficient justification for treatment waning assumptions	4.2.5	Transparency and methods	Additional justification and evidence that assesses treatment	+	No	The justification and analyses requested by the EAG in clarification question B9 should be provided

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			waning in the observed data			
Suboptimal approach for the estimation of utility values	4.2.7	Methods	Informing HSUVs with a full model including (but not limited to) treatment arm, disease progression, and time-to-death	+/-	No	Results of a fully fitted model informing health state utilities. This approach can incorporate a disutility penalty based on (continuous) time-to-death weighted at each cycle. Full model results including details regarding covariate selection, coefficients (and associated 95% CIs) and full model diagnostics should be provided
Use of treatment-dependent utilities	4.2.7	Methods	Results of a full regression model that explored treatment group as a covariate	+	No	Results of a fully fitted model informing health state utilities. This approach can incorporate a disutility penalty based on (continuous) time-to-death weighted at each cycle. Full model results including details regarding covariate selection, coefficients (and associated 95% CIs) and full model diagnostics should be provided
Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes	4.2.7	Methods	Use the NICE reference mapping function	+/-	No	Use the NICE reference mapping function
Suboptimal approach for the modelling of the acquisition costs	4.2.8	Methods	Use a per pack costing approach for sotorasib, in line with the NICE	+	Yes	Use a per pack costing approach for sotorasib, in line with the NICE process and methods guide

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
			process and methods guide			
Transparency issues related to insufficient responses to the clarification questions posed by the EAG	5.2.1	Transparency	Share information requested during clarification phase	+/-	No	Share information requested during clarification phase
^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator ^b Explored CAS = Cancer Analysis System; CE = cost effectiveness; DSU = Decision Support Unit; EAG = Evidence Assessment Group; HSUV = Health State Utility Value; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; ROBINS-I = Risk Of Bias In Non-randomised Studies - of Interventions; RWE = real-world evidence; TSD = Technical Support Document; TTD(D) = time to treatment discontinuation (or death)						

5.2.5 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 5.2.2 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 5.5 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 5.5. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the “EAG” sheet provides an overview of the cells that were altered for each adjustment).

Table 5.5: Deterministic/probabilistic 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								
CS base-case								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£44,669	-0.53	-0.21
				1.2	████	£37,224	-0.45	-0.12
				1.7	████	£26,276	-0.23	0.09
EAG_1 FV: per pack costing approach for docetaxel and sotorasib acquisition costs (per treatment day in CS base-case)								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£47,653	-0.60	-0.25
				1.2	████	£39,711	-0.51	-0.17
				1.7	████	£28,031	-0.29	0.05
EAG_2 MJ: individually fitted Gamma from CodeBreaK 200 for sotorasib OS (jointly fitted generalised Gamma from CAS RWE in CS base-case) and crossover-adjusted HR from CodeBreaK 200 for docetaxel OS (jointly fitted generalised Gamma from CAS RWE in CS base-case)								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£84,188	-0.71	-0.40
				1.2	████	£70,157	-0.67	-0.36
				1.7	████	£49,522	-0.56	-0.25
EAG_3 MJ: individually fitted log-logistic from CodeBreaK 200 for sotorasib and docetaxel PFS (jointly fitted generalised Gamma from CAS RWE in CS base-case)								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	████	██████	1.0	████	£43,883	-0.52	-0.20
				1.2	████	£36,569	-0.43	-0.11

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
				1.7	████	£25,813	-0.21	0.10
EAG_4 MJ: HR estimated using PFS and time on treatment from CodeBreaK for sotorasib and docetaxel TTD (individually fitted generalised Gamma from CAS RWE in CS base-case)								
Docetaxel	████	████	-	-	-	-	-	-
Sotorasib	████	████	████	1.0	████	£56,799	-0.80	-0.39
				1.2	████	£47,333	-0.71	-0.30
				1.7	████	£33,411	-0.49	-0.08
EAG_5 MJ: include treatment waning starting at 2 years with gradual decline over 5 years (no treatment waning in CS base-case)								
Docetaxel	████	████	-	-	-	-	-	-
Sotorasib	████	████	████	1.0	████	£47,132	-0.55	-0.23
				1.2	████	£39,276	-0.47	-0.15
				1.7	████	£27,725	-0.27	0.05
EAG_6 MJ: treatment-independent utilities based on MMRM sotorasib utilities for sotorasib and docetaxel (treatment-dependent utilities based on descriptive analysis in CS base-case)								
Docetaxel	████	████	-	-	-	-	-	-
Sotorasib	████	████	████	1.0	████	£53,468	-0.60	-0.28
				1.2	████	£44,557	-0.53	-0.21
				1.7	████	£31,452	-0.35	-0.03
EAG base-case								
Docetaxel	████	████	-	-	-	-	-	-
Sotorasib	████	████	████	1.0	████	£122,395	-0.68	-0.41
				1.2	████	£101,996	-0.65	-0.38
				1.7	████	£71,997	-0.59	-0.32

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Probabilistic								
CS base-case								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	████████	████████	1.0	████	£45,837	-0.56	-0.23
				1.2	████	£38,198	-0.47	-0.14
				1.7	████	£26,963	-0.26	0.07
EAG base-case								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	████████	████████	1.0	████	£131,445	-0.69	-0.42
				1.2	████	£109,537	-0.67	-0.40
				1.7	████	£77,321	-0.61	-0.33
CAS = Cancer Analysis System; CS = company submission; EAG = External Assessment Group; FV = fixing violation; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MMRM = mixed models for repeated measures; MJ = matter of judgement; 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; WWT = willingness-to-pay								

Table 5.6: Deterministic/probabilistic scenario analyses (conditional on 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								
EAG base-case								
Docetaxel	██████	████	-	-	-	-	-	-
Sotorasib	██████	██████	██████	1.0	████	£122,395	-0.68	-0.41
				1.2	████	£101,996	-0.65	-0.38
				1.7	████	£71,997	-0.59	-0.32

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
EAG_7 Scenario analysis: Median RDI from CodeBreaK 200 for sotorasib and docetaxel (Mean RDI in CS and EAG base-case)								
Docetaxel	████████	████	-		-	-	-	-
Sotorasib	████████	████	████████	1.0	████	£141,553	-0.81	-0.49
				1.2	████	£117,961	-0.78	-0.47
				1.7	████	£83,267	-0.71	-0.40
Probabilistic								
EAG base-case								
Docetaxel	████████	████	-	-	-	-	-	-
Sotorasib	████████	████	████████	1.0	████	£131,445	-0.69	-0.42
				1.2	████	£109,537	-0.67	-0.40
				1.7	████	£77,321	-0.61	-0.33
EAG_7 Scenario analysis: Median RDI from CodeBreaK 200 for sotorasib and docetaxel (Mean RDI in CS and EAG base-case)*								
Docetaxel	████████	████	-		-	-	-	-
Sotorasib	████████	████	████████	1.0	████	-£14,175	0.21	0.18
				1.2	████	-£11,813	0.24	0.21
				1.7	████	-£8,338	0.30	0.27
CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; NHB = net health benefit; QALY = quality-adjusted life-year; RDI = relative dose intensity; WTP = willingness-to-pay.								
*Details regarding the observed discrepancy between deterministic and probabilistic results for EAG_7 are discussed in EAG comment b) in Section 4.2.8								

5.2.6 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1 was £109,537 per QALY gained with a severity modifier of 1.2. The probabilistic EAG base-case analyses indicated CE probabilities of [REDACTED] and [REDACTED] at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were alternative assumptions regarding the choice of clinical source (and parametric survival curves) to inform the modelling of sotorasib and docetaxel OS and the choice of clinical source and approach to inform the modelling of sotorasib and docetaxel TTD. The ICER increased most in the scenario analysis with alternative assumptions regarding RDI for sotorasib and docetaxel.

5.3 Decision modifiers

5.3.1 QALY weighting for severity

A QALY shortfall analysis was performed in line with the NICE manual²⁷ and NICE DSU TSD 23,⁴⁵ using the QALY shortfall calculator⁴⁶ with the reference case,⁴⁷ ONS general population mortality rates from 2017-2019⁴⁸ and general population utility values as well as a discount rate of 3.5%. Time-to-death utilities, as well as patient baseline characteristics from CodeBreak 200 were used as inputs (with treatment effectiveness informed by CAS RWE).

Table 5.7: Summary of the company's QALY shortfall analysis[†]

Treatment	QALY weight	Proportional shortfall	Absolute shortfall
Docetaxel	x1.7	0.9503	10.89
[†] Please note that the average for absolute and proportional shortfall was calculated based on population aged 63 and 64 years old to align with the population in the model (average age of 63.5 years). QALY = quality-adjusted life year			

Table 5.8: Summary of company's assumptions for general population QALY shortfall estimates

Factor	Value	Reference to Section CS
Sex distribution	40.9%	3.2.1 and 3.6
Starting age	63.50	3.2.1 and 3.6
Expected years of life (undiscounted)	0.94	3.6/health economic model
Quality of life by age	Not provided	
Discount rate	3.5%	Clarification question B23
CS = company submission; QALY = quality-adjusted life year		

No relevant subgroups with regard to severity were identified by the company. TA781 does not mention a severity modifier.

EAG comment: The main concern of the EAG relates to uncertainty around the input values for severity calculations.

The EAG noted uncertainty relating to input values for the severity calculation, particularly the source to inform patient characteristics and assumptions related to the modelling of OS and PFS which impact

the remaining QALYs of the untreated. For the EAG, the source for modelled baseline characteristics and the source to inform treatment effectiveness should ideally match. In the CS base-case, however, there is a mismatch between the source of baseline characteristics (CodeBreaK 200) and the source of informing treatment effectiveness (CAS RWE) for the health economic modelling (see EAG comment c) in the EAG report Section 4.2.3). The EAG acknowledges the company's reasoning that some features were not available in CAS RWE, yet the baseline characteristics required for severity calculations are available from CAS RWE² (Table 40), allowing for harmonisation of sources.

There was also uncertainty regarding the modelling of OS and PFS, with the EAG voicing different preferences than the company (EAG report Section 4.2.5). Currently, the company's severity modifier is 1.7. If both patient baseline characteristics and effectiveness evidence were taken from CAS RWE, a severity modifier of 1.2 would apply. Furthermore, the company presented additional analyses aligning populations and efficacy sources (albeit for CodeBreaK 200, Flatiron 2L+ US RWE was used to adjust for crossover in docetaxel OS) (⁷, Table 11), as well as using utility values based on progression,⁷ (Table 12), consistently resulting in a severity modifier of 1.2.

Following the EAGs preference of using CodeBreaK 200 as its source for the modelling of baseline characteristics and treatment effectiveness, as well as different preferences related to the modelling of OS and PFS for sotorasib and docetaxel, a severity modifier of 1.2 was applicable for the EAG base-case. Nevertheless, the EAG also reported its results (Section 5.2) including severity modifiers of 1.0 and 1.7 in light of the aforementioned uncertainties.

5.3.2 *Uncaptured benefits*

No uncaptured benefits have been proposed by the company.

5.3.3 *Health inequalities*

No information has been presented by the company about health inequalities.

5.4 Conclusions of the CE section

The CS, Appendices E, F and G and response to clarification^{2, 7, 8} provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in patients with metastatic KRAS-mutated NSCLC. Searches were conducted February 2020 and updated in January 2021 and March 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases and conference proceedings were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The company's CE model partly complied with the NICE reference case. Deviations from the NICE reference case related to the use of a different function for the mapping EQ-5D-5L to EQ-5D-3L outcomes and the use of a different approach for the modelling of the acquisition costs for oral treatments. The most prominent issues highlighted by the EAG are reported in the key issue tables in Section 1.3.

Firstly, various subgroup analyses listed in the final NICE scope were not provided, which the EAG considers an important limitation as differences in baseline risks, HRQoL, resource use, and cost could all impact CE, even if relative efficacy is similar. Secondly, the company used the non-randomised CAS RWE study to inform treatment effectiveness in their economic model, risking bias due to observed

imbalances, and unobserved imbalances (e.g. unknown KRAS G12C mutation and brain metastasis status) between treatments. The EAG alternatively prefers using the CodeBreaK 200 RCT to inform treatment effectiveness, for which selecting the appropriate parametric survival curves was jeopardised by incomplete information. The EAG also prefers CodeBreaK 200 to inform TTD(D) in its base-case, as TTD(D) in CAS RWE (company preference) was an indirectly estimated exploratory endpoint which potentially resulted in misclassification of TTD(D). Thirdly, the EAG considers the company's assumption of no treatment effect waning (based on the statement that the length of patient follow-up in CAS RWE was sufficient to capture any decline in treatment effectiveness) a strong assumption given the available evidence on (the longevity of) the relative effectiveness of sotorasib versus docetaxel. Evidence and justification for treatment waning in CodeBreaK 200 was not provided by the company, but considering its relative immature data and the converging trend of cumulative hazards for OS, the EAG implemented treatment waning in line with the ERG's preferred approach in TA781 in its base-case. Fourthly, there were several issues related to the estimation of utility values. The company did not use the mapping algorithm recommended by the NICE reference case, and it modelled treatment dependent utility values without providing sufficient evidence and justification. Furthermore, there is uncertainty regarding the approach of modelling utility values, for which the EAG suggested an analysis including a progression-based approach in which disutility penalties are incorporated based on time-to-death that was not provided by the company. Fifthly, sotorasib acquisition costs were modelled per treatment day, which is not in line with the NICE process and methods guide stating that the costs of oral treatments dispensed in tablet packs should be evaluated on a per pack basis. A per pack costing scenario analysis was provided by the company, which the EAG adopted in its base-case. Finally, the company did not comprehensively address a substantial number of questions posed by the EAG in its clarification letter, which is regarded a serious transparency issue by the EAG as it is unable to verify various company assumptions.

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was £109,537 per QALY gained with a severity modifier of 1.2. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of ■■■% and ■■■% at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were alternative assumptions regarding the choice of clinical source (and parametric survival curves) to inform the modelling of sotorasib and docetaxel OS and the choice of clinical source and approach to inform the modelling of sotorasib and docetaxel TTD. The ICER increased most in the scenario analysis with alternative assumptions regarding RDI for sotorasib and docetaxel.

There is large remaining uncertainty about the effectiveness and CE of sotorasib, which can be partly resolved by the company. For CodeBreaK 200, this includes providing additional subgroup analyses, details of NICE DSU TSD 14 and 21 criteria for parametric survival curve selection, analyses directly fitting parametric survival curves to the observed TTD(D) data, additional justification and evidence that assesses treatment waning, and mixed effects regression models and the appropriate mapping algorithm for the estimation of utility values. Additionally, a risk of bias assessment (ROBINS-I) for CAS RWE and any remaining lacking responses and analyses in response to clarification should be provided. Therefore, according to the EAG, the CS nor the EAG report contains an unbiased estimate of sotorasib compared with docetaxel.

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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]**

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 9 September 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **'confidential'** should be highlighted in turquoise and all information submitted as **'depersonalised data'** in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Factual inaccuracy. “In addition, the EAG clinical expert stated that he agreed with the exclusion of docetaxel as a comparator. “ Page 30	We believe the EAG intended for this to read “In addition, the EAG clinical expert stated that he agreed with the exclusion of docetaxel and nintedanib as a comparator. “	Both EAG and Company agree that docetaxel is the appropriate comparator.	Corrected. In addition the EAG has changed ‘nintedinib with docetaxel’ to docetaxel with nintedinib’ throughout the report.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Extraneous word in a sentence. “This was a comparative, retrospective, new-user cohort study using the CAS database in England to generate evidence on the comparative effectiveness of	Remove unrequired “in”. “This was a comparative, retrospective, new-user cohort study using the CAS database in England to generate evidence on the comparative effectiveness of sotorasib monotherapy in 2L+ patients with locally advanced or metastatic NSCLC who have previously	Clarity of meaning.	Corrected.

sotorasib monotherapy in 2L+ <u>in</u> patients with locally advanced or metastatic NSCLC who have previously been treated with platinum-doublet chemotherapy and/or PD 1/PD-L1 targeted immunotherapy.” Page 40.	been treated with platinum-doublet chemotherapy and/or PD 1/PD-L1 targeted immunotherapy.”		

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Factual inaccuracy. “In conclusion, the fact the CAS RWE study is not a RCT, and lack of access to patient-level data raise doubts as to its validity in estimating the effectiveness of sotorasib versus <u>nintedanib</u>, which indicates a key issue.”	We believe the EAG intended for this to read “In conclusion, the fact the CAS RWE study is not a RCT, and lack of access to patient-level data raise doubts as to its validity in estimating the effectiveness of sotorasib versus <u>docetaxel</u>, which indicates a key issue.”	Clarity of meaning	Corrected.

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Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG is of the opinion that there is a lack of transparency around the CAS analysis. “However, the EAG notes that the company did not have access to patient-level data, relying instead on outputs from the original CAS analysis. This lack of direct access limits transparency, reproducibility, and the ability to test alternative modelling assumptions (e.g. uncensored follow-up, different parametric forms), thereby increasing uncertainty around the	The company disagrees with the EAG and would appreciate an acknowledgement that there is enough detail in the Technical report for the CAS RWE study for independent researchers to reproduce the analysis carried out.	Any amendment which more accurately reflects the ownership and availability of data and analysis is appreciated and should be made clear in the EAG report.	Not a factual inaccuracy. The EAG do not criticise the company for lack of access to the individual patient data, but instead identify the lack of access to the individual patient data as a potential problem given the inherent challenges of using real world evidence as opposed to a randomised controlled trial.

reliability of the comparative effectiveness estimates.”			
Page 46 (and elsewhere)			

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incomplete sentence “This potentially the source of patient characteristics has potentially implications for the severity modifier (see Section 5.3 of this report).” Page 88	Provide the missing word(s) “This potentially (<u>sic</u>) the source of patient characteristics has potentially implications for the severity modifier (see Section 5.3 of this report).”	Clarity of meaning	Amended.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Incomplete sentence “The EAG noted uncertainty relating to input values for the severity calculation, particularly the source to	Provide the missing word(s) “The EAG noted uncertainty relating to input values for the severity calculation, particularly the source to inform patient	Clarity of meaning	Amended.

inform patient characteristics and assumptions related to the modelling of OS and PFS which impact the input of the remaining QALYs of the untreated.” Page 120/1	characteristics and assumptions related to the modelling of OS and PFS which impact the input of the remaining QALYs of the untreated <u>(sic)</u> .”		

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG suggests that the PFS results for CAS RWE are inflated relative to those for CB200. “The company make a good case for using proxies given that PFS was not available in the CAS RWE. However, it should be noted that using the CAS RWE led to a larger treatment effect than using PFS from the CodeBreak 200 trial i.e. hazard ratio (HR) of HR: 0.567; 95% CI: 0.485,	It should be remembered that the CAS RWE data set uses TTNT(D) as a proxy for PFS (since formal disease progression is rarely recorded in practice). The sensitivity analysis of PFS (as assessed by BICR) in CB200 (Table 26 of the CS and Table 3.10 on page 59 of the EAG report) includes an analysis of PFS where initiation of a new anticancer therapy is treated as a PFS event. The company believes that this is the appropriate outcome for	Consistency of comparisons of patient outcomes in CAS RWE and the pivotal RCT CB200.	Not a factual inaccuracy. It is true that the sensitivity analysis where initiation of a new anticancer therapy is counted as a PFS event is more favourable for sotorasib. However, the company submission made no explicit justification for preferring this analysis over the primary analysis.

0.663; p<0.001) instead of 0.663 (95% CI 0.509, 0.864), and there seems to be little justification for believing that the treatment effect on PFS in the trial would be biased.” Page 20 (and elsewhere)	comparison between the two sources of evidence. This HR [0.599 (0.474, 0.757)] is well aligned with the HR for TTNT(D) in CAS RWE [0.567 (0.485, 0.663)].		

(please cut and paste further tables as necessary)

Location of incorrect marking	Description of incorrect marking	Amended marking
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

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

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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on 24 November 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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

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About you

Table 1 About you

Your name	Katie Breslin
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Amgen UK
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.	Not Applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Technical engagement response form

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

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Uncertainty as whether docetaxel with nintedanib is a comparator.	No	Amgen is pleased that the External Assessment Group (EAG) (and their clinical expert) agrees with our position that nintedanib in combination with docetaxel is NOT a relevant comparator for this appraisal. This is in line with the opinion and position of clinical experts, who reported that there is very limited use of docetaxel plus nintedanib in the UK, and that there is no meaningful regional variation in use of docetaxel plus nintedanib (Amgen DoF, 2025).

Technical engagement response form

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

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2. Uncertainty as to which of the two main comparative analyses is the most valid.	No	Amgen welcomes the EAG's agreement with our arguments supporting the use of the CAS Real World Evidence (RWE) data set compared to the results of CodeBreakK200 (<i>i.e.</i> <i>there was a high rate of withdrawal from the docetaxel arm of the randomised controlled trial (RCT)</i> <i>there was crossover from docetaxel to sotorasib in the RCT, which might be incompletely adjusted for</i> <i>the CAS RWE study is UK based, efforts were made to ensure recruitment of most patients who received docetaxel in the same population as who received sotorasib, and statistical analyses were conducted to adjust for any remaining differences in prognostic factors/treatment effect modifiers</i> <i>sensitivity analyses were also applied to address uncertainty in analysis population and statistical adjustment</i> We note however the EAG's concern that "<i>there is always the possibility of remaining bias in the CAS RWE study.</i>" We maintain that the CAS RWE analysis is more valid than CodeBreakK200 for comparing sotorasib vs docetaxel in the NHS, for three main reasons: (1) Crossover and dropout bias is eliminated, (2) The data reflect a UK patient population and setting (increasing relevance to NHS practice), and (3) Robust statistical adjustments were applied to account for prognostic differences. We consider that the study exemplifies best practices in RWE generation and directly addresses the EAG's concerns regarding bias, confounding, comparability, and endpoint validity. The introduction of a protocol amendment, driven by the Food and Drugs Administration (FDA), into CodeBreakK200, resulted in significant crossover from docetaxel to sotorasib with 33.9% of docetaxel subjects either crossing over per protocol (onto sotorasib) or receiving commercial KRAS G12C inhibitor. Given this, the unadjusted overall survival (OS) benefit of docetaxel is substantially overestimated. Despite efforts to adjust for this crossover, the OS results produced lack face-validity when compared to other key studies, and the opinion of clinical experts. The decision to commission the CAS RWE study, as well as key elements of its design, were agreed through consultation with both NICE and National Health Service England (NHSE) due to recognised challenges with the docetaxel arm of the CB200 trial. The CAS RWE study is UK-based, efforts were made to ensure recruitment of patients

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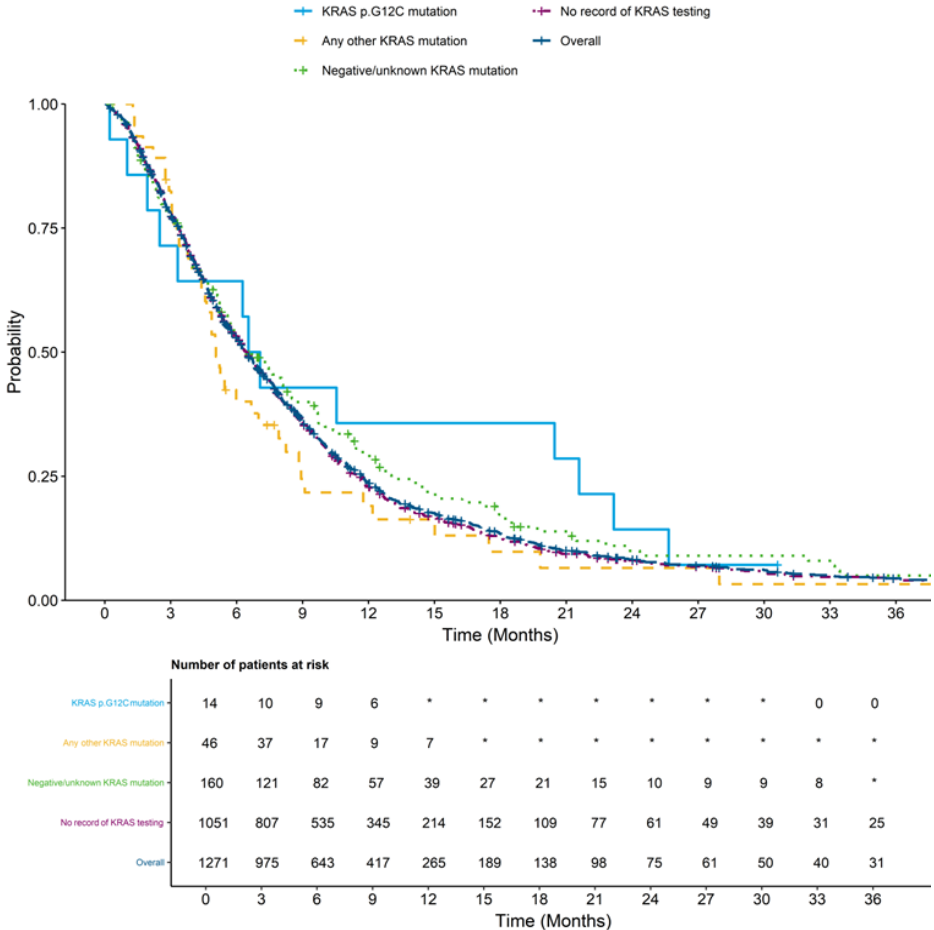
	who received docetaxel in the same population as who received sotorasib and statistical analyses were conducted to adjust for remaining differences in prognostic factors /effect modifiers, As described in our response to Issue 4, we have completed not only the quality assessment results for CAS RWE in the original CS (Table 24, as provided in the submission document template from NICE), but also complied with the EAG's request for an additional critical appraisal of that study using the ROBINS-I tool (Appendix A). Use of either of these tools suggests an overall low-moderate risk of bias for the CAS RWE. There are two main structural limitations associated with the CAS dataset; mutation status of patients receiving docetaxel and smoking history of all patients. These limitations are likely to have a very minor impact on the results. 1. Data for patients who received docetaxel is derived from patients with a <i>KRAS</i> unknown status. This is inevitable given the routine use of genetic testing for <i>KRAS G12C</i> mutations is dependent on the wide availability of a recognised targeted therapy for that mutation. Thus, patients potentially eligible for inclusion in the CAS RWE study before the availability of sotorasib, via the Cancer Drugs Fund (CDF) in 2022, would NOT be routinely tested for the <i>KRAS</i> mutation. Similarly, patients who were diagnosed AFTER the introduction of sotorasib to the NHS (either through enrolment to a clinical study, acceptance onto an early access scheme or following reimbursement on the CDF) would be highly likely to receive sotorasib. Furthermore, as described in the CS (Section 1.3.1.2.1, page 22-29), the relative efficacy of non-targeted therapies (such as docetaxel) in <i>KRAS</i> mutant positive patients is unclear (as illustrated by the results from the CAS RWE study presented in Figure 1). Clinical experts consulted on this issue (Amgen DoF, 2025) noted while <i>KRAS</i> mutation status may have prognostic influence, it is heavily confounded by smoking history, co-mutation patterns, and comorbidities. It is not a consistent independent predictor of outcomes with standard-of-care chemotherapy. Therefore, it is unclear whether outcomes data for <i>KRAS</i> unknown patients in CAS RWE study represent an accurate or conservative estimate of outcomes for <i>KRAS G12C</i> patients and the <i>KRAS</i>-unknown docetaxel group remains an acceptable comparator for real-world outcome estimation.

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Figure 1 - Unweighted KM plot for OS among patients who initiated docetaxel monotherapy, overall and stratified by *KRAS* mutation status



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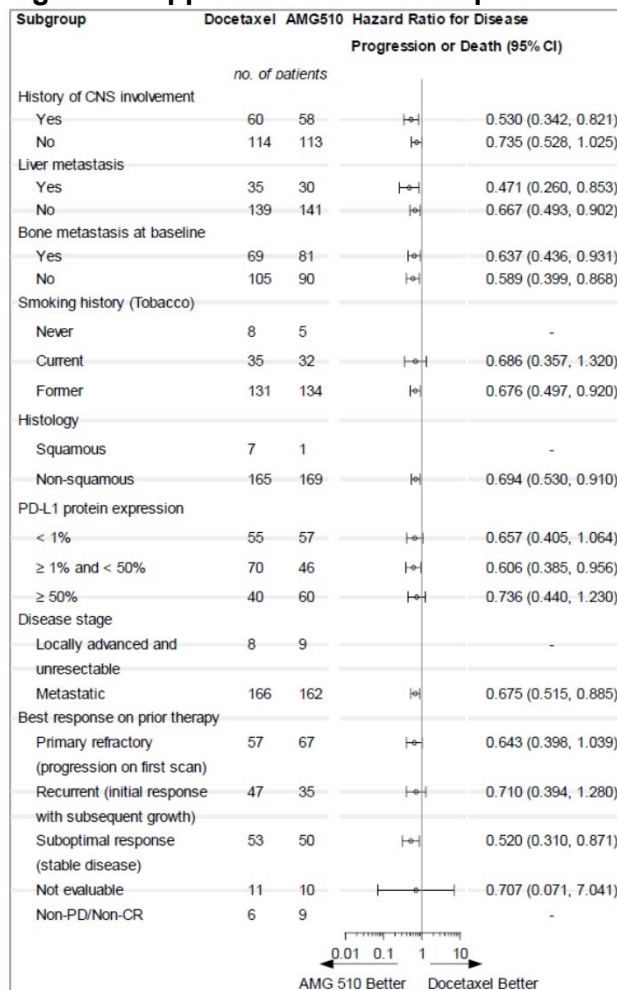
		2. Smoking history is not recorded in the CAS dataset (or any other affiliated sources: SACT, ONS, etc). Smoking history has the potential to be an unmeasured confounder in the CAS RWE study, however there is no evidence that smokers and non-smokers have different outcomes with docetaxel or sotorasib. The CS presented a subgroup analysis of progression free survival (PFS) by Blinded Independent Committee Review (BICR) from CodeBreakK200 (CS Figure 8, Appendix C.1.1, Figure 2 below) which suggests similar hazard ratios for current vs former smokers (never smokers were too small a subgroup to measure). Clinical experts have also noted that omission of smoking history does not materially affect comparative validity and that CodeBreakK200 demographics confirm high smoking prevalence in <i>KRAS G12C</i> patients (Amgen DoF, 2025) Finally, it is also worth noting that smoking history in lung cancer patients is highly likely to be correlated with programmed death-ligand 1 (PD(L)-1) expression and eligibility for appropriate immunotherapy (Zaleskis 2021). Prior immunotherapy treatment was recorded in the CAS RWE study (via Systemic Anti-Cancer Therapy [SACT]) and was adjusted for in analyses.

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Figure 2 - Appendix C.1.1: Forest plot of subgroup analyses of PFS as assessed by the BICR (FAS)



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		Abbreviations: AMG 510, sotorasib; BICR, blinded independent central review committee; CI, confidence interval; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival. Notes: Randomisation stratification factors are number of prior lines of therapy in advanced disease (1 vs 2 vs ≥ 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). Hazard ratios and 95% CIs are estimated using a stratified Cox proportional hazards model. A hazard ratio <1.0 indicates a lower average event rate and a longer PFS for sotorasib relative to docetaxel. History of CNS involvement is the presence of brain metastasis at baseline. If number of subjects in a level of subgroup is less than 10 in any treatment group then only the numbers of events and/or subjects are displayed for that subgroup, but not the inferential statistics. Clinical expert opinion was sought on the use of CAS RWE over CodeBreakK200, including the plausibility of the CAS RWE survival curves (Amgen DoF, 2025). It was validated that the survival curves in CAS RWE align with the expectations of UK practice, supporting its suitability as an external benchmark for docetaxel outcomes. We maintain that CAS RWE serves as the most appropriate evidence base for decision-making, supported by the consistent OS benefit (hazard ratio [HR] = 0.63), comparable with both the US RWE study (FLATIRON, HR = 0.65) and the MAIC analysis of CodeBreakK100 and SELECT-1 (which informed TA781, HR = 0.61) (see Figure 3).

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		Figure 3 - Overall survival for sotorasib vs docetaxel across studies Overall Survival Sotorasib vs. docetaxel <table border="1"> <thead> <tr> <th>Study</th> <th>Hazard Ratio</th> <th>HR [95% CI]</th> </tr> </thead> <tbody> <tr> <td>CodeBreakK 100 vs. SELECT-1</td> <td></td> <td></td> </tr> <tr> <td>Unadjusted</td> <td>0.65</td> <td>[0.49; 0.87]</td> </tr> <tr> <td>Adjusted (MAIC)</td> <td>0.61</td> <td>[0.45; 0.83]</td> </tr> <tr> <td>CodeBreakK 200</td> <td></td> <td></td> </tr> <tr> <td>Two-stage adjusted</td> <td>0.82</td> <td>[0.41; 1.66]</td> </tr> <tr> <td>US FLATIRON (real-world)</td> <td></td> <td></td> </tr> <tr> <td>2L+ unweighted</td> <td>0.63</td> <td>[0.48; 0.83]</td> </tr> <tr> <td>2L+ weighted</td> <td>0.65</td> <td>[0.49; 0.87]</td> </tr> <tr> <td>UK CAS (real-world)</td> <td></td> <td></td> </tr> <tr> <td>2L+ base case</td> <td>0.63</td> <td>[0.53; 0.74]</td> </tr> </tbody> </table>	Study	Hazard Ratio	HR [95% CI]	CodeBreakK 100 vs. SELECT-1			Unadjusted	0.65	[0.49; 0.87]	Adjusted (MAIC)	0.61	[0.45; 0.83]	CodeBreakK 200			Two-stage adjusted	0.82	[0.41; 1.66]	US FLATIRON (real-world)			2L+ unweighted	0.63	[0.48; 0.83]	2L+ weighted	0.65	[0.49; 0.87]	UK CAS (real-world)			2L+ base case	0.63	[0.53; 0.74]
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3. Missing subgroup analyses.	No	Clinicians consulted by Amgen did not consider any additional subgroups relevant to UK clinical practice or necessary for the appraisal (Amgen DoF, 2025).																																	
4. Non-randomised study to inform the treatment effectiveness of	Yes	The NICE submission template includes critical appraisal tools for the quality assessment of both RCTs and non-randomised or non-controlled studies (Section 2.5 of NICE instructions for completing TA submission template document). These were completed for both CodeBreakK200 [Table 23 in the CS] and CAS RWE [Table 24 in the CS].																																	

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sotorasib and
docetaxel.

At clarification questions, the EAG requested an alternative critical appraisal tool to be completed (the QuEENS checklist) for the CAS RWE study (Priority question A3 4.). Our response to that request was to clearly reference the critical appraisal already provided as part of the submission template and reaffirm to the EAG that:

*“The study design and analytical approaches were informed by the **target trial emulation framework**, which provides a formal methodology for designing studies aimed to estimate causal effects using real-world data and is the **preferred approach of NICE**.” (Our highlighting)*

Nevertheless, in the interests of transparency, using the materials provided in the CS supporting documents (i.e. CAS RWE protocol and report), we have completed a ROBINS-I checklist (Appendix A) and provide a summary of the results here (see Table 1):

Table 1: ROBINS-1 summary results

Risk of Bias Domain	Risk of Bias Level	Likely direction of bias
1. Confounding	Low	
2. Classification of interventions	Low	Favours comparator (docetaxel)
3. Selection of participants	Low	
4. Deviations from intended interventions	Low	
5. Missing data	Serious	Unpredictable
6. Measurement of the outcomes	Low	Unpredictable
7. Selection of the reported result	Low	Unpredictable

This confirms the result of the original critical appraisal in the company submission (CS), which concluded low-moderate risk of bias in CAS RWE study.

Additional, more detailed, discussion of sources of potential bias and the likely magnitude and direction of impact in CAS RWE study is provided in response to Key Issue 2.

A recent report from the HTA Innovation Laboratory (Improving the use of real-world evidence from managed access: the Systemic Anti-Cancer Therapy data set) appears to validate a lot of our methods, approach and preferences concerning

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		the use of data from non-randomised sources such as CAS (HTA Lab project working group, 2025). The DSU was commissioned to expand on a pilot project that examined 4 technology appraisals after CDF exit. By incorporating differences in OS and time-on-treatment between the real-world data and trial outcomes, into economic models through scenario analyses, the DSU demonstrated that using SACT-based results is feasible and can be informative (HTA Lab project working group, 2025). The report concluded that these analyses could support NICE committee decision-making in a number of ways (HTA Lab project working group, 2025): • As a scenario analysis, particularly where SACT data suggests different survival or different time on treatment compared with trial populations. • To inform estimates of likely ICER ranges, helping committees understand how results might vary under real-world conditions. • To supplement trial evidence, especially if trial data is immature or not fully generalisable to NHS populations. • To ensure that managed access data is used meaningfully, adding value to the data collection already built into the CDF process. Furthermore, the authors provided some recommendations on how the collection and use of SACT data could be improved further (HTA Lab project working group, 2025). The collaborative approach to design and execution of the CAS RWE study by Amgen, NICE and NHSE is a proof of principle for future projects.
5. Incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreak 200.	Yes	The EAG outlined that their preferred approach for modelling outcomes to inform the cost-effectiveness model was to utilise CodeBreak200 data for OS and PFS. The EAG selected an OS base case of a gamma model fitted to the sotorasib arm and applied a hazard ratio to model OS in patients randomised to docetaxel (although they preferred to fit individual curves as the proportional hazard assumption was uncertain, EAR, page 95). For PFS the EAG base case was to use individually fitted log-logistic models to each arm. (EAR page 95) We have provided all diagnostic materials requested by the EAG in Appendix B to support their continued decision-making with respect to curve selection and have presented selected important figures here for convenience. Parametric curve selection for OS When reviewing the smoothed hazards for sotorasib and docetaxel plotted against each other (Figure 4) in combination with the log-cumulative hazard plot (as well as other diagnostic plots requested by the EAG and provided in Appendix B), it is clear that the proportional hazards assumption is violated. The smoothed hazard begins apart and starts to converge

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until they are almost equal at approximately 8 months, before diverging again for the remainder of the observed period. Given this it would be inappropriate to utilise jointly fitted survival models or, as the EAG propose in their base case, modelling docetaxel OS by fitting a time-constant hazard ratio to the sotorasib arm. The most robust approach would be to fit separate parametric survival models to each arm individually.

Figure 4: Log-cumulative hazard plot for CodeBreak 200 OS

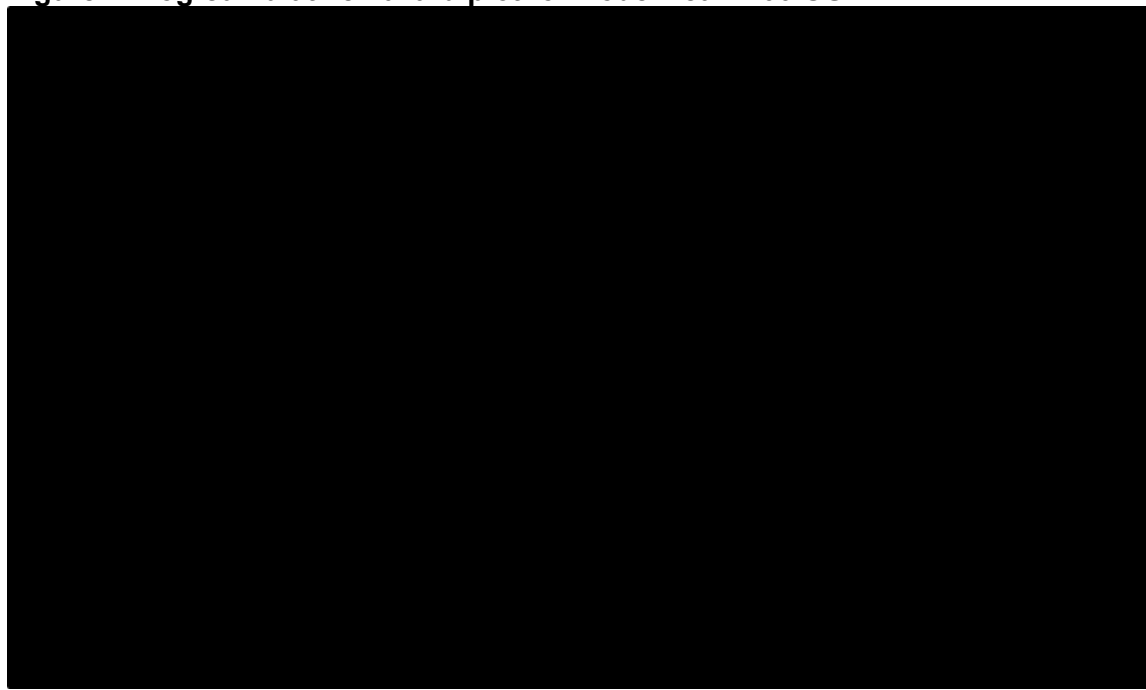
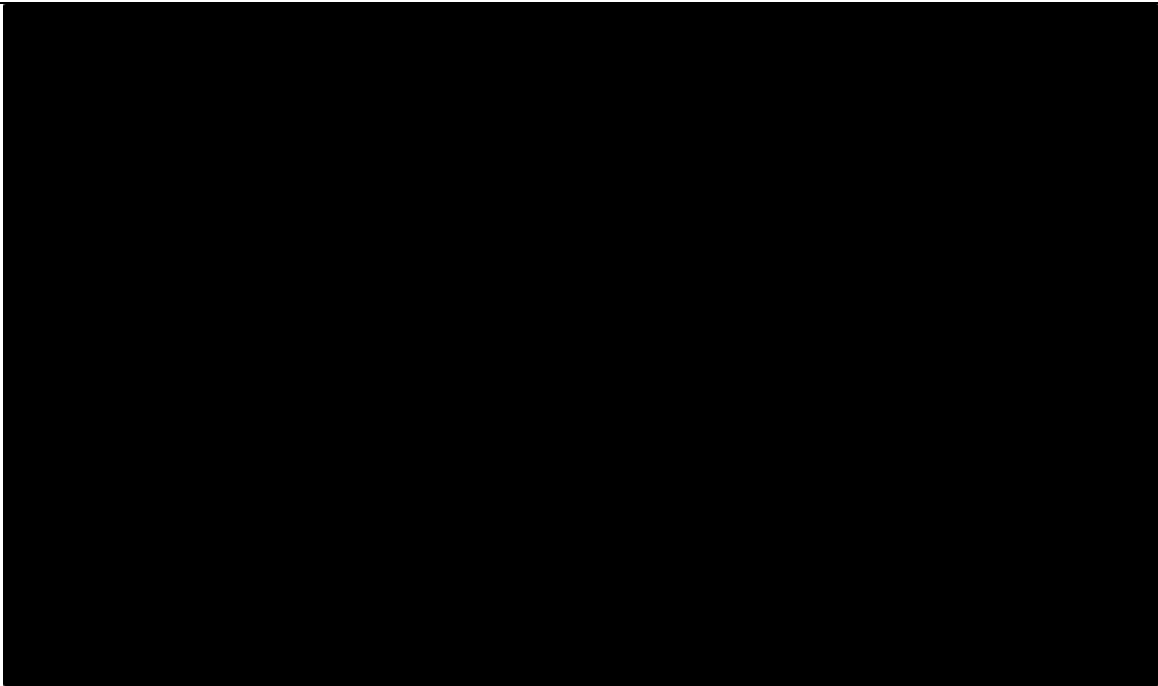


Figure 5: Smoothed hazards by treatment for CodeBreak 200 OS

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The EAG excluded the selection of the survival models with the best statistical fit to the sotorasib data (log-normal, log-logistic and generalised gamma) as they overestimated the 3-year and 5-year estimates of the EAG clinical experts (■■■■ and ■■■■, respectively). The 3- and 5-year survival for each arm are presented in Table 2. While fully respecting the expert opinion on sotorasib outcomes, their 3-year estimate is contradicted by the observed results from the CAS RWE study where 3-year OS was ■■■■ on sotorasib. Beyond 3 years the estimated OS falls by a similar amount to what was predicted by the expert, with each model predicting a drop of ■■■■% between years 3 and 5. This suggests the expert may have provided estimates consistent with CodeBreakK 200 extrapolations if they were aware of the 3-year survival observed in the CAS RWE study. Considering this, we recognise that the ■■■■ 3-year OS modelled by the generalised-gamma may be optimistic, but we do not believe that the log-logistic and log-normal models should be discounted.

Table 2: Landmark OS results by parametric survival model

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Survival model	3-year survival		5-year survival	
	Sotorasib	Docetaxel	Sotorasib	Docetaxel
Exponential	■	■	■	■
Gompertz	■	■	■	■
Weibull (PH)	■	■	■	■
Gamma	■	■	■	■
Gen. Gamma	■	■	■	■
Log-logistic	■	■	■	■
Log-normal	■	■	■	■
CAS RWE study	■	■	-	-
EAG clinical opinion	■	-	■	-

When considering the smoothed hazards of sotorasib and docetaxel versus the models fitted to each arm (Figure 5) we believe that the difference in the hazard profiles of the two treatments is sufficient to justify different models fitted to each arm. The sotorasib hazard is initially lower than the docetaxel hazard, but slowly increases until approximately 8 months where the hazards almost converge. Beyond this point the hazards begin to separate again, the sotorasib hazard has a clear turning point, whereas the docetaxel hazard remains level, if not marginally increases. Reviewing the modelled hazard profiles for sotorasib (Figure 6) and docetaxel (Figure 7) shows that there is not a single distribution that can comply with both observed hazard profiles. The EAG preferred gamma model does not reflect the observed sotorasib hazard, with the gamma modelling a monotonically increasing profile, not one with a turning point. The log-logistic, log-normal and generalised-gamma models provide the best approximation of the sotorasib hazard as they are the only ones to reflect the observed turning point. Whereas in the docetaxel arm, the log-logistic, log-normal and generalised-gamma are not justifiable as there is no evidence that the docetaxel hazard is decreasing. In this instance, the gamma model does provide a good approximation of the hazard profile, as do the Gompertz and Weibull model. An optimistic interpretation of the docetaxel hazard could be that the OS hazard is monotonic and that the exponential model is appropriate.

Figure 6: Smoothed versus modelled hazard for sotorasib CodeBreaK 200 OS

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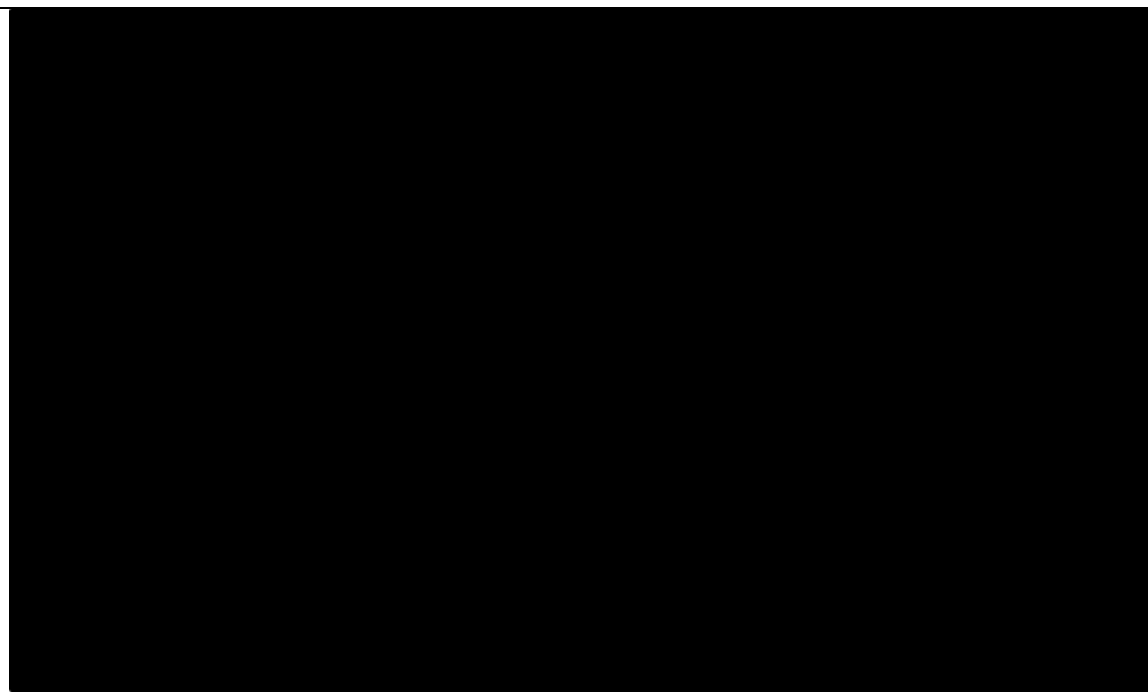
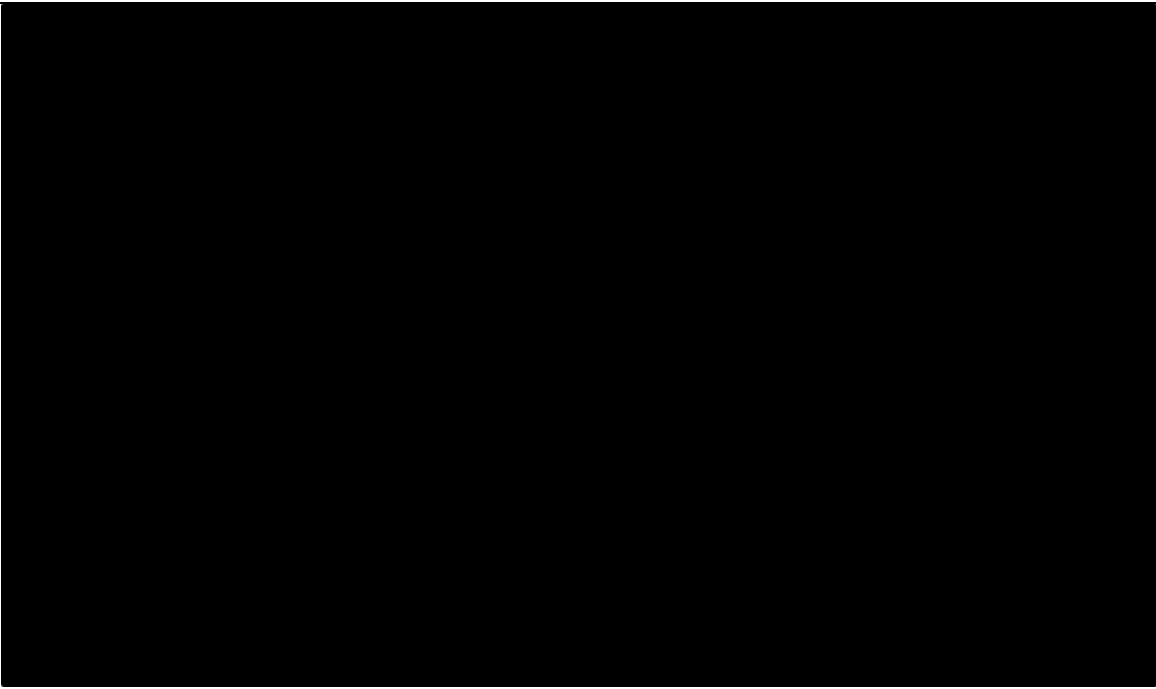


Figure 7: Smoothed versus modelled hazard for docetaxel CodeBreak 200 OS

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		The alignment between the modelled and observed hazards defines a clear group of appropriate models for each arm. For sotorasib it is the generalised-gamma, log-logistic and log-normal. As previously stated, the generalised-gamma provides the most optimistic 3-year OS estimate, although it does best align with the decreasing sotorasib hazard. We consider one of the other two models in our CodeBreakK 200 preferred settings, to provide a conservative estimate for sotorasib. Of the log-logistic and log-normal we prefer the log-normal, which has the better statistical fit. It has a marginally higher 3-year survival estimate than the log-logistic but is slightly lower at 5-years (the difference in both instances is less than 1%).	

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	When selecting a preferred model for docetaxel we excluded the Gompertz as it results in an implausibly low 3-year OS estimate (■■■■), leaving the Weibull and gamma with viable hazard profiles. These two models are almost identical in statistical and observed fit, they provide almost the same long-term estimates and their hazards are equally plausible projections of docetaxel. We propose using the Weibull with the gamma as a logical alternative. Accounting for all the above, in a scenario where CodeBreak 200 is used to appraise the cost-effectiveness of sotorasib, we believe the most appropriate approach to modelling OS would be individually fitted models, with the log-normal fitted to the sotorasib arm and the Weibull fitted to the docetaxel arm. Parametric curve selection for PFS The cost-effectiveness model outcomes are largely insensitive to the survival model used to extrapolate PFS, the CodeBreakK 200 data is mature and therefore the models do not provide significant variations in long-term predictions. Nevertheless, for completeness we have provided the same suite of diagnostics for model selection as OS and conducted a similar model selection process. The proportional hazards assumption appears to be violated, the log-cumulative hazard plot (Figure 8) for each arm come together and then diverge at several points. The smoothed hazards also cross at approximately 12 months (Figure 9). Given the proportional hazards assumption does not appear to hold, it is most appropriate to consider separately fitted models as the EAG has done. Figure 8: Log-cumulative hazard plot for CodeBreakK 200 PFS

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Figure 9: Smoothed hazards by treatment for CodeBreaK 200 PFS

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		 As with OS, when comparing the PFS smoothed hazards to the fitted models it is possible to quickly narrow down an appropriate set of survival models. In the sotorasib arm (Figure 10) the hazard is almost flat, with a slight downward trend as the confidence interval gets wider. This would exclude the models that project a monotonically increasing hazard (Gompertz, gamma or Weibull). The accelerated-failure time models that project a steep initial turning point and then a decreasing hazard (generalised-gamma, log-logistic and log-normal) do not provide a good approximation either. Figure 10: Smoothed versus modelled hazard for sotorasib CodeBreakK 200 PFS

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		 The exponential model appears to provide the best alignment by assuming a constant hazard over time, but it has a poor statistical fit to the data, and it appears to slightly underestimate the PFS. As a conservative estimate, the exponential is appropriate for the extrapolation of sotorasib PFS, with the gamma and log-normal representing pessimistic and optimistic scenarios, respectively. The gamma is the best fitting model with an increasing hazard over time, while the log-normal has the best statistical fit of the models with a decreasing hazard. For the docetaxel arm the smoothed hazard is consistent with the shape provided by accelerated failure time models (Figure 11), a high initial hazard with a turning point and then decreasing thereafter. This excludes the exponential, gamma, Gompertz and Weibull, which all predict constant or increasing hazard over time. Of the three remaining models

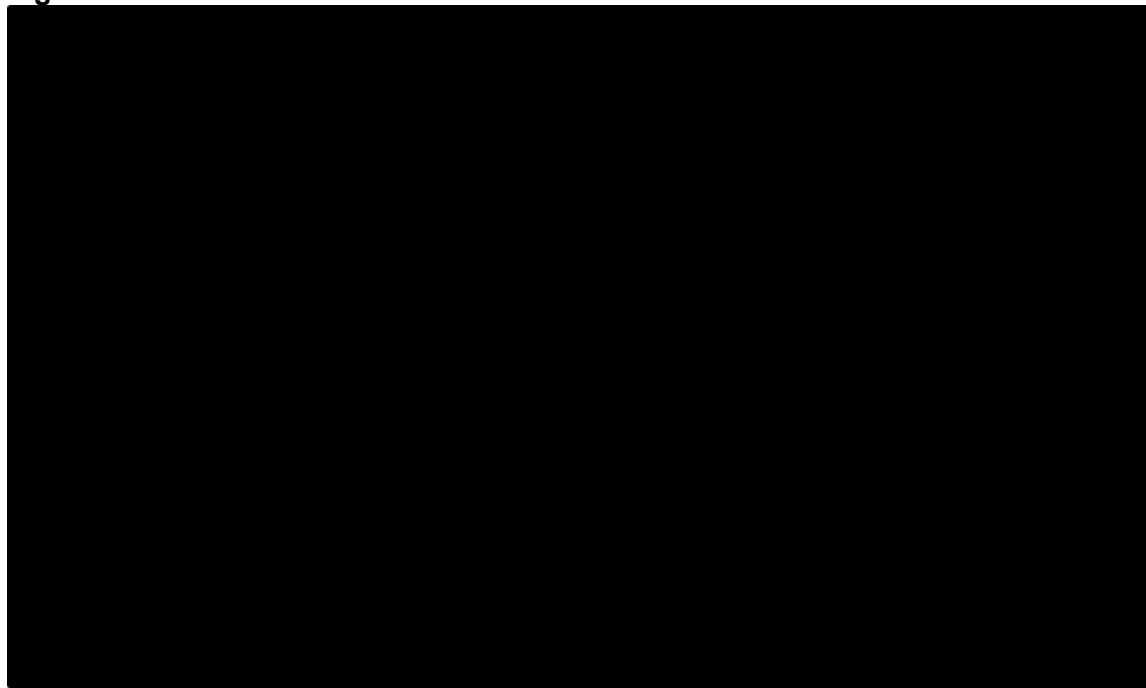
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(generalised gamma, log-logistic and log-normal) the log-logistic provides the best long-term approximation, although the initial peak is slightly overestimated (but within the 95% confidence interval).

Figure 11: Smoothed versus modelled hazard for docetaxel CodeBreakK 200 PFS



Of the models that accurately match the docetaxel profile, they all provide similar long-term estimates (■■■ PFS at 3 years and ■■■ at 5-years). The log-logistic has the best statistical fit and so, with little to choose between the three models, is preferred.

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		In conclusion, when using CodeBreak200 for decision making, we believe that individually fitted models are most appropriate for PFS. Given the difference in hazard profiles, it may be necessary to select different distributions for each arm. We believe an exponential model for sotorasib and a log-logistic model for docetaxel are the most appropriate pair.						
6. Issues related to the modelling of TTD(D).	Yes	In the company’s base-case analysis, parametric survival models were fitted to time to treatment discontinuation or death (TTDD) data derived from CAS RWE. The EAG raised concerns regarding potential misclassification of TTDD in CAS RWE, given that this endpoint was derived indirectly using a line-of-treatment algorithm. However, the risk of material misclassification is considered low due to the robust structure of the CAS dataset, which includes precise cycle start dates for all SACT regimens. This enables an accurate calculation of treatment duration, as the number of recorded treatment cycles per patient is directly known. While end dates are not explicitly recorded in CAS, regimen end dates were systematically derived by estimating the median cycle duration for each unique treatment regimen, calculated as the median time between cycle start dates among patients with at least two recorded cycles, and adding this duration to the last recorded cycle start date for each patient. This consistent method was applied across all regimens and both treatment arms, ensuring that any potential classification error would be non-differential and therefore unlikely to bias comparative results. In scenario analyses, TTDD was alternatively informed using data from the CodeBreak 200 trial. Contrary to the EAG’s understanding, the company did not use a Cox regression or time-varying hazard ratios to estimate TTDD. Instead, TTDD was modelled by applying the observed probability of patients remaining on treatment while in the PF state to the corresponding proportion of patients in that health state (Company response to Clarification Questions, page 39-42). The probabilities of treatment continuation were estimated over three distinct time intervals, less than one month, between one month and one year, and beyond one year, to capture the observed temporal trends in treatment persistence from CodeBreak 200. These intervals were defined to best reflect the empirical relationship between PFS and treatment duration observed in the trial, as shown in Table 3. Table 3: Proportion of Patients Remaining on Treatment (Among PF Patients, Investigator Assessed, CodeBreak 200) <table><tr><th>Timeframe</th><th>Sotorasib</th><th>Docetaxel</th></tr><tr><td>Month 0-1</td><td>■</td><td>■</td></tr></table>	Timeframe	Sotorasib	Docetaxel	Month 0-1	■	■
Timeframe	Sotorasib	Docetaxel						
Month 0-1	■	■						

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		Month 1-12	■	■
		Month 12+	■	■
		Note: The confidence intervals are given in the brackets (Lower bound, Upper bound)		
The EAG's preferred approach, fitting parametric survival curves directly to observed TTDD data from CodeBreak 200, produced results that are not plausible for UK clinical practice. In this approach, the modelled TTDD curve crossed the PFS curve (Figure 12), suggesting that patients were continuing treatment after disease progression. Although the CodeBreak 200 trial allowed patients to continue with sotorasib treatment post-progression, such a pattern is inconsistent with UK clinical practice, as confirmed by the UK CAS data and further validated in our engagements with clinicians. In conclusion it cannot be considered realistic for decision-making. Overall, the company considers the CAS RWE based parametric approach the most reliable and methodologically sound method for modelling TTDD in the base case. The alternative method using the CodeBreak 200 proportion-based approach represents an appropriate scenario analysis that aligns with the observed trial data and avoids the implausible treatment continuation effects observed under the EAG's proposed approach.				
Figure 12: Sotorasib TTD (KM vs modelled)				

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Figure 13: Time-on-treatment from CAS RWE and CodeBreaK200

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Table 4: Time-on-treatment quartiles for docetaxel by study

Quantile	Duration of docetaxel treatment (Months)	
	CAS RWE	CodeBreakK 200
25%	■	■
50% (median)	■	■
75%	■	■

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7. Insufficient justification for treatment waning assumptions.	No	The company considers the assumption of no additional treatment waning on top of the fitted parametric curve in the base case to be appropriate, and evidence based. In the main 2L+ analysis set, the median follow-up time from index date was 8.62 months (Q1–Q3: 4.47–13.90) for the sotorasib cohort and 6.11 months (Q1–Q3: 3.22–10.87) for the docetaxel cohort. Among patients treated with sotorasib (N = 394), 61.2% had died and 19.0% had initiated a new line of therapy during follow-up. In the docetaxel cohort (N = 1,271), 88.8% had died and 17.7% had initiated a new line of therapy. These data indicate sufficient follow-up duration and completeness to capture the treatment effect. There is no evidence from the CAS RWE or clinical trial data to suggest an additional decline in the treatment effect of sotorasib over time. Patients who remained on therapy or in follow-up beyond the median period continued to experience sustained benefit. The observed survival outcomes in the RWE are consistent with those reported in the pivotal clinical trials, supporting the generalisability and reliability of the CAS data (see Figure 3 in response to Key Issue 2). The EAG’s exploratory scenario introducing a gradual decline in treatment effect from two years onwards, extending over five years, produced only a minor increase in the incremental cost-effectiveness ratio (ICER). This indicates that any plausible degree of waning would have minimal impact on cost-effectiveness conclusions. In summary, the company maintains that the assumption of no treatment waning in the base case is appropriate and supported by the available RWE and the limited influence of waning on model outcomes. The EAG retains the flexibility to implement alternative waning assumptions within their scenario analyses if desired.																		
10. Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.	Yes	Key issues 8, 9 and 10 have been presented out of order, starting with Key issue 10, for ease of interpretation. The mapping of EuroQol-FiveDimension-5Levels (EQ-5D-5L) to EQ-5D-3L values was completed in line with methodology provided by the NICE decision support unit (Hernandez-Alava et al., 2022). Applying the UK preferences tariff to derive a utility value for each response, summary statistics have been estimated for the CodeBreakK200 data by progression status and by TTD. Each set of statistics is presented alongside the equivalent values using the Van Hout cross-walk (Van Hout, 2012) for EQ-5D-5L to 3L with the progression-based values presented in Table 5 and the TTD values presented in Table 6. Table 5: Summary statistics by progression status, treatment arm and mapping algorithm <table border="1"> <thead> <tr> <th data-bbox="566 1222 1151 1262">Progression-status</th><th colspan="2" data-bbox="1151 1222 2134 1262">Mean (SE)</th></tr> <tr> <th data-bbox="566 1262 1151 1310"></th><th data-bbox="1151 1262 1563 1310">Van Hout mapping</th><th data-bbox="1563 1262 2134 1310">Hernandez-Alava mapping</th></tr> </thead> <tbody> <tr> <td data-bbox="566 1310 1151 1358">Overall</td><td data-bbox="1151 1310 1563 1358"></td><td data-bbox="1563 1310 2134 1358"></td></tr> <tr> <td data-bbox="566 1358 1151 1406">Sotorasib</td><td data-bbox="1151 1358 1563 1406"></td><td data-bbox="1563 1358 2134 1406"></td></tr> <tr> <td data-bbox="566 1406 1151 1453">Docetaxel</td><td data-bbox="1151 1406 1563 1453"></td><td data-bbox="1563 1406 2134 1453"></td></tr> <tr> <td data-bbox="566 1453 1151 1501">ITT</td><td data-bbox="1151 1453 1563 1501"></td><td data-bbox="1563 1453 2134 1501"></td></tr> </tbody> </table>	Progression-status	Mean (SE)			Van Hout mapping	Hernandez-Alava mapping	Overall			Sotorasib			Docetaxel			ITT		
Progression-status	Mean (SE)																			
	Van Hout mapping	Hernandez-Alava mapping																		
Overall																				
Sotorasib																				
Docetaxel																				
ITT																				

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		Pre-progression - Sotorasib				
		Post-progression - Sotorasib				
		Pre-progression - Docetaxel				
		Post-progression - Docetaxel				
		Key: SE, standard error				
		Table 6: Summary statistics by time-to-death, treatment arm and mapping algorithm				
		Time-to-death - treatment	Mean (SE)			
			Van Hout mapping		Hernandez-Alava mapping	
		≥ 6 months - Sotorasib				
		3 – 6 months - Sotorasib				
		1 – 3 months - Sotorasib				
		< 1 month- Sotorasib				
		≥ 6 months - Docetaxel				
		3 – 6 months - Docetaxel				
		1 – 3 months - Docetaxel				
		< 1 month - Docetaxel				
		Key: SE, standard error				
The Hernandez-Alava mapping function resulted in higher utility values than the Van Hout crosswalk, this result was consistent with findings reported in the literature (Maervoet and Bergemann, 2024). The study by Maervoet and Bergemann reported that utility values were consistently higher (0.01 to 0.09) when using the Hernandez-Alava mapping function and the difference was greatest in groups that were in neither perfect nor extremely poor health, which is consistent with the population for this appraisal. This increase has led to the pre-progression sotorasib value being higher than the age and sex-matched general population utility. The CodeBreak200 population at baseline (63.5 years						

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		old and 41% female) has an expected utility of 0.81 based on the general-population utility estimates (Ara and Brazier, 2010). We consider this inflation to be an artefact of the Hernandez-Alava mapping process and leads to a level of utility that is not consistent with the experience of patients. The Van Hout crosswalk provides utilities that are more closely aligned with the values that were considered appropriate for decision making in TA781 and reflect the consensus on the impact of NSCLC on people's quality of life. For completeness, when deriving the mixed models with repeated measures (MMRM) based utility estimates the analyses have been conducted on both Hernandez-Alava mapped and Van Hout cross-walked values. All the models have then been included in the cost-effectiveness model. In the revised company base case we incorporate utility values using the Van Hout crosswalk to provide an accurate reflection of the experience of people who have NSCLC and to ensure consistency with the original appraisal of sotorasib in TA781.
8. Suboptimal approach for the estimation of utility values.	Yes	In response to this issue a full model specification and covariate selection process has been undertaken. When specifying MMRM models progression, TTD and treatment were considered as relevant covariates for inclusion. The link between progression and quality of life is well established in oncology, recent work has also established the link between time-to-death and utility in non-small cell lung cancer (Hatswell et al., 2023). The impact of treatment on patient quality of life was explored due to indicative evidence in the summary statistics and clinical rationale. The results of mapped EQ-5D-5L surveys completed at baseline in CodeBreak200 suggested that the quality of life among patients in each group was similar. The mean utility value at baseline was [REDACTED] in the docetaxel arm and [REDACTED] in the sotorasib arm, the median utility values were identical ([REDACTED]). The remaining summary statistics then show that the quality of life in each arm diverged after initiation, with a consistent difference between arms across all summary statistics. This quality-of-life improvement for sotorasib patients may be associated with the method of administration, with sotorasib administered orally rather than by intravenous infusion, or the reduced rate of treatment-related adverse events. The following specifications were explored with and without treatment covariates: • Progression • TTD as a categorical variable with the levels presented in Table 6 • TTD as a continuous variable on the natural log scale – log(TTD)

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- TTD as a continuous variable transformed using $1/\sqrt{TTD}$

For modelling TTD as a continuous variable, $\log(TTD)$ and $1/\sqrt{TTD}$ transformations were investigated. These were the best fitting transformation in the preeminent publication on continuous TTD (Hatswell et al., 2023). The paper does recommend widening the number of candidate models tested to identify the best approach, however using the best transformations from the study was considered a pragmatic solution given the time to develop responses was limited. The EAG requested that a model incorporating both progression and TTD be explored, this was not carried out as it is not possible to implement the outcomes within the cost-effectiveness model. It is not known whether patients within the progression-free state of the cost-effectiveness model are transitioning to the post-progression or death state, due to the structural assumptions underpinning a partitioned survival model. This means that TTD within the progression-free health state cannot be established. It would not be possible to implement in a state-transition model either, as specific patients are not tracked when they transition between the progression-free and post-progression states. This means TTD could not be established for patients that are progression-free and then go on to die in the post-progression state.

The detailed model fitting and selection of best-fitting specification is described in detail in Appendix C. Akaike Information Criterion (AIC) was used to assess the statistical fit of model specifications to the observed data. It should be noted that the progression and TTD models cannot be compared using AIC as they utilise different datasets. The AIC of each specification is reported in Table 7, for both the Van Hout mapped cross walked data and the Hernandez-Alava mapped data.

Table 7: Statistical fit of MMRM specifications

Model specification	AIC for models fitted to Van Hout mapped data	AIC for models fitted to Hernandez-Alava mapped data
Progression	-3228.78	-4099.78
Progression + treatment	-3233.76	-4108.09
Categorical TTD	-851.99	-1097.33
Categorical TTD + treatment	-858.56	-1106.47
Continuous TTD as $\log(TTD)$	-867.30	-1113.70

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		<table><tr><td>Continuous TTD as log(TTD) + treatment</td><td>-874.21</td><td>-1123.11</td></tr><tr><td>Continuous TTD as $1/\sqrt{TTD}$</td><td>-831.41</td><td>-1070.30</td></tr><tr><td>Continuous TTD as $1/\sqrt{TTD}$ + treatment</td><td>-837.84</td><td>-1079.30</td></tr></table>	Continuous TTD as log(TTD) + treatment	-874.21	-1123.11	Continuous TTD as $1/\sqrt{TTD}$	-831.41	-1070.30	Continuous TTD as $1/\sqrt{TTD}$ + treatment	-837.84	-1079.30																							
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Continuous TTD as $1/\sqrt{TTD}$ + treatment	-837.84	-1079.30																																
		The results presented in Table 7 unanimously demonstrate the improved statistical fit of the MMRMs when a treatment covariate is included. Considering this and the clinical rationale for patients on sotorasib to have a better quality of life than those on docetaxel, the specifications including a treatment covariate were preferred for modelling utility values. As discussed previously in response to Key Issue 10, the Van Hout crosswalk is preferred to the Hernandez-Alava mapping as it produces utility values that are consistent with the previous appraisal of sotorasib and the experience of people with NSCLC. The TTD approach is preferred to progression-based modelling as it has been shown to more closely reflect the deterioration in quality of life than progression-based modelling (Hatswell et al., 2020). The continuous TTD models are preferred to the categorical approach, aligning with the EAG’s preference. Of the continuous specifications, the log(TTD) transformation has the best statistical fit to the data, however it produces sotorasib estimates that exceed the age- and sex-matched general population (0.829) estimates for any TTD that exceeds 16 months. This was considered to be implausible and therefore the $1/\sqrt{TTD}$ was investigated as a plausible base case model for estimating patient utility. The $1/\sqrt{TTD}$ transformation produces plausible utility estimates that are broadly consistent with the MMRM estimated by categorical TTD. Table 8 presents the utility values previously presented in response to clarification question B15, while Figure 14 plots utility values over time for each treatment arm. Using the continuous measure the sotorasib utility value peaks at approximately ■■■, with the highest docetaxel value being ■■■. Table 8: MMRM utility analysis by categorical TTD <table><tr><th>Treatment arm</th><th>Time-to-death</th><th>Estimate</th><th>SE</th><th>p-value</th><th>Lower CI</th><th>Upper CI</th></tr><tr><td rowspan="4">Sotorasib</td><td>Intercept (i.e., Time-to-death > 6 months)</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td></tr><tr><td>Time-to-death- Below 1 month</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td></tr><tr><td>Time-to-death -Between 1 and 3 months</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td></tr><tr><td>Time-to-death -Between 3 and 6 months</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td><td>■■■</td></tr></table>	Treatment arm	Time-to-death	Estimate	SE	p-value	Lower CI	Upper CI	Sotorasib	Intercept (i.e., Time-to-death > 6 months)	■■■	■■■	■■■	■■■	■■■	Time-to-death- Below 1 month	■■■	■■■	■■■	■■■	■■■	Time-to-death -Between 1 and 3 months	■■■	■■■	■■■	■■■	■■■	Time-to-death -Between 3 and 6 months	■■■	■■■	■■■	■■■	■■■
Treatment arm	Time-to-death	Estimate	SE	p-value	Lower CI	Upper CI																												
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	Time-to-death- Below 1 month	■■■	■■■	■■■	■■■	■■■																												
	Time-to-death -Between 1 and 3 months	■■■	■■■	■■■	■■■	■■■																												
	Time-to-death -Between 3 and 6 months	■■■	■■■	■■■	■■■	■■■																												

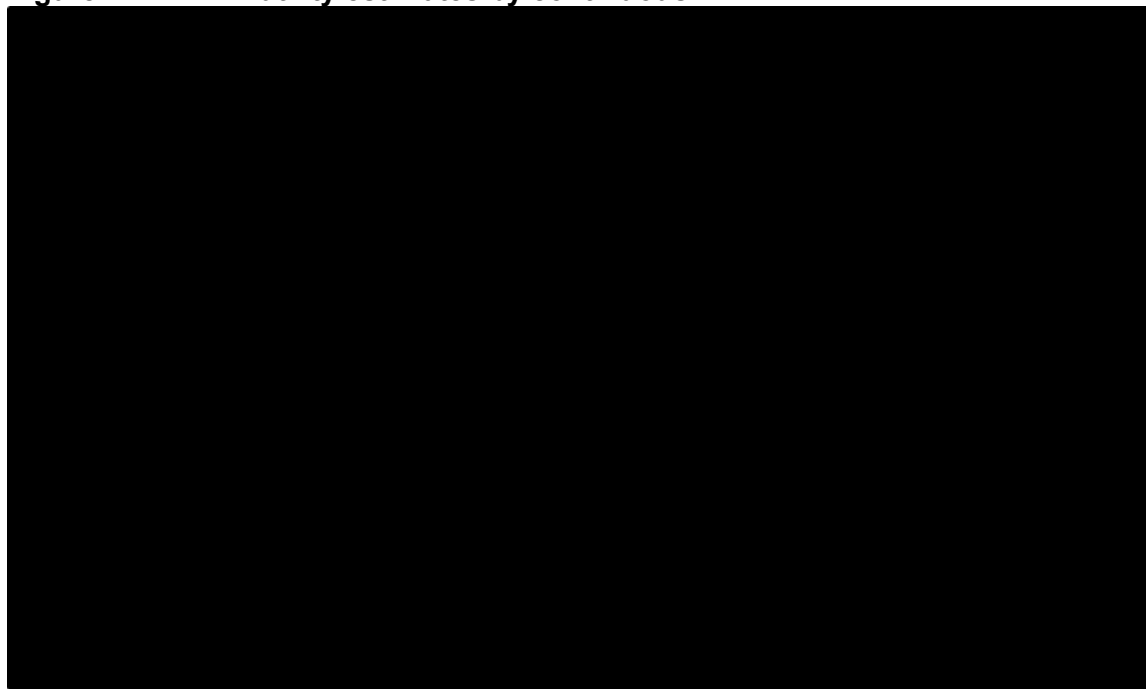
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[illegible]

Figure 14: MMRM utility estimates by continuous TTD



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		The updated model base case includes patient utility derived using a MMRM fitted to the Van Hout cross-walked EQ-5D-5L values observed in CodeBreak 200. The MMRM is specified by continuous TTD using the transformation $1/\sqrt{TTD}$ and includes a covariate for treatment arm.
9. Use of treatment-dependent utilities	Yes	The justification of treatment-dependent utility values has already been discussed in response to Key issue 8. There is clinical rationale for patients to experience an improved quality of life when being treated with sotorasib compared to docetaxel, owing to the reduced treatment-related adverse events and the less burdensome method of administration. This improvement was then observed in the CodeBreak200, where the utility of patients that were well matched at baseline diverged following the initiation of treatment, with the mean utility value of a sotorasib patient often [REDACTED] greater than the equivalent docetaxel patient (Table 5 and Table 6). When fitting MMRMs to the utility data from CodeBreak200, specifications were tested with and without a covariate for treatment. On every occasion the model that included a treatment covariate was shown to provide a statistically significantly improved fit to the observed data compared to the equivalent specification without a treatment covariate. We therefore concluded that any comparison between sotorasib and docetaxel should account for the observed improvement in quality of life associated with sotorasib.
11. Suboptimal approach for the modelling of the acquisition costs.	No	Amgen acknowledges this issue and agrees with the EAG that a “per pack” costing approach is more appropriate than a “per day” approach.
12. Transparency issues related to insufficient responses to the clarification questions posed by the EAG.	No	Amgen is keen to respond to the comments within Issue 12 that there are “transparency issues related to insufficient responses to the clarification questions posed by the EAG”. We are disappointed by this perception and wanted to state clearly that we continue to place high importance on this process and always look to conduct ourselves with integrity and professionalism. I believe that my team has acted transparently and constructively at every stage, providing all information and analyses that are available within the constraints of the underlying evidence sources. Providing additional evidence is at the heart of Amgen’s approach to the ongoing assessment of sotorasib. The company’s objective in seeking placement of sotorasib within the CDF was precisely to enable the collection and assessment of new data to address areas of uncertainty identified in the original appraisal. The current submission

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	therefore represents the culmination of extensive evidence generation activities, including the analysis of mature data from the NHS Digital CAS, which offers the most comprehensive real-world evidence on sotorasib in UK clinical practice to date. Amgen has worked diligently to ensure that all available evidence from both the clinical trial programme and the CAS RWE study has been provided to NICE and the EAG. It is important to clarify that certain limitations highlighted by the EAG arise from structural features of the CAS dataset, rather than from any lack of transparency or cooperation on the part of the company. As explained in the clarification responses, Amgen does not have access to patient-level CAS data; all analyses are conducted by NHS Digital in accordance with data governance and confidentiality requirements. As a result, certain additional analyses requested by the EAG—such as further subgroup analyses, re-modelling of post-progression survival, or examination of temporal treatment trends—could not be undertaken. Furthermore, NHS Digital’s rules on statistical disclosure control require suppression of small numbers (≤ 5 patients), which limits the ability to present detailed stratified data. These are external constraints designed to protect patient privacy, not omissions by Amgen. Within these limits, Amgen has fully and transparently addressed each request raised during the clarification phase. The company has provided detailed methodological explanations, justification of assumptions, and supplementary materials where re-analyses were not possible. All feasible updates to the health economic model were implemented and clearly documented, including a full change log within the ModelChangesJuly 2025 tab, to ensure complete traceability and reproducibility of results. Where data were not available for additional modelling or validation, the company explicitly stated the reasons and explained the practical constraints of data access. Throughout both the appraisal and the clarification process, Amgen has maintained an open and cooperative dialogue with NICE, the EAG, and NHS Digital, with the shared goal of ensuring that decision-making is informed by the best possible evidence. The company’s actions demonstrate a consistent commitment to transparency, responsiveness, and collaboration within the framework of NICE’s evidence standards. Amgen therefore respectfully does not agree with any suggestion that it has withheld information or been uncooperative. The company has provided all data and analyses within its control, and it continues to support evidence generation through the CDF to address residual uncertainties. Amgen remains committed to maintaining open engagement with

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		NICE and the EAG to ensure that the appraisal of sotorasib is based on the most comprehensive, accurate, and relevant evidence for the benefit of NHS patients.

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Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Age- and sex-adjustment of utility values in the cost-effectiveness model	EAR 4.2.7.3, EAG comment d, page 99	Yes	The EAG highlighted that the utility values in the cost-effectiveness model were not adjusted to account for the population aging. This has been incorporated using the regression for UK general population utilities by age and sex reported in Ara and Brazier (2010).

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
			ICER (£/QALY)	ICER with x1.7 weighting (£/QALY)
Company base case result			44,669	26,276
Key Issue 8: Suboptimal approach for the estimation of utility values.	Utility values estimated using the summary statistics of CodeBreak 200 by time to death and treatment arm	Following a thorough model selection process, base case utilities are derived using a MMRM fitted to the Van Hout cross-walked EQ-5D-5L values observed in CodeBreak 200. The MMRM is specified by continuous TTD using the transformation $1/\sqrt{\text{TTD}}$ and includes a covariate for treatment arm.	44,335 (-334)	26,080 (-196)
Additional issue 1: Age-adjusted utilities	Age-adjusted utilities not included in the cost-effectiveness model	Age-adjustment applied using the regression established by Ara and Brazier for UK general-population utility values by age and sex (Ara and Brazier, 2010).	45,238 (+569)	26,611 (+335)

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Key issue 11: Suboptimal approach for the modelling of the acquisition costs	The cost of sotorasib acquisition estimated using a 'per day' cost	Aligned with the EAG's preference for acquisition costs per opened pack	47,653 (+2,984)	28,031 (+1,755)
Company's base case following technical engagement (or revised base case)	Incremental QALYs: ■ or ■ with x1.7 weighting	Incremental costs: ■	47,893	28,172

Sensitivity analyses around revised base case

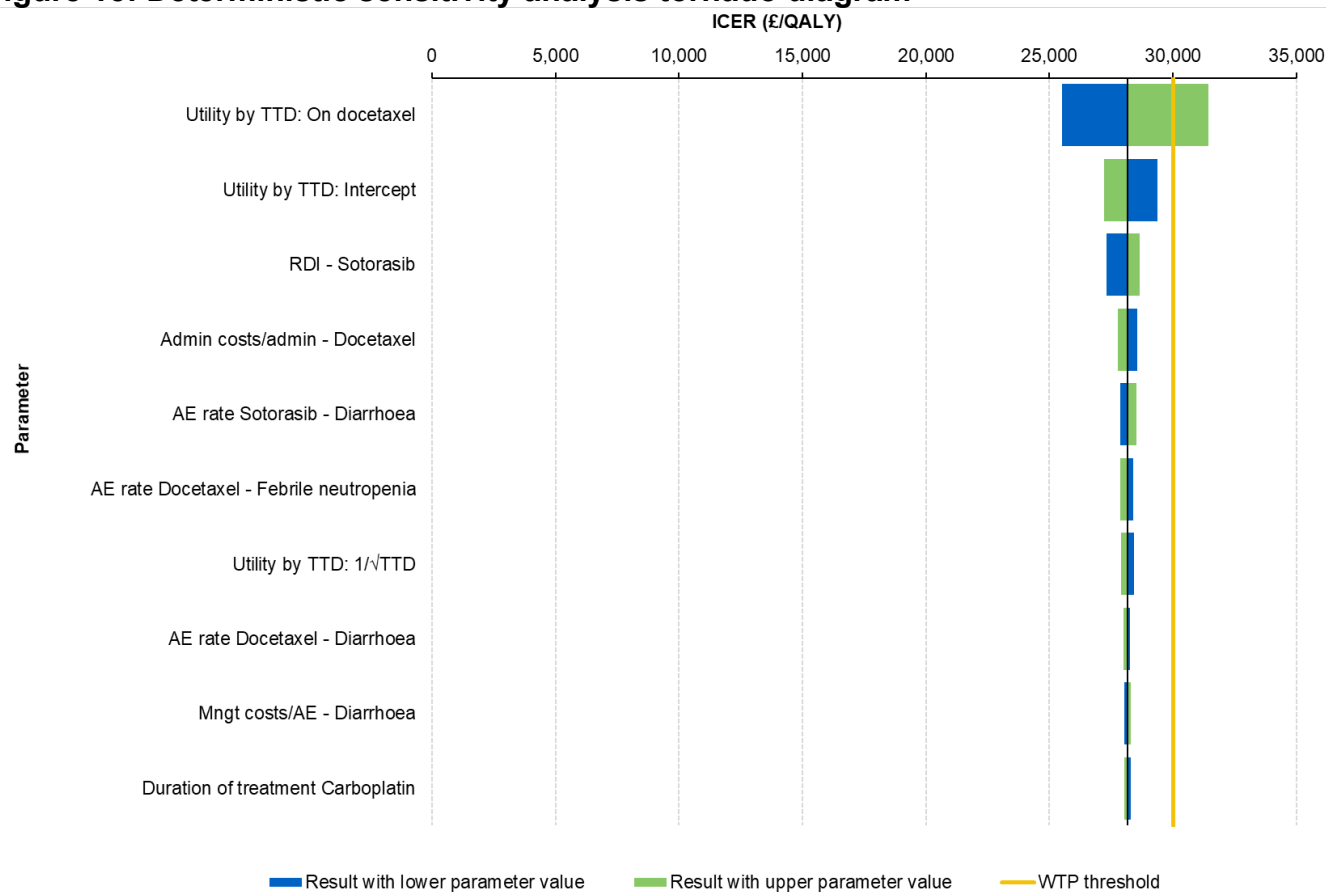
The deterministic and probabilistic sensitivity analyses were rerun incorporating the updated company base case. Figure 15 presents the variation from the 10 most influential parameters on deterministic results.

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Figure 15: Deterministic sensitivity analysis tornado diagram



Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; 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 9 and are consistent with the updated deterministic base case results. Figure 16 presents the cost-effectiveness acceptability plane and the cost-effectiveness plan is presented on Figure 17.

Table 9: Probabilistic cost-effectiveness results with updated company base case

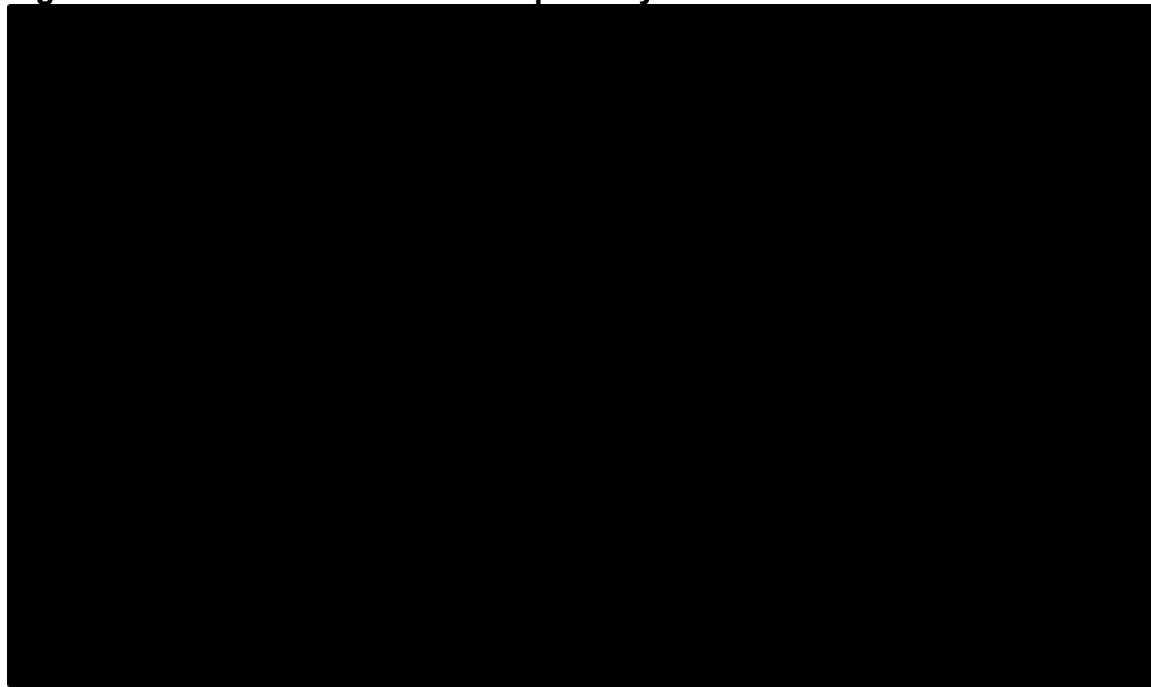
Intervention	Mean probabilistic costs (£)	Mean probabilistic QALYs	Incremental costs (£)	Incremental QALYs (with x1.7 weighting)	ICER with x1.7 weighting (£ per QALY)
Docetaxel	11,664				
Sotorasib					28,595

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Figure 16: Cost-effectiveness acceptability curve

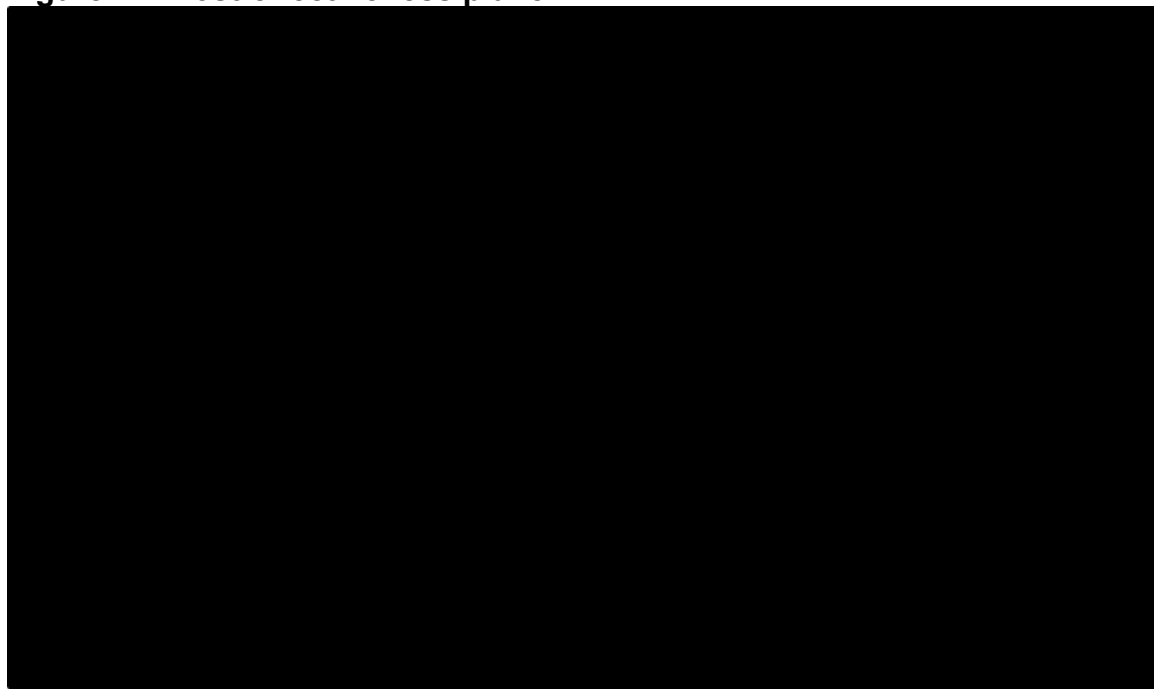


Key: QALY, quality-adjusted life year; WTP, willingness-to-pay.

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Figure 17: Cost-effectiveness plane



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

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Single Technology Appraisal

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Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in section 1.3 to 1.5. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

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In [part 3](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm on 24 November 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]
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We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

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

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Part 1: Treating previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Qamar Ghafoor
2. Name of organisation	University Hospitals Birmingham
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? ☒ A specialist in the clinical evidence base for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

Clinical expert statement

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

8. What is the main aim of treatment for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To shrink the tumour, delay progression and improve patients' Quality of Life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Given the previous standard of care – docetaxel, was IV, exceptionally toxic and made QOL poor in many patients I would suggest – stability in the tumour size. If there is a reduction in the size, this would be a bonus. To improve progression free survival would be key clinically
10. In your view, is there an unmet need for patients and healthcare professionals in previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer?	With sotorasib available, the unmet need would be 3rd line options
11. How is previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer currently treated in the NHS? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	So, there are 2 options on local and national protocols. These would be docetaxel or sotorasib. Since sotorasib became available, this is the main therapy used. There was national real life evidence we collected in the UK, that was presented at ESMO and BTOG, and has been submitted for publication. The QOL and patient outcomes strongly support this being the appropriate therapy for this patient group.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? How does healthcare resource use differ between the technology and current care?	The current technology – diagnostic labs, oncology pharmacy and clinical knowledge would support this. This is currently being done without issues.

Clinical expert statement

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

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It will allow a treatment that has shown clinical benefit, better patient experience and QOL as well as reduction in NHS burden (SACT and Day unit chair time, nurse requirements and pharmacy time) to continue.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with KRAS G12C mutation
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It will be easier – less hospital resource, less clinical time needed.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	These are already in place.

Clinical expert statement

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

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes As a patient – taking a tablet daily at home rather than an IV treatment every 3 weeks – improves QOL. Less time in hospital. Less payment in transport and parking. Less needles and procedures
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a ‘step-change’ in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	It is an advancement. Using molecular driven results to target the right patient population with an effective treatment.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient’s quality of life?	From the UK Real life evidence, the toxicity was exceptionally well managed and QOL was better for patients on it.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	They do. And the UK Real World Evidence show that the Codebreak data is effective and representative.

Clinical expert statement

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

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	UK real world evidence https://www.annalsofoncology.org/article/S0923-7534(24)02961-2/fulltext A further update has been submitted for publication
22. How do data on real-world experience compare with the trial data?	Frailer patients than in the trials can tolerate treatment. Also algorithms to manage toxicity have allowed the drug to be used in a more controlled manner.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could - exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation - lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population - lead to recommendations that have an adverse impact on disabled people.	I don't think this will be the case in the UK

Clinical expert statement

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

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

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

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Uncertainty as whether docetaxel with nintedanib is a comparator.	In real life in the UK, Nintedanib is very rarely used in combination with Docetaxel. So better to not use that.
Uncertainty as which of the two main comparative analyses is the most valid.	
Missing subgroup analyses.	Ultimately all patients gain benefit. It is better to keep as an option for all, rather than use subgroup analysis.

Clinical expert statement

Sotorasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (MA review of TA781) [ID6287]
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Non-randomised study to inform the treatment effectiveness of sotorasib and docetaxel.	Real life evidence is large for this population. This is probably more relevant as it represents what clinicians with expertise are doing, based on their knowledge and skillset.
Incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreakK 200.	
Issues related to the modelling of TTD(D).	
Insufficient justification for treatment waning assumptions.	
Suboptimal approach for the estimation of utility values.	
Use of treatment-dependent utilities.	
Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.	

Clinical expert statement

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

Suboptimal approach for the modelling of the acquisition costs.	
Transparency issues related to insufficient responses to the clarification questions posed by the EAG.	
Are there any important issues that have been missed in EAR?	

Clinical expert statement

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

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Patient reported impact on QOL, hospital attendance is hugely improved with Sotorasib over previous agents

The impact on clinical time and NHS resource has been positively impacted by using Sotorasib, as an oral compound, as opposed to IV docetaxel.

UK RWE discussions have made it clear that Sotorasib is the preferred option for clinicians across the UK

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our [privacy notice](#).

Clinical expert statement

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

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

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

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **as soon as possible**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

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

Part 1: Treating previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Toby Talbot
2. Name of organisation	Royal Cornwall Hospitals NHS Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

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

8. What is the main aim of treatment for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment is to increase progression free survival; this was the primary endpoint in the CodeBreak200 trial.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction in symptom burden would be the most important clinical response.
10. In your view, is there an unmet need for patients and healthcare professionals in previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer?	Yes. No other KRAS G12C directed therapy is available for this group of patients. Docetaxel is considered standard of care as second line treatment and was the control arm in the CodeBreak200 trial, however, it is widely considered a toxic treatment and is often rejected as a treatment option in favour of supportive care alone.
11. How is previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Standard of care for previously treated KRAS G12C+ patients is with Docetaxel, either as single agent or occasionally in combination with Nintedanib. Please see comments above regarding the concerns over degree of toxicity with these approaches. Docetaxel is very well established as a chemotherapy agent and is in use across the whole NHS. Most oncologists would be familiar with its use in clinical practice; many would share concern over risk of toxicity, particularly in the second line setting in lung cancer. Sotorasib is an oral treatment so does not require chair-time on the systemic therapy unit.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Sotorasib has been available in England through the Cancer Drug Fund (CDF) with widespread uptake. Clinical practice would not be expected to change.

Clinical expert statement

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

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	If considering Docetaxel as current standard of care, Sotorasib offered some resource advantages in that it is an oral agent and therefore does not need chair-time on the systemic therapy units. There would be little/no need for venous access devices such as indwelling central lines. This technology would be used universally in secondary care, through specialist oncology clinics which already exist. No additional facilities would be needed to introduce this technology.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The CodeBreak200 trial met its primary endpoint with a statistically significant increase in progression free survival. The trial also reported reduced toxicity of Sotorasib vs Docetaxel which has been the experience in the oncology clinic. Yes. Quality of life is improved compared to those patients treated with Docetaxel (my clinical experience) and toxicity was lower with Sotorasib in the clinic trial.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Sotorasib is only known to be effective in patients with non-small cell lung cancer with the specific KRAS G12C mutation; this is seen in around 10-15% of NSCLC.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Being an oral treatment, there are considerable advantages including ease of use, dosing agility, lack of need for chair-time and/or venous access devices. The main risk with Docetaxel is neutropenia and opportunistic infections leading to sepsis and hospital admission. The risks of hospital admission is much lower with Sotorasib.

Clinical expert statement

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

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	All patients need to be tested for KRAS mutations; this is standard of care across the NHS and no additional testing is required. Treatment would be stopped if there it is not tolerated or there is cancer progression.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Oral treatments are generally easier and avoid interventions such as venous access devices. There is no doubt that Sotorasib is better tolerated than Docetaxel based treatment. The risk of acute admission to hospital is lower with Sotorasib which is an important consideration with the emergency portals in nearly all hospitals in the NHS under major pressure.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Sotorasib is the first clinically available KRAS G12C directed therapy which has been shown to be superior to standard of care chemotherapy. I would consider this a step-change as the first KRAS directed treatment in lung cancer. It provides a treatment option for any patients unwilling to be treated with further chemotherapy.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects of Sotorasib include diarrhoea which can erode quality of life. Other side effects include fatigue, nausea and abnormal liver function tests. All side effects seem to be fully reversible with dose interruptions, supportive medication and dose adjustments.
20. Do the clinical trials on the technology reflect current UK clinical practice? If not, how could the results be extrapolated to the UK setting?	The CodeBreak200 trial used single agent Docetaxel as the control arm. In England, an option is to combine Docetaxel with Nintedinib (and oral VEGFR inhibitor – NICE TA347) which may have additional anti-cancer effects at the expense of additional toxicity. The use of Nintedinib is variable across the NHS.

Clinical expert statement

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

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The primary endpoint was PFS which is very much standard in second line lung cancer studies.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Published real world data series appear similar to the results formally reported from the CodeBreak200 trial. My own clinical experience is also similar.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	None

Clinical expert statement

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

- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

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[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Sotorasib is the first clinically available KRAS G12C directed therapy

The safety and tolerability profile is superior to Docetaxel based treatment

Oral treatment provides ease of use for patient and reduces capacity strain on the systemic therapy units

Patients will often prefer supportive care alone to further chemotherapy and therefore decline Docetaxel

The risk of acute admission to hospital is lower with Sotorasib than Docetaxel therefore reducing strain on the emergency portals in hospitals

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Clinical expert statement

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

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer or caring for a patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

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

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Your response should not be longer than 15 pages.

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Patient expert statement

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

Part 1: Living with this condition or caring for a patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer

Table 1 About you, previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer, current treatments and equality

1. Your name	Jane Scott
2. Are you (please tick all that apply)	☐ A patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	NA
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? If you are a carer (for someone with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer) please share your experience of caring for them	I cared for my husband Pete, progressively once he was diagnosed with lung cancer. Initially this involved mental health and well being support, deciphering cancer terminology, attendance at scans and appointments. We were fortunate that we have a large support network of family and friends but the majority of the care was provided by me and our son. Fortunately, the cancer unit was a short drive away. We were able to take Pete to appointments and stayed with him. Pete had commenced investigations for lung cancer from January 24 and in April 2024, Pete had a left upper lobectomy and lymph node dissection. Pete recovered well from surgery and then commenced carboplatin chemotherapy from this point he experienced impaired breathing, fatigue and pain from fractures to his ribs from surgery. I took on more household tasks, readjusted my work schedule to accommodate additional care needs, dressings, attendance at appointments. In September 24, Pete experienced increased pain and after various scans and tests he was diagnosed with stage 4, metastatic lung cancer and received emergency radiotherapy for cancer lesions on his vertebrae. We were both in shock from the rapid deterioration and the discussion with the oncologist that radiotherapy followed by Sotorasib was the most suitable life extending treatment. I remember nearly crashing the car in the car park as I drove us home. Pete experienced severe breathlessness after receiving radiotherapy and five days later commenced Sotorasib when his symptoms became worse and he was hospitalized. At this point

Patient expert statement

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

	I was with Pete all of the time, I fed him and helped with personal care. When he was admitted to hospital he was diagnosed with blood clots, a chest infection and pneumonitis. These are all symptoms of an adverse reaction to Sotorasib and the drug was stopped. Pete was treated in hospital for four weeks he died on the 13.11.24. I cared for him in the hospital and slept regularly overnight with him. I made and brought in food. I looked after his personal needs, showering, dressing and liaised with the hospital staff and consultants. I still worked flexibly.
7a. What do you think of the current treatments and care available for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I think overall the standard of care that Pete received was of a good quality. There were areas for improvement and also some exceptional staff who cared above and beyond. I am not aware of others who were receiving treatment for the same condition.
8. If there are disadvantages for patients of current NHS treatments for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	It was clear that the ease of use was preferable to an appointment in hospital and time spent receiving treatment through IV. However, Pete only took Sotorasib for 5 days after which treatment stopped and he was hospitalised for four weeks prior to his death. For Pete, whilst it was not conclusive that Sotorasib caused the adverse symptoms there was not a clear process or guidance to eliminate other causes. In addition there appeared to be differences of medical opinion regarding the guidance for timing in issuing Sotorasib post radiotherapy
9a. If there are advantages of sotorasib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	I cannot comment.

Patient expert statement

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

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does sotorasib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	I cannot comment. Ease of use, reduced time in hospital unless and until a reaction or adverse reaction.
10. If there are disadvantages of sotorasib over current treatments on the NHS please describe these. For example, are there any risks with sotorasib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As described above Pete experienced the most severe adverse reactions although the medical opinion was not conclusive that this was due to taking the Sotorasib. As above there did not appear to be clear guidance in testing for other causes of the reactions in order to isolate whether it was caused by Sotorasib.
11. Are there any groups of patients who might benefit more from sotorasib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Most patients who are able to understand the instructions including those for timings for stomach acid reducing medication and have the dexterity to administer would generally benefit from not being in hospital and receiving treatment through IV.
12. Are there any potential equality issues that should be taken into account when considering previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer and sotorasib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	I would suggest equality issues may manifest for those patients with mental health and or who are neurodivergent, have dementia, MS, Parkinsons Disease, may experience self-administering difficult. Patients with physical disabilities dependent upon individual circumstances may experience challenges with self-administering Sotorasib.

Patient expert statement

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

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	The importance of treatment guidelines to assess the suitability and safety of Sotorasib. To be clear about the potential impact of Sotorasib on the quality of life as well as life span.

Patient expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The importance of care and support for patients and their families, carers.
- The impact of severe adverse reactions for patients, families, carers and hospital staff and resources
- Clearer guidelines to assess the interface between treatments and to isolate other factors that can contribute to diagnosis through thorough screening.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

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Patient expert statement

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

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer or caring for a patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

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

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **as soon as possible**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Patient expert statement

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

Part 1: Living with this condition or caring for a patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer

Table 1 About you, previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer, current treatments and equality

1. Your name Tina Cobb	Tina Cobb
2. Are you (please tick all that apply)	☒ A patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer? If you are a carer (for someone with previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer) please share your experience of caring for them	I was diagnosed with NCSLC in June 2024 and have had chemoradiation, immunotherapy and am now on sotorasib.
7a. What do you think of the current treatments and care available for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	This current method of treatment means that I can take tablets at home without the need for frequent hospital visits and enables me to live a better balanced life between monitoring scans which are 3 monthly.
8. If there are disadvantages for patients of current NHS treatments for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (for example, how they are given or taken, side	The side effects of chemotherapy and radiotherapy in my experience were far worse than those of sotorasib. Nausea and fatigue being the worst

Patient expert statement

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

effects of treatment, and any others) please describe these	
9a. If there are advantages of sotorasib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does sotorasib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	Able to take as a daily tablet which means no more IV infused drugs are needed. I did have a PICC line which did restrict daily life and that is no longer needed. My quality of life has improved immensely. I am currently unable to drive so he need to visit hospital less frequently has really helped my independence as I collect my tablets from my local mobile cancer unit. It gives me a bit more independence with less hospital visits needed. Side effect are much less.
10. If there are disadvantages of sotorasib over current treatments on the NHS please describe these. For example, are there any risks with sotorasib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The only slight side effect I have is diarrhoea which I am currently able to manage and slight fatigue but I found these were also side effects of other treatment as well.
11. Are there any groups of patients who might benefit more from sotorasib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Remembering to take the required dose of tablets every day may be an issue for someone with cognitive impairments.
12. Are there any potential equality issues that should be taken into account when considering previously treated KRAS G12C mutation-positive advanced non-	I don't think that there would be any potential equality issues that would need to be taken into account with taking this medication.

Patient expert statement

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

small-cell lung cancer and sotorasib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	None

Patient expert statement

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

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Sotorasib is an important medication which should be available to all patients that would benefit from it.
- Much less invasive treatment that can be taken at home, giving back a degree of control.
- Less frequent hospital visits
- Possibility of far less side effects.
- Targeted specifically for this type of mutation.

Thank you for your time.

Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

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Patient expert statement

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

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

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

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on 24 November 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Oncogene Cancer Research
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.	None.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Technical engagement response form

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

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

https://www.google.co.uk/intl/en-GB/about/products?tab=rh Key issue	Does this response contain new evidence, data or analyses?	Response
1. Uncertainty as whether docetaxel with nintedanib is a comparator.	No	From a patient perspective in the UK, patients in our community tend to receive docetaxel alone – not in combination with nintedanib. We are unable to comment further.
2. Uncertainty as which of the two main comparative analyses is the most valid.	No	From a patient perspective, the most meaningful comparative analysis is the one that compares sotorasib to the treatment pathway patients would actually have received in routine NHS care, because this better reflects the outcomes that affect daily life and access to care.
3. Missing subgroup analyses.	No	Patients' experiences and needs vary depending on disease stage, previous treatments, and whether the cancer has spread to the liver or brain. People with more advanced disease or CNS involvement often have more complex symptoms and different treatment priorities. While we cannot provide new subgroup analyses, we ask the committee to consider that Sotorasib's benefits and impact on quality of life may differ across patient groups, and that this variation is important when assessing value.
4. Non-randomised study to inform the treatment	No	Patients understand and support the ethical decision to permit crossover in CodeBreak 200 when early evidence suggested clinical benefit from a KRAS G12C inhibitor. Allowing people in the control arm to cross over to targeted therapy

Technical engagement response form

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

effectiveness of sotorasib and docetaxel.		after progression is humane and reflects real-world clinical decision-making, where clinicians aim to offer the best available option. However, from an appraisal perspective, we understand that crossover makes it more difficult to interpret overall survival differences. For this reason, we ask the committee to keep in mind that crossover helped patients get the treatment they needed, and to judge the results fairly because of this. Patients also feel there is an important difference in how each treatment is taken. docetaxel is administered intravenously in an infusion clinic, whereas sotorasib is an oral targeted therapy taken at home as a monotherapy. Even when clinical effectiveness is similar, patients consistently prefer oral therapies due to a substantially lower time burden, reduced disruption to work and family responsibilities, and fewer emotionally distressing experiences associated with repeated hospital visits. Infusion appointments require travel, waiting times, pre-treatment checks, post-treatment observation and exposure to infection risk. Many patients describe infusion environments as reinforcing a sense of being seriously unwell, whereas oral therapy at home enables greater autonomy, dignity and quality of life. These real-world factors are highly relevant for a population living with incurable disease. In addition, we also believe results showing how long the cancer stays controlled and how symptoms are managed still clearly show benefit, even with crossover. These matter to patients, and we ask the committee to consider these points.
5. Incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreak 200.	No	Patients recognise that selecting how long a treatment works is a technical matter. From a patient perspective, it's important that the models reflect what people actually experience. Some patients respond to sotorasib for a long time, and benefits can last beyond the short-term data in the trial. We ask the committee to make sure the assumptions used in the model do not underestimate the real benefit people may get from treatment.

Technical engagement response form

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

6. Issues related to the modelling of TTD(D).	No	Patients may stop or pause treatment for various reasons such as side effects, fatigue, or personal circumstances, rather than only due to strict protocol schedules. In NHS practice, treatment breaks are commonly used to help us patients stay on therapy longer while maintaining our quality of life. We ask the committee to ensure that the models of treatment duration reflect this real-world experience, so the estimated benefits and costs of sotorasib are meaningful for patients.
7. Insufficient justification for treatment waning assumptions.	No	In the patient community we note some people experience lasting benefit from sotorasib, including ongoing tumour control and maintained quality of life. It's important that models do not assume the treatment effect fades too quickly because this would underestimate the real-world benefit patients can experience.
8. Suboptimal approach for the estimation of utility values.	No	Patients report that taking sotorasib as an oral therapy at home is generally less disruptive than intravenous chemotherapy. It involves fewer hospital visits, less fatigue, and allows people to maintain their daily routines and responsibilities. These aspects of quality of life are highly important to patients and should be reflected in the utility values used in economic models.
9. Use of treatment-dependent utilities.	No	Taking sotorasib as a daily pill at home is much easier for patients than going into hospital for chemotherapy like docetaxel. Hospital visits can be long, tiring, and stressful, and being hooked up to an IV every few weeks can be stressful and create huge amounts of anxiety. Docetaxel often causes hair loss, extreme tiredness, nausea, mouth sores, and tingling in hands or feet. Losing your hair can be very upsetting and make you feel less like yourself, adding to the mental strain. Oral treatment allows people to stay at home, keep their normal routines, spend more time with family, and feel more in control. It also reduces pressure on NHS staff and hospital resources. These differences matter a lot for patients and should be considered when thinking about quality of life on each treatment.

Technical engagement response form

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

10. Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.	No	Patients highly prefer taking oral therapies like sotorasib because they are taken at home rather than given as an intravenous chemotherapy – especially one like docetaxel. Hospital visits for infusions can be long, tiring, and stressful, and being in a hospital repeatedly can cause anxiety and worry for both patients and families. Docetaxel often causes hair loss, fatigue, nausea, mouth sores, and tingling in the hands or feet. Hair loss, in particular, is deeply distressing, affecting self-image and mental wellbeing. Oral therapy allows people to stay at home, maintain daily routines, spend more time with family, and feel more in control. It also reduces the pressure on NHS staff and hospital resources. These experiences are an important part of patients' quality of life and should be reflected accurately in models.
11. Suboptimal approach for the modelling of the acquisition costs.	No	Although acquisition costing is a technical issue, patients' concerns are about any model that might reduce access to treatment. As mentioned elsewhere, patients again note that oral therapies taken at home reduce hospital visits and staff time, which is an important real-world consideration.
12. Transparency issues related to insufficient responses to the clarification questions posed by the EAG.	No	We encourage clear and open communication between all parties so those living with KRAS G12C lung cancer can get and retain access to the best treatments they desperately need.

Technical engagement response form

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

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Technical engagement response form

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

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	...	...	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

Technical engagement response form

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

Single Technology Appraisal

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

Technical engagement response form

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If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

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

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The deadline for comments is **5pm on 24 November 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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

About you

Your name	██████████
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Roy Castle Lung Cancer Foundation
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator	RCLCF has received the following funding : - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project, ongoing); £12,000 awareness of support needs for sclc; £330 meeting honorarium) - BMS (£30,000 for 1 year funding of GLCC project, ongoing; £594 for Advisory board Honorarium; 3750 Speaker honorarium) - Lilly (£30,000 for 1 year funding of GLCC project, ongoing) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project, ongoing; £4900 for Advisory boards) - Roche (1 year funding of GLCC project, ongoing; £10,000 for Lung cancer Awareness Month initiative) - Novartis (£30,000 for 1 year funding of GLCC project, ongoing); - Iovance (£30,000 for 1 year funding of GLCC project, ongoing) - Pfizer (£30,000 for 1 year funding of GLCC project, ongoing) - Astra Zeneca (£30,000 for 1 year funding of GLCC project, ongoing) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project, ongoing) - Takeda (£30,000 for 1 year funding of GLCC project, ongoing)

Technical engagement response form

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

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

- Regeneron (£30,000 for 1 year funding of GLCC project, ongoing; £346 for Advisory Board)
- Gilead (£30,000 for 1 year funding of GLCC project, ongoing)
- Merck (£30,000 for 1 year funding of GLCC project, ongoing)
- J & J (30,000 for 1 year funding of GLCC project, ongoing)

None of the above is related to any mentioned product.

Technical engagement response form

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

or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Table 1 About you

Technical engagement response form

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

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Uncertainty as whether docetaxel with nintedanib is a comparator.	No	On anecdotal discussion with clinicians, it seems that nintedanib is rarely used.
2. Uncertainty as which of the two main comparative analyses is the most valid.	No	CAS is real world data, from patients in the UK. Note - KRAS is generally considered to be a poor prognostic indicator in non small cell lung cancer. So, would have anticipated a known population with KRAS mutation would have worse outcomes.
3. Missing subgroup analyses.	No	
4. Non-randomised study to inform the treatment effectiveness of sotorasib and docetaxel.	No	In both CodeBreak and CAS RWD, people treated with sotorasib lived longer overall than those treated with docetaxel. Note – sotorasib is an oral treatment and Docetaxel intravenous. Patients often report on the severity of the nature of docetaxel's side effects – referred to by some as “docetaxel”.
5. Incompleteness of information required for the selection of parametric	No	

Technical engagement response form

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

distributions based on observed data from CodeBreak 200.		
6. Issues related to the modelling of TTD(D).	No	
7. Insufficient justification for treatment waning assumptions.	No	
8. Suboptimal approach for the estimation of utility values.	No	
9. Use of treatment-dependent utilities.	No	
10. Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.	No	
11. Suboptimal approach for the modelling of the acquisition costs.	No	
12. Transparency issues related to insufficient responses to the clarification questions posed by the EAG.	No	

Technical engagement response form

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

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Technical engagement response form

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

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	...	...	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

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Technical engagement response form

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

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

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

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

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Technical engagement response form

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

About you

Table 1 About you

Your name	Tom Newsom Davis/ [REDACTED]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	British Thoracic Oncology Group
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.	Yes BTOG Annual conference March 25 Sponsorship £33,000+ VAT
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	No

Technical engagement response form

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

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Uncertainty as whether docetaxel with nintedanib is a comparator.	No	Docetaxel + Nintedanib is a comparator for UK practice, where it is routinely used. The additional benefit of this over Docetaxel alone is minor. Given limited RWE data, clinical expert opinion may be the best approach to this area.
2. Uncertainty as which of the two main comparative analyses is the most valid.	Yes	RWE data likely to be most valid, although bias remains. UK now has considerable experience with sotorasib in real-world, and so expert opinion will be possible.
3. Missing subgroup analyses.	Yes	Although CE may differ between subgroups, this may not result in clinically meaningful results given the small numbers and lack of stratification of some of these groups.
4. Non-randomised study to inform the treatment effectiveness of sotorasib and docetaxel.	Yes	A bias assessment would be a helpful step to inform of reliability of RWE data
5. Incompleteness of information required for the selection of parametric distributions based on	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Technical engagement response form

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

observed data from CodeBreak 200.		
6. Issues related to the modelling of TTD(D).	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
7. Insufficient justification for treatment waning assumptions.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
8. Suboptimal approach for the estimation of utility values.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
9. Use of treatment-dependent utilities.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
10. Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
11. Suboptimal approach for the modelling of the acquisition costs.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
12. Transparency issues related to insufficient responses to the clarification questions posed by the EAG.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Technical engagement response form

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

Additional issues

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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Technical engagement response form

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

Summary of changes to the company's cost-effectiveness estimate(s)

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

Technical engagement response form

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



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 technical engagement

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Nigel Armstrong, Health Economics Manager, KSR Ltd, United Kingdom (UK) Willem Witlox, Health Economist, Maastricht University Medical Center+ (UMC+), the Netherlands (NL) Bram Ramaekers, Health Economist, Maastricht UMC+, the NL Teresa Holly, Health Economist, Maastricht UMC+, the NL Bradley Sugden, Health Economist, Maastricht UMC+, the NL Maria Katsipataki, Systematic Reviewer, KSR Ltd, UK Xiaoyu Tian, Systematic Reviewer & Health Economist, KSR Ltd, UK Sabine Grimm, Health Economist, Maastricht UMC+, NL Mabel Wieman, Health Economist, Maastricht UMC+, NL Lisa Stirk, Senior Information Specialist, KSR Ltd, UK Manuela Joore, Health Economist, Maastricht UMC+, the NL Huiqin Yang, Reviews Manager, KSR Ltd, UK

1. EAG critique of company response to technical engagement

This document contains the EAG critique of the company response to technical engagement.¹

1.1 Key issue 1. Uncertainty as whether docetaxel with nintedanib is a comparator.

The company continue to argue that docetaxel with nintedanib is not an appropriate comparator.

EAG comment: The EAG considers that this is probably the case, although it might be better to rule out any patients who currently receive the combination treatment as ineligible for sotorasib.

1.2 Key issue 2. Uncertainty as which of the two main comparative analyses is the most valid.

The company continue to argue that the CAS RWE study is the more valid source of comparative evidence, although they acknowledge the possibility of confounding by characteristics for which there are no or large amounts of missing data i.e. KRAS mutation and smoking status. For the former they present some OS survival curves, stratified by status, most patients (1,051 out of 1,271) having missing data (see Figure 1). For the latter the company present the results of subgroup analyses for PFS from CodeBreak 200 (see Figure 2).

Figure 1 - Unweighted KM plot for OS among patients who initiated docetaxel monotherapy, overall and stratified by *KRAS* mutation status

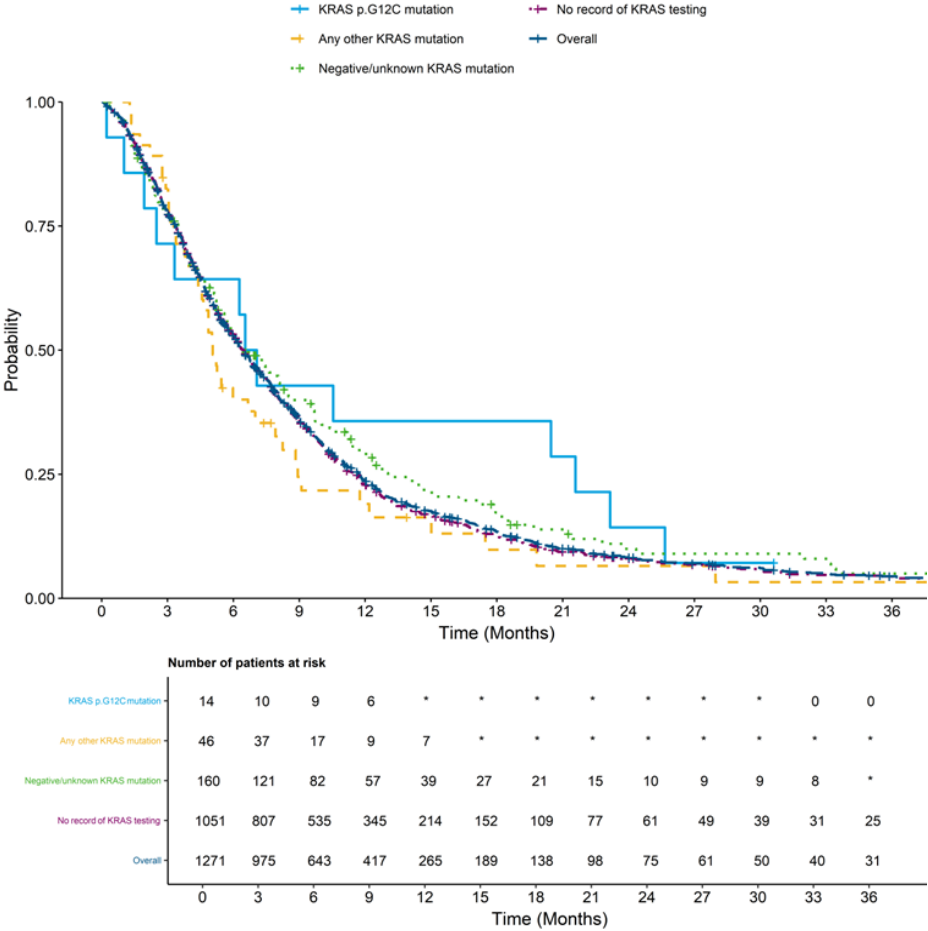
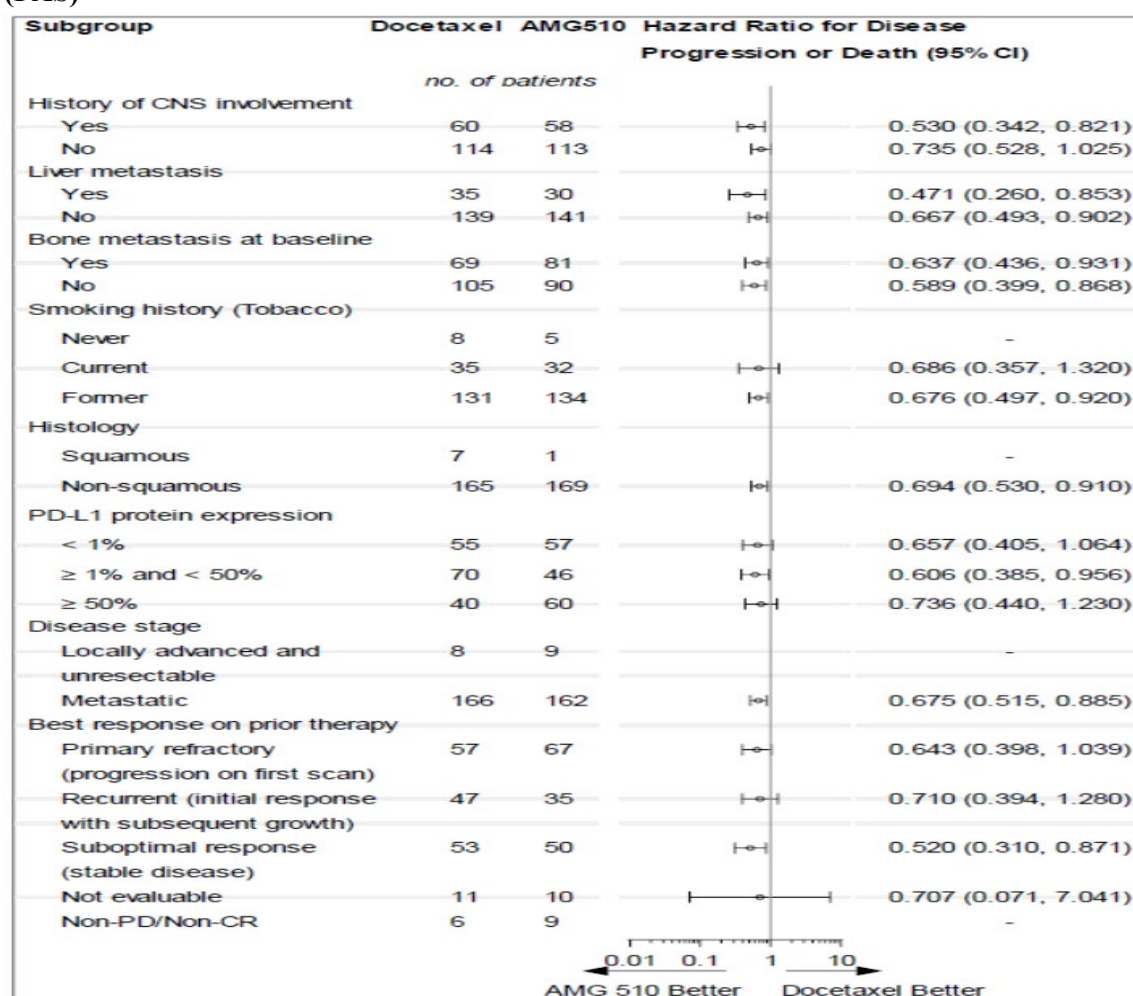


Figure 2 - Appendix C.1.1: Forest plot of subgroup analyses of PFS as assessed by the BICR (FAS)



EAG comment: The survival curves do seem to show there is no clear difference according to KRAS mutation status, although it is clear that there are probably too few data for any confidence in this conclusion. The results of the subgroup analyses do seem to show no effect of smoking status on PFS hazard ratio (HR) in terms of current, 0.686 (0.357, 1.320) vs. former, 0.676 (0.497, 0.920), with too few patients in the never category (n=13).

1.3 Key issue 3. Missing subgroup analyses.

The company stated:¹ “Clinicians consulted by Amgen did not consider any additional subgroups relevant to UK clinical practice or necessary for the appraisal (Amgen DoF, 2025).”

EAG comment: The EAG have no further comment.

1.4 Key issue 4. Non-randomised study to inform the treatment effectiveness of sotorasib and docetaxel.

The company have presented a quality assessment of the CAS RWE study, as requested by the EAG, the summary for which is in the table below. They stated that:¹ “This confirms the result of the original

critical appraisal in the company submission (CS), which concluded low-moderate risk of bias in CAS RWE study.”

Table 1: ROBINS-1 summary results

Risk of Bias Domain	Risk of Bias Level	Likely direction of bias
Confounding	Low	
Classification of interventions	Low	Favours comparator (docetaxel)
Selection of participants	Low	
Deviations from intended interventions	Low	
Missing data	Serious	Unpredictable
Measurement of the outcomes	Low	Unpredictable
Selection of the reported result	Low	Unpredictable

EAG comment: The EAG continues to agree with the company’s arguments for preferring the CAS RWE study, although not necessarily the conclusion that it is unequivocally better than the CodeBreak 200 RCT, not least because there is always the possibility of remaining bias in the CAS RWE study, and the outcomes from this study favour sotorasib.² The EAG also disputes the finding of low to moderate risk of bias: the detailed assessment presented in the appendices indicates that if one domain is at serious risk of bias, which is the case for ‘Missing data’, then this indicates an overall finding of serious risk of bias.³ In fact, the EAG would argue that the domain ‘Confounding’ should probably also be at serious risk on the basis of the following factors not being controlled for: KRAS mutation status, liver metastases and existing brain metastases. The company themselves in the Technical Report for the CAS RWE study identify the potential for residual confounding as a limitation:⁴ *“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.”* As stated above, there is no clear evidence of an effect of mutation status on prognosis on docetaxel, but the evidence is sparse. 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.⁴ Nevertheless, these two characteristics, which the company state could be cofounders, were not adjusted for, and this would imply that the CAS RWE study might actually be at critical risk of bias due to two domains (Confounding and Missing data) being at serious risk of bias.

1.5 Key issue 5. Incompleteness of information required for the selection of parametric distributions based on observed data from CodeBreak 200.

The company provided the requested information required for the parametric survival curve selection of OS and PFS (as outlined in NICE DSU TSD 14) for CodeBreak 200. However, no validation assessment of the long-term extrapolations of CodeBreak OS and PFS data with relevant external data (other than CAS RWE for OS as reported in Table 2 of the company’s technical engagement response) and/or expert opinion was provided, as was requested by the EAG in clarification question B8f.

EAG comment: Based on the additional information on OS in CodeBreak 200 provided by the company, the EAG remains unsure whether the PH assumption is violated, but prefers individually

fitted curves in its base-case based on the convergence of log-cumulative hazards (Appendix B, Figure 2) and smoothed hazards (Appendix B, Figure 8). However, Schoenfeld residuals indicated proportionality of hazards, and the observed hazards for docetaxel from 9 months onwards should be interpreted with caution due to the low number of patients at risk.

The assessment of statistical and visual fit indicates that, for sotorasib, the log-normal, generalized gamma, and log-logistic distributions provide the best alignment with the observed data. For docetaxel, all candidate models are within a reasonable range. Examination of the hazards suggests that, for sotorasib, the shape is most consistent with the log-normal, generalized gamma, and log-logistic. For docetaxel the gamma and Weibull seem plausible candidates, but interpretation was more challenging due to limited patient numbers at the point where the hazard seems to increase. Long-term validation against EAG expert estimates indicate that, for sotorasib, the log-normal, generalized gamma, and log-logistic models substantially overestimate OS at three and five years, whereas the gamma and Weibull provide close approximations. For docetaxel, gamma and Weibull underestimated OS at these time points, and also none of the alternatives align well with EAG expert expectations. Of note, the 5-year EAG expert estimate for sotorasib in Table 2 of the company's response to technical engagement seems incorrect (should be [REDACTED] instead of [REDACTED]), and EAG expert estimates of 3-year ([REDACTED]) and 5-year ([REDACTED]) OS for docetaxel were not reported in this Table.

Overall, the EAG considers the company's validation of long-term OS extrapolations limited. Alignment of long-term OS with EAG expert estimates was poor, particularly for parametric survival models fitted to docetaxel OS data. This warrants exploring more flexible approaches, such as spline-based models. In its updated base-case, the EAG selects the individually fitted gamma to extrapolate OS for sotorasib based on its long-term estimates being in line with EAG expert estimates, and explores the individually fitted log-logistic in a scenario analysis based on its statistical and visual fit, and hazard shape. For docetaxel, the EAG also prefers the individually fitted gamma to extrapolate OS in its base-case based on the considerations above. For PFS, the EAG remains using the individually fitted log-logistic for both sotorasib and docetaxel in its base-case for the reasons highlighted in section 4.2.5 of the EAG rapport. In addition, the smoothed versus modelled hazard plots in Figure 10 and Figure 11 of the company's response to technical engagement indicate that the log-logistic is a suitable candidate to capture the first increasing and then decreasing hazards observed for sotorasib and docetaxel.

1.6 Key issue 6. Issues related to the modelling of TTD(D).

The company stated that, contrary to the EAG's understanding, it did not use a Cox regression or time-varying hazard ratios to estimate TTDD. Instead, the observed probability of patients remaining on treatment while in the PF state was applied to the corresponding proportion of patients in that health state. The company further argued that the EAG's preferred approach of fitting parametric survival curves directly to observed TTDD data from CodeBreak 200 produced implausible results. The modelled TTDD curve crossed the PFS curve (Figure 12 of the company's technical engagement response), suggesting that patients were continuing treatment after disease progression. Although this was allowed in CodeBreak 200, this was considered inconsistent with UK clinical practice by the company.

EAG comment: The EAG's initial understanding of the company's estimation of TTDD from CodeBreak 200 was based on the company's response to clarification question B10, stating "*The TTDD curves for the CodeBreak 200 scenario analysis were generated via pairwise Cox regressions performed on PFS versus TTDD for each treatment arm in CodeBreak 200 to generate time-varying*

HRs". This response by the company to clarification seems inconsistent with the company's explanation in response to technical engagement. Furthermore, the EAG considers the chosen time intervals (i.e. month 0-1, month 1-12 and month 12+) to be arbitrary, as well as the implicit assumption of this approach that the HR of discontinuing treatment versus PFS would remain the post month 12. Hence, the EAG's preferred approach remains to inform TTDD directly by fitting parametric survival curves to the observed TTDD data in CodeBreak 200, as reported in section 4.2.5 of the EAG report.² The company's example showing crossing of TTDD and PFS seemed to be based on a single fitted TTDD curve (unclear which one). As the company noted, this crossing likely reflects the fact that patients in CodeBreak 200 were permitted to continue treatment beyond disease progression. While treatment beyond disease progression may not align with UK clinical practice, such continued treatment could have potentially improved OS in these patients. Consequently, it may be reasonable to model TTD consistent with clinical effectiveness, as reflected by OS. Alternatively, scenario analyses could be explored where extrapolated TTDD curves are capped to the modelled PFS curve to prevent crossing. In absence of the requested EAG preferred approach, it uses the time-varying HRs from CodeBreak 200 to inform the modelling of TTDD in its updated base-case (as in the EAG report²).

1.7 Key issue 7. Insufficient justification for treatment waning assumptions.

The company repeated that the assumption of no additional treatment waning was appropriate as their main 2L+ analysis set indicate sufficient follow-up duration and completeness to capture the treatment effect. The company additionally stated that there is no evidence from the CAS RWE or clinical trial data to suggest an additional decline in the treatment effect of sotorasib over time, and that the EAG's waning analysis only minorly impacted the incremental cost-effectiveness ratio.

EAG comment: Although not explicitly provided and discussed by the company to address key issue 7, the smoothed hazard plots by treatment for CodeBreak 200 OS and PFS provided in response to key issue 5 both indicate converging hazards. For OS the hazards seem to diverge again from 9 months onwards, but with high uncertainty for docetaxel due to low patient numbers towards the end of follow-up. Therefore, considering the relatively immature observed CodeBreak 200 data and the converging trend of cumulative and smoothed hazards, the EAG remains modelling a gradually declining (over 5 years) sotorasib treatment effect starting at 2 years in its base-case (in line with the ERG's preferred approach in TA78).

1.8 Key issue 8. Suboptimal approach for the estimation of utility values.

In response to technical engagement, the company explored the following MMRMs with and without treatment covariates:

- Progression
- TTD as a categorical variable
- TTD as a continuous variable on the natural log scale – $\log(\text{TTD})$
- TTD as a continuous variable transformed using $1/\sqrt{\text{TTD}}$

The company did not provide the mixed effects model for repeated measures (MMRM) including both progression and TTD as requested by the EAG, stating that it is not possible to implement the outcomes within the cost-effectiveness model: *"It is not known whether patients within the progression-free state of the cost-effectiveness model are transitioning to the post-progression or death state, due to the structural assumptions underpinning a partitioned survival model. This means that TTD within the*

progression-free health state cannot be established. It would not be possible to implement in a state-transition model either, as specific patients are not tracked when they transition between the progression-free and post-progression states. This means TTD could not be established for patients that are progression-free and then go on to die in the post-progression state.”.

In its updated base-case, the company prefers the continuous TTD approach using the $1/\sqrt{\text{TTD}}$ transformation as this resulted in more plausible estimates than the $\log(\text{TTD})$ transformation (exceeding age- and sex-matched general population estimates for any TTD exceeding 16 months).

EAG comment: Despite the difficulties mentioned by the company in its response to technical engagement, the EAG’s requested analysis did not mention time to death penalties to be health state dependent. Hence, the company could have assumed an equal time to death penalty for both health states (i.e. based on a MMRM without interaction terms between the covariates). For analyses assuming time to death penalties to be health state dependent, reasonable assumptions could be made, and uncertainty surrounding these assumptions could be assessed in scenario analyses. To resolve the company’s statement that: *“It is not known whether patients within the progression-free state of the cost-effectiveness model are transitioning to the post-progression or death state”*, an assumption should be made what proportion of patients would transit to post-progression and what proportion would transit to death (from pre-progression). These proportions may vary over time. To resolve the company’s statement that: *“It would not be possible to implement in a state-transition model either, as specific patients are not tracked when they transition between the progression-free and post-progression states”*, an assumption should be made regarding health state-specific transition probabilities to death from pre- and post-progression. This approach could be considered an improvement over the current analysis, as it allows long-term mortality to be health state-specific.

Overall, the EAG considers the company’s arguments of not providing the requested MMRM including both progression and time to death insufficiently justified. In addition to the regression diagnostics provided in Appendix C it would like to see the number of observations per TTD category for all MMRMs including TTD as a categorical variable. In absence of the requested analyses, the EAG adopted a continuous TTD approach in its current base-case. It noted that the company did not consider all candidate models from Hatswell et al. and limited their candidate models to the two best transformations (i.e. $\log(\text{TTD})$ and $1/\sqrt{\text{TTD}}$) in that study.⁵ Using the EAG preferred mapping function by Hernandez Alava et al. (see key issue 10), the EAG noted that capping to UK general population estimates was required for both transformations, and preferred the $1/\sqrt{\text{TTD}}$ (in line with the company) as the time to death where the estimated utility value met the UK general population estimate was slightly longer (i.e. 8.51 months for $1/\sqrt{\text{TTD}}$ and 6.67 months for $\log(\text{TTD})$).

1.9 Key issue 9. Use of treatment-dependent utilities

The company stated that there is clinical rationale for patients to experience an improved quality of life when being treated with sotorasib compared to docetaxel, owing to the reduced treatment-related adverse events and the less burdensome method of administration. In addition, the company explored the following MMRMs with and without treatment covariates:

- Progression
- TTD as a categorical variable
- TTD as a continuous variable on the natural log scale – $\log(\text{TTD})$
- TTD as a continuous variable transformed using $1/\sqrt{\text{TTD}}$

The company noted that in all MMRMs considered, adding the treatment covariate improved the statistical fit of the model.

EAG comment: In addition to the company's observation that adding a treatment covariate improved the statistical fit of all MMRMs compared to the same model without treatment covariate, the EAG noted that in all MMRMs including a treatment covariate, the coefficient of the treatment covariate was statistically significantly worse for docetaxel compared to sotorasib. Based on the MMRMs explored by the company, the EAG therefore considers the use of treatment-dependent utility values justified, although it would still like to see the impact of treatment in a full MMRM including progression, TTD and treatment.

1.10 Key issue 10. Incorrect function for mapping EQ-5D-5L to EQ-5D-3L outcomes.

The company provided an analysis mapping EQ-5D-5L outcomes to EQ-5D-3L using the mapping function by Hernandez Alava et al. (UK tariff), as requested by the EAG and in line with the NICE HTA manual. This resulted in the pre-progression sotorasib utility (■) being higher than the age and gender matched general population utility estimate (0.81). In their revised base-case, the company remain using the Van Hout crosswalk to provide an accurate reflection of the experience of people who have NSCLC and to ensure consistency with the original appraisal of sotorasib in TA781.

EAG comment: While acknowledging that utility values should not exceed those observed in the age and gender matched general population, the EAG prefers the use of estimates derived from the mapping function by Hernandez Alava et al. recommended in the NICE HTA manual. To overcome the issue of utility values exceeding general population estimates, values are capped at general population levels when necessary.

1.11 Key issue 11. Suboptimal approach for the modelling of the acquisition costs.

The company acknowledged this key issue and aligned its approach of modelling acquisition costs with the EAG's preferred per-pack costing approach.

EAG comment: The EAG have no further comments.

1.12 Key issue 12. Transparency issues related to insufficient responses to the clarification questions posed by the EAG.

The company incorporated the majority of outstanding questions posed by the EAG in its response to technical engagement.

EAG comment: The EAG appreciates the company's effort of addressing outstanding questions in its technical engagement response.

1.13 Severity

A summary of the QALY shortfall analysis based on the EAGs updated base-case is provided in Table 2 below. Although a severity modifier of 1.2 is applicable for the EAG base-case, results in section 1.14 and 1.15 are also provided for severity modifiers of 1.0 and 1.7.

Table 2: Summary of the QALY shortfall analysis based on the EAGs updated base-case.

	Value	Source
Treatment	Docetaxel	Company submission
Age (years)	63.5 (rounded to 64)	CodeBreaK 200
Female (%)	40.9 (rounded to 41)	CodeBreaK 200
QALY for the untreated (discounted)	■	Economic model
Absolute shortfall	10.60	Schneider et al. QALY shortfall calculator
Proportional shortfall (%)	93.97	Schneider et al. QALY shortfall calculator
QALY weighting	1.2	Schneider et al. QALY shortfall calculator
Abbreviations: QALY = quality-adjusted life year.		

1.14 Updated deterministic and probabilistic company and EAG base-case

Table 3: 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	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£47,893	-0.60	-0.26
				1.2	██	£39,911	-0.51	-0.17
				1.7	██	£28,172	-0.30	0.04
EAG_1: use of utility values derived from the mapping function by Hernandez Alava et al.								
Docetaxel	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£45,395	-0.58	-0.23
				1.2	██	£37,829	-0.49	-0.14
				1.7	██	£26,703	-0.26	0.08
EAG_2: individually fitted gamma from CodeBreaK 200 for sotorasib and docetaxel OS								
Docetaxel	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£74,637	-0.74	-0.40
				1.2	██	£62,198	-0.68	-0.35
				1.7	██	£43,904	-0.55	-0.21
EAG_3: individually fitted log-logistic from CodeBreaK 200 for sotorasib and docetaxel PFS								
Docetaxel	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£47,102	-0.58	-0.25
				1.2	██	£39,252	-0.50	-0.16

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
				1.7	■	£27,707	-0.28	0.06
EAG_4: HR estimated using PFS and time on treatment from CodeBreaK for sotorasib and docetaxel TTD								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	£59,999	-0.86	-0.43
				1.2	■	£49,999	-0.77	-0.34
				1.7	■	£35,294	-0.56	-0.13
EAG_5: include treatment waning starting at 2 years with gradual decline over 5 years								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	£50,427	-0.62	-0.28
				1.2	■	£42,022	-0.54	-0.20
				1.7	■	£29,663	-0.33	0.01
EAG base-case								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	£58,348	-0.54	-0.27
				1.2	■	£48,623	-0.48	-0.21
				1.7	■	£34,322	-0.34	-0.07
Probabilistic								
Company's updated base-case								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	£48,611	-0.61	-0.27
				1.2	■	£40,509	-0.53	-0.18
				1.7	■	£28,595	-0.31	0.03
EAG's updated base-case								

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
Docetaxel	████	██	-		-	-	-	-
Sotorasib	████	██	████	1.0	██	£61,706	-0.55	-0.28
				1.2	██	£51,422	-0.50	-0.23
				1.7	██	£36,298	-0.37	-0.09
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								

1.15 Updated deterministic and probabilistic scenario analyses

Table 4: 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	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£58,348	-0.54	-0.27
				1.2	██	£48,623	-0.48	-0.21
				1.7	██	£34,322	-0.34	-0.07
EAG_6: Median RDI from CodeBreaK 200 for sotorasib and docetaxel								
Docetaxel	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£67,384	-0.67	-0.35

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
				1.2	■	£56,153	-0.61	-0.30
				1.7	■	£39,637	-0.47	-0.15
EAG_7: individually fitted log-logistic from CodeBreaK 200 for sotorasib OS								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	£44,829	-0.47	-0.19
				1.2	■	£37,357	-0.39	-0.11
				1.7	■	£26,370	-0.21	0.08
Probabilistic								
Updated EAG base-case								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	£61,706	-0.55	-0.28
				1.2	■	£51,422	-0.50	-0.23
				1.7	■	£36,298	-0.37	-0.09
*EAG_6: median RDI from CodeBreaK 200 for sotorasib and docetaxel								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	Dominant	0.35	0.32
				1.2	■	Dominant	0.40	0.38
				1.7	■	Dominant	0.54	0.51
EAG_7: individually fitted log-logistic from CodeBreaK 200 for sotorasib OS								
Docetaxel	■	■	-		-	-	-	-
Sotorasib	■	■	■	1.0	■	£47,907	-0.50	-0.21
				1.2	■	£39,922	-0.43	-0.14
				1.7	■	£28,181	-0.25	0.04

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
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 *Details regarding the observed discrepancy between deterministic and probabilistic results for EAG_6 are discussed in EAG comment b) in Section 4.2.8 of the EAG report.²								

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]: Technical engagement response form [Data on file]*. London: NICE, 2025. 43p.
- [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*. York: Kleijnen Systematic Reviews Ltd., 2025. 126p.
- [3] 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]: Appendices - Company technical engagement response [Data on file]*. London: NICE, 2025. 85p.
- [4] Amgen Inc. *Sotorasib observational research study report: 20240164 FINAL (v1.0). 23 May 2025 [Data on File]*, 2025. 153p.
- [5] Hatswell AJ, Chaudhary MA, Monnickendam G, Moreno-Koehler A, Frampton K, Shaw JW, et al. Modelling health state utilities as a transformation of time to death in patients with non-small cell lung cancer. *Pharmacoeconomics* 2024; 42(1):109-116

We had a few queries and wondered if you could help with these.

1. Key issue 5: Please could you provide extrapolations beyond 36 months for OS and PFS from the CodeBreak 200 trial? The survival plots in the Company's TE response appendices (figure 11 and figure 12), only extrapolate to 36 months, and ideally we would like to present graphs for a lifetime horizon. They may be clearer if they only included the KMs and the EAG's and company's preferred models, but I'll let you advise on that.

EAG comment: These plots are not readily available in the current economic model, but should be easy to provide by the company.

2. Key issue 5: In the company's TE response, table 2, the company have provided landmark OS results using different survival models. The Weibull estimates in the table say "(PH)" which I assume means proportional hazards and thus are results of a combined model? Their preferred model is an independent Weibull model, so I wondered if the estimates would be different. Have I misunderstood this? If they are different, please could you provide these?

EAG comment: PH here indeed refers to proportional hazards. This is specified for the Weibull as it can either be parameterised as a PH model or an accelerated failure time model. This relates to how the treatment effect is handled within the Weibull model when two treatment are compared. NICE DSU TSD 14 provides more details on this. I can confirm that the landmark estimates in Table 2 of the company's TE response match the individually fitted 3y and 5y Weibull estimates in the economic model.

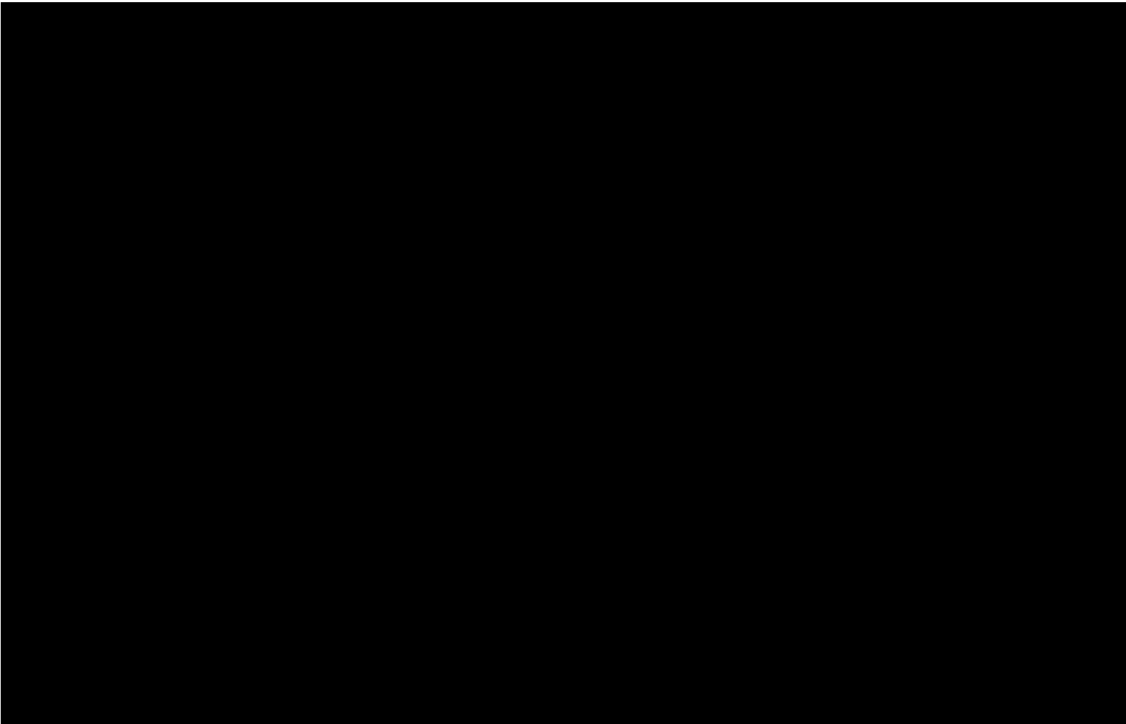
3. Key issue 6: For modelling time to treatment discontinuation (TTDD), the data provided in the company TE response (such as Table 3, Figure 12, Figure 13 and Table 4) of the different modelling approaches are not that easy to compare. Please could you provide summary statistics (such as completing the table below) to help committee compare the outcomes of the EAG and company's approaches? Alternatively, please could you provide the TTDD curves used in the model (both EAG's and company's preferred models). I tried to do this using the updated Company model, but wasn't confident I had amended all the settings correctly. If the committee prefer to use CAS RWE in the base case for OS and TTNTD (proxy for PFS), please could you confirm the EAG's preference for approach to modelling TTDD (in case it changes)?

EAG comment: It is unclear to the EAG where the docetaxel time-on-treatment quartiles were retrieved from by the company and the EAG was unable to identify these numbers in the economic model. Hence, the information requested in the Table below should be provided by the company.

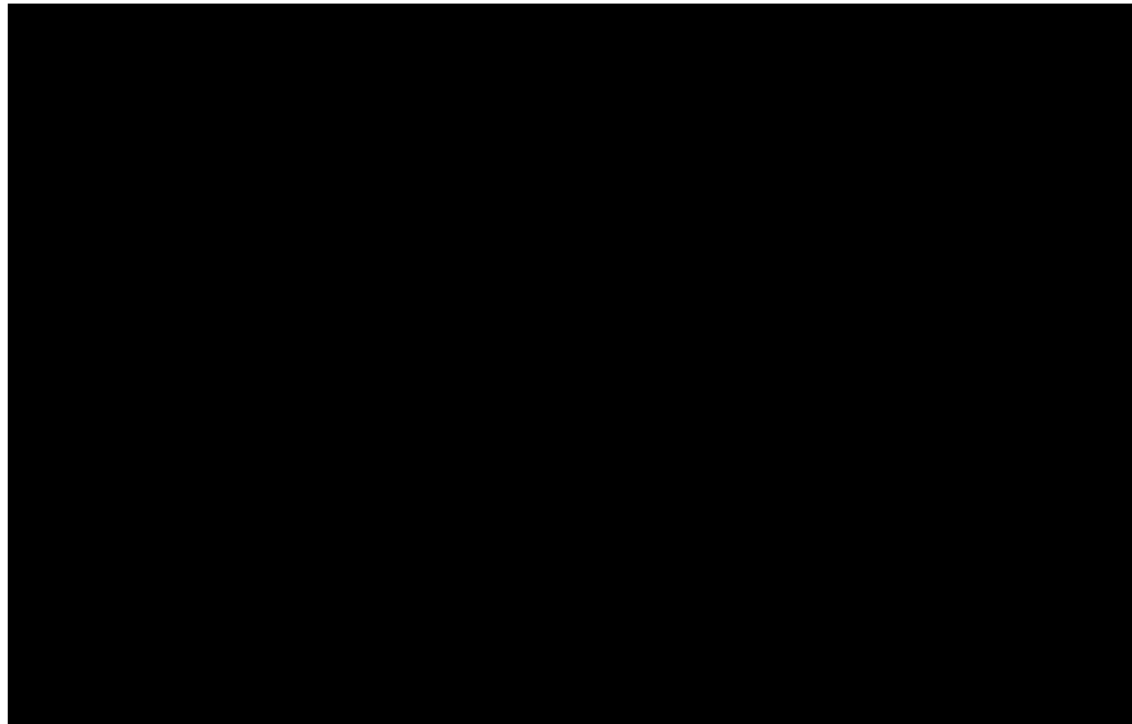
Quantile	Duration of docetaxel treatment (months)			Duration of sotorasib treatment (months)		
	Company BC: CAS RWE	Company SA: CB200	EAG BC: CB200	Company BC: CAS RWE	Company SA: CB200	EAG BC: CB200
25%	■	■				
50% (median)	■	■				
75%	■	■				

Please find the company’s and EAG’s base-case PFS and TTD curves in the plots below:

PFS and TTD curves used in company base-case (retrieved from the TTD sheet in the economic model with company settings).



PFS and TTDD curves used in EAG base-case (retrieved from the TTD sheet in the economic model with EAG settings).



As stated in section 4.2.5 of the EAG report, the EAG prefers CodeBreakK 200 as the source to inform TTDD. However, if the committee prefer to use CAS RWE in the base case for OS and TTNTD (proxy for PFS), it would be reasonable to also inform TTDD based on CAS RWE (despite its limitations). If the EAG had to select the most suitable TTDD curves based on CAS RWE, it would select the individually fitted log-logistic for sotorasib and the individually fitted gamma for docetaxel based on 1) the evidence suggesting violation of the PH assumption (CS Figures 45 and 46), and 2) their best statistical fit (AIC/BIC, CS Table 47) to the relatively mature KM data (i.e. [REDACTED] and [REDACTED] for sotorasib and docetaxel respectively).

4. Key issue 6: In the TE response critique, you mention that scenario analysis could be explored where the TTDD curve is capped at PFS to prevent crossing of curves (which would mean that in the model, patients cannot continue treatment after progression). Is it possible to provide this scenario analyses?

EAG comment: TTDD is capped at PFS for all currently provided analyses (see cell E100 on the Settings tab in the economic model).

5. In the EAG report, section 4.2.5 e), you mention that you disagree with the company's choice of parametric model for OS and TTNTD (proxy for PFS) when using CAS RWE. Please could you complete the table below to help committee compare the different approaches?

EAG comment: Please find the numbers in the completed Table below.

Estimates	Company model		EAG model		EAG clinical expert	
	Sot	Doc	Sot	Doc	Sot	Doc
3-year OS	■	■	■	■	■	■
5-year OS	■	■	■	■	■	■
3-year TTNTD	■	■	■	■	■	■

6. If the committee were to decide to use CAS RWE as their main data source, we would need to present cost effectiveness results and scenario analyses using this data source, but with some of the EAG's preferred assumptions. Please could you provide these by completing the table below? If there are any further scenario analyses that you think could help with decision-making, please could you provide these too? For example, using progression-based approach to utilities?

(Adapted from table 3 of EAG critique)

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	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£47,893	-0.60	-0.26
				1.2	██	£39,911	-0.51	-0.17
				1.7	██	£28,172	-0.30	0.04
Jointly fitted gamma from CAS RWE for OS (EAG's preferred model for CAS RWE data)								
Docetaxel	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£56,235	-0.66	-0.32
				1.2	██	£46,862	-0.58	-0.24
				1.7	██	£33,079	-0.40	-0.06
Jointly fitted Weibull for TTNTD (proxy for PFS) from CAS RWE (EAG's preferred model for CAS RWE data)								
Docetaxel	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£47,811	-0.60	-0.26
				1.2	██	£39,842	-0.51	-0.17
				1.7	██	£28,124	-0.30	0.05
Individually fitted log-logistic for sotorasib TTDD and individually fitted gamma for docetaxel TTDD from CAS RWE								
Docetaxel	██████	██	-		-	-	-	-
Sotorasib	██████	██	██████	1.0	██	£53,273	-0.72	-0.33
				1.2	██	£44,395	-0.63	-0.25
				1.7	██	£31,337	-0.41	-0.03

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY	NHB (£20,000 WTP)	NHB (£30,000 WTP)
EAG_5: include treatment waning starting at 2 years with gradual decline over 5 years								
Docetaxel	████	██	-		-	-	-	-
Sotorasib	████	██	████	1.0	██	£50,427	-0.62	-0.28
				1.2	██	£42,022	-0.54	-0.20
				1.7	██	£29,663	-0.33	0.01
EAG preferred scenario if CAS RWE data were used for clinical efficacy inputs								
Docetaxel	████	██	-		-	-	-	-
Sotorasib	████	██	████	1.0	██	£64,946	-0.78	-0.41
				1.2	██	£54,121	-0.71	-0.34
				1.7	██	£38,203	-0.54	-0.16
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								

7. Please could you provide an updated model with inputs set to the EAG's base case and instructions on how to switch the model between the Company and EAG base case? This will help us carry out threshold analysis.

EAG comment: The updated model with inputs sets to the EAG's base case and instruction on how to switch the model to company base-case were uploaded on NICE docs on 05-01-2026.

Would it be possible to have the updated EAG model (with instructions) as soon as possible? Please could we have a response to the remainder of the queries by 12 January 2026? We look forward to hearing from you. Thanks for all your work so far.

Many thanks, Enna