For public – redacted

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

Technology appraisal committee B

Chair: Baljit Singh

Lead team: Andrew Makin, Will Sullivan

External assessment group: Kleijnen Systematic Reviews (KSR)

Technical team: Enna Christmas, Alex Filby, Elizabeth Bell

Company: Amgen

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on KRAS G12C mutation-positive advanced non-small-cell lung cancer

KRAS G12C mutations associated with poor outcomes

Epidemiology

- NSCLC accounts for 80 to 85% of lung cancers in the UK.
- Non-squamous cell carcinoma (adenocarcinoma 66%; large cell 2%) is the main sub-type
- KRAS G12C mutation occurs in ~13% NSCLC → around 5,400 cases in the UK each year

KRAS G12C mutation

- The most common KRAS mutation in NSCLC is the KRAS G12C mutation → KRAS mutations are drivers of tumour proliferation and growth
- KRAS mutations are generally acknowledged as negative prognostic factors for treatment response and survival outcomes

Symptoms and prognosis

- NSCLC often diagnosed at advanced stage contributing to a poor prognosis → 5 year survival is ~16%
- Symptoms include fatigue and pain

Abbreviations: KRAS, Kirsten ras sarcoma; NSCLC, non-small cell lung cancer;

Patient perspectives

Patients consistently prefer oral therapies at home compared to infusions in hospital

Submissions from

- Oncogene Cancer Research
- Roy Castle Lung Cancer Foundation

Statements from

- 2 patient experts

Perspectives

- Patients prefer oral therapies due to a substantially lower time burden, reduced disruption to work and family responsibilities, and fewer emotionally distressing hospital visits
- Infusion appointments require travel, waiting, pre-treatment checks, post-treatment observation and exposure to infection risk. These real-world factors are highly relevant
- Docetaxel has severe side effects. It often causes hair loss, extreme tiredness, nausea, mouth sores, and tingling in hands or feet

Oral therapy at home enables greater autonomy, dignity and quality of life

Responses highlighted the importance of getting and retaining access to the best treatments they desperately need

Clinical perspectives

Sotorasib shows clinical benefit, better patient quality of life and a reduction in NHS burden

Submissions from

- Consultant clinical oncologist, lung specialist
- British Thoracic Oncology Group

Perspectives

- Docetaxel is exceptionally toxic and reduces quality of life in many patients
- Having a daily tablet rather than coming to the hospital every 3 weeks is less burdensome on both the patient and NHS (e.g. day unit chair time, nurse requirements, pharmacy time)
- Real world evidence shows toxicity is managed exceptionally well

Frailer patients than in the trials can tolerate treatment

It [sotorasib] is an advancement. Using molecular driven results to target the right patient population with an effective treatment

Other considerations

Equality considerations

Patient experts:

- Those who are neurodivergent, have cognitive impairments or physical disabilities may struggle with self-administering sotorasib
- People who can understand the instructions (such as timings to manage side effects and dosages) and remember to take the required dose every day are likely to benefit from sotorasib

Uncaptured benefits

- None identified by submissions for this evaluation

Sotorasib (LUMYKRAS, Amgen)

Marketing authorisation	MHRA conditional MA Sept 2021 for '*the treatment of 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*'
Mechanism of action	Irreversible small molecule inhibitor of KRAS. It binds specifically to the G12C mutant form of KRAS protein, locking it in an inactive conformation. Inactivation of the KRAS protein prevents signalling to downstream effectors that control proliferation and mechanisms of cell survival.
Administration	Administered orally, 960 mg (given as 8 x 120 mg tablets or 4 x 240 mg tablets) once daily until disease progression or unacceptable toxicity
Price	• £6,907 per 30-day supply (pack of 240 tablets of 120mg or 120 tablets of 240 mg) • List price 12 months treatment £84,093 • Company has confidential PAS discount in place

TA781 (March 2022)

- Sotorasib recommended in CDF within full MA
- Main uncertainties: use of unanchored ITC; utility and disutility values; magnitude of treatment waning and whether it meets EOL criteria (no longer applicable, severity can be considered)
- Data collection: Primary trials CodeBreak100 and 200 and CAS RWE

ID6287: Managed access review (2025)

- This appraisal has had a technical engagement stage

Abbreviations: MHRA, Medicines and Healthcare products Regulation Agency, KRAS, Kirsten ras sarcoma; NSCLC, non-small cell lung cancer; PAS, patient access scheme; PD-L1, programmed cell death ligand 1, CDF, Cancer Drugs Fund, MA, marketing authorisation; ITC indirect treatment comparison, EOL, end of life; CAS RWE, cancer analysis system real world evidence;

Key issues for discussion

Link	Key issue	ICER impact
1	Is docetaxel the only relevant comparator?	Unknown
2	• Should OS, PFS and TTDD be informed by the same evidence source? • Which evidence source (CB200 or CAS RWE) should be used to inform OS, PFS and TTDD in the economic model?	Large
3	If CB200 trial is used as clinical efficacy source: • Sotorasib: should OS be modelled using independent log-normal or gamma? • Docetaxel: should OS be modelled using independent Weibull or gamma?	Large
4	If CAS RWE study is used as clinical efficacy source: • Should OS be modelled using jointly fitted generalised gamma or gamma?	Small
5	Is the company's approach to modelling utilities appropriate for decision-making?	Small/ unknown
6	Is it appropriate to apply a QALY severity weighting of x1.2 or x1.7?	Large

Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer Analysis System real world evidence; OS, overall survival; PFS, progression free survival; TTNTD, time to next treatment or death; TTDD, time to treatment discontinuation or death; QALY quality adjusted life year;

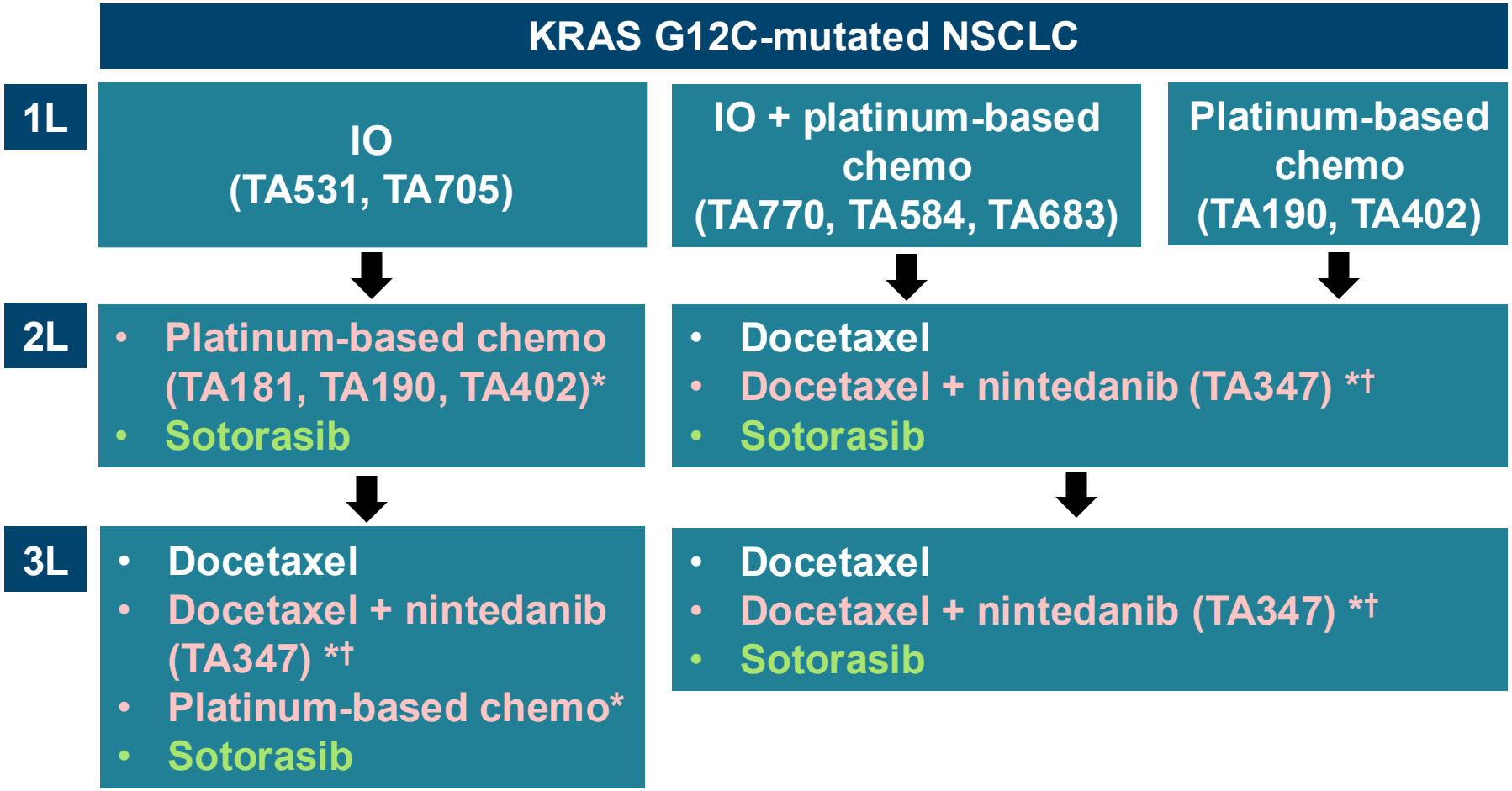
Other issues

	Resolved issues	ICER impact
1	Sotorasib acquisition costs – using per pack instead of per day costs – EAG and company agree	N/A
2	Use of treatment-dependent utilities – EAG and company agree	N/A
3	Incomplete information provided for parametric model selection (CB200 data)	Small
4	Transparency issues due to insufficient responses – resolved at technical engagement	N/A

Link	Unresolved issues	ICER impact
1	Lack of subgroup analysis – company position within the full MA	Unknown
2	Use of non-randomised study to inform treatment efficacy (CAS RWE) - unresolvable	Large
3	Modelling approach to PFS when using CodeBreak 200 data source	Small
4	Modelling approach to TTNTD (proxy for PFS) when using CAS RWE data source	Small
5	Modelling of relative treatment effect waning	Small
6	Using mapping function that is not in NICE reference case	Small

Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer Analysis System real world evidence; OS, overall survival; PFS, progression free survival; TTNTD, time to next treatment or death; TTDD, time to treatment discontinuation or death; QALY quality adjusted life year;

Treatment pathway



Key

- **Green:** technology being appraised
- **Pink (*):** rarely used treatment and so not considered comparators
- **†:** Nintedanib is only reimbursed for patients with adenocarcinoma; other histologies receive docetaxel monotherapy

See decision problem

Abbreviations: IO, immunotherapy; 1L, first line; 2L second line; 3L, third line; KRAS, Kristen ras; NSCLC, non-small cell lung cancer

Unknown impact

Key issue 1: Relevant comparators

Company exclude nintedanib + docetaxel as a comparator

Background: TA781 – nintedanib + docetaxel was relevant comparator and company provided analysis

Company

- Docetaxel is only relevant comparator. In CAS RWE study, few patients received nintedanib + docetaxel (~5% of patients after 2L+ chemotherapy and less than 9 patients in 2L)
- Only docetaxel is recognised in NICE lung cancer guideline (NG122, updated 2024)
- Recent RWE (Heseltine 2022) suggests nintedanib + docetaxel has poorer outcomes than suggested in the pivotal trial that nintedanib recommendation was based on (LUME-Lung 1)
- Platinum-based chemo not in NICE scope and excluded as rarely used after 1L immunotherapy (alone) for KRAS G12C-mutation population

EAG comments

- Reasonable to exclude nintedanib + docetaxel and EAG clinical expert in agreement
- Requested clarification of declining use but company could not provide due to NHS Digital reporting rules

Technical engagement:

Clinical experts – 1 said nintedanib + docetaxel is rarely used, 1 said it is routinely used

Patient experts – Patients tend to receive docetaxel alone

Abbreviations: CAS RWE, Cancer Analysis System real world evidence; 2L, second line;

Is docetaxel the only relevant comparator?

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

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Key clinical studies: overview

See baseline characteristics

		Study data used in economic model	
	CodeBreak 100 (n=174)	**CodeBreak 200 FAS (n=345)**	**CAS RWE study (n=1,665)**
Design	Single-arm open-label Phase 1/2 trial	Phase 3, multicentre, randomised, open-label, active-controlled study	Comparative, retrospective, new-user cohort study using secondary RWE*
Population	Confirmed *KRAS G12C*-mutated NSCLC; >1-3 prior lines of treatment	Locally advanced/ unresectable or metastatic *KRAS G12C*-mutated NSCLC; ≥1 prior treatment	Locally advanced or metastatic NSCLC. KRAS G12C mutation status unknown for docetaxel
Intervention	Sotorasib	Sotorasib	Sotorasib
Comparator(s)	None	Docetaxel	Docetaxel
Duration	Ongoing. Data cut: 28 + 36-month KMs presented for PFS + OS respectively	Ongoing. Data cut: 26 months	39 months
Key outcomes	PFS, OS, response rates, AEs, HRQoL	PFS, OS, response rates, AEs, HRQoL	OS, TTDD, TTNTD
Used in model?	No	Yes – EAG base case	Yes – company base case

*Datasets used: Cancer Outcomes and Services Dataset (COSD), Systemic Anti-Cancer Therapy (SACT), and Molecular Diagnostics (MDx)

Abbreviations: FAS, full analysis set; AE, adverse event; PFS, progression free survival; OS, overall survival; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; KRAS, Kristen ras; TTDD, time to treatment discontinuation or death; TTNTD, time to next treatment or death; CAS, Cancer Analysis System; KM, Kaplan-Meier

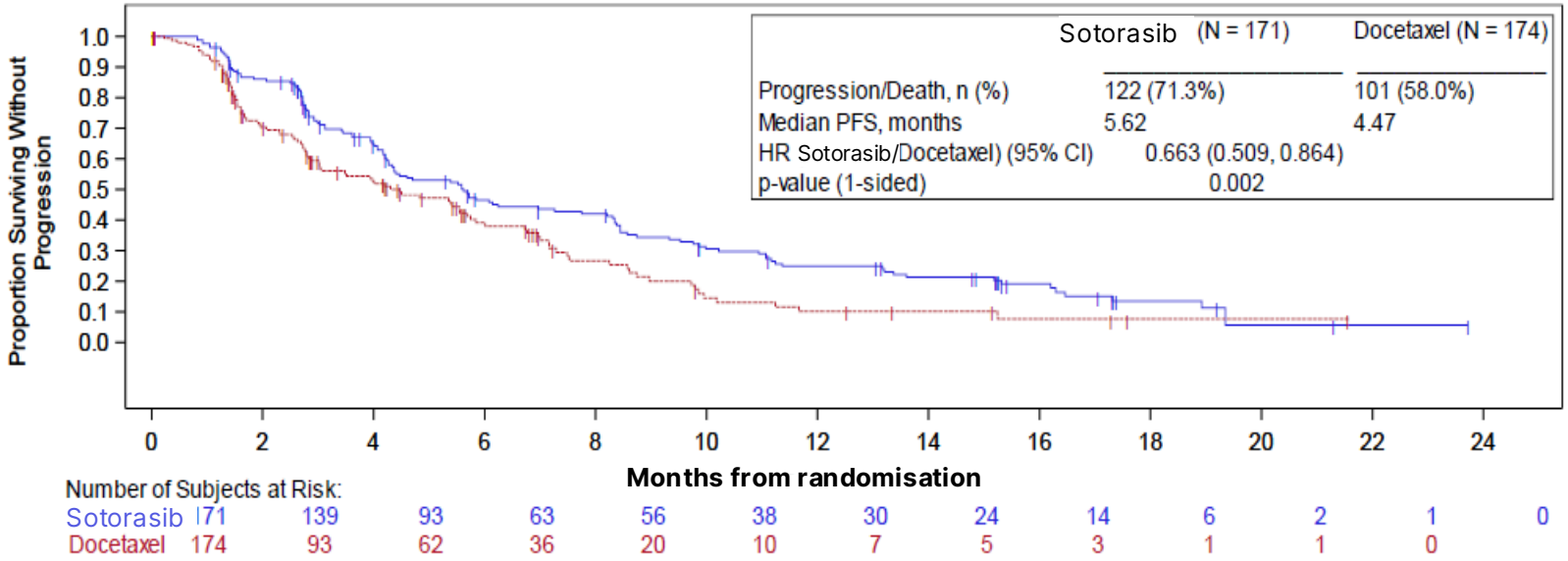
Key clinical trial results – CodeBreak 200

Sotorasib shows statistically significant improvement in primary end point, PFS

See OS not adjusted for crossover

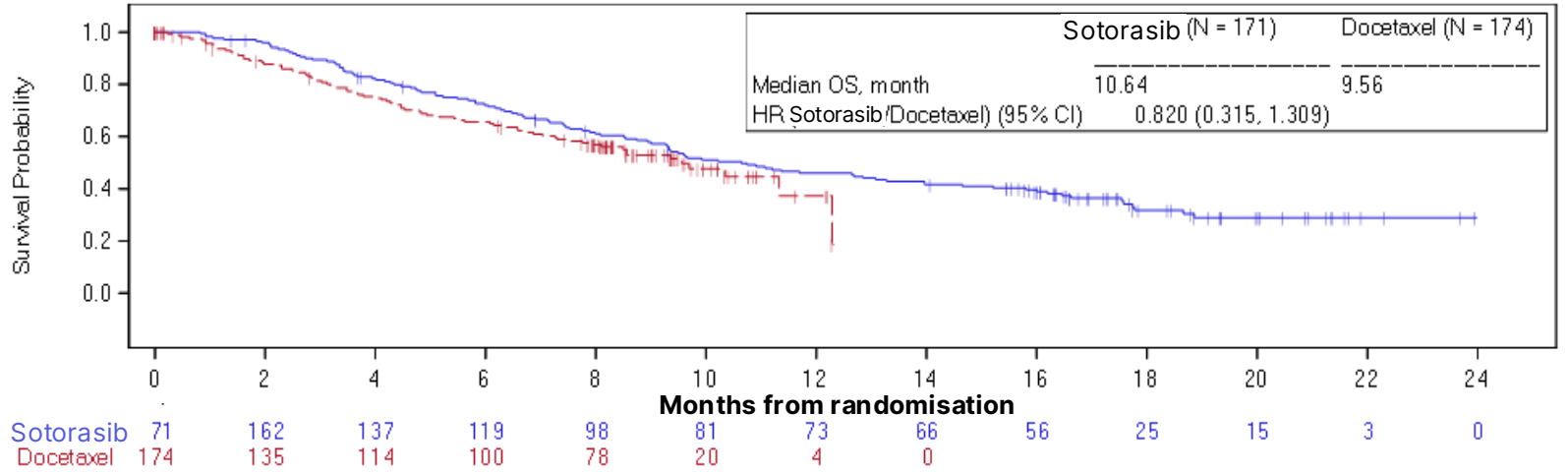
PFS by BICR (FAS) KM plot

- PFS HR 0.663 (95% CI: 0.51 to 0.86)
- Sotorasib improves PFS compared to docetaxel



OS KM plot

- Adjusted for treatment switching (two-stage estimation)
- OS HR: 0.820 (95% CI: 0.32 to 1.31)
- No statistically significant difference in adjusted OS compared to docetaxel



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; FAS, final analysis set;

Key clinical study results – CAS RWE

See baseline characteristics

Sotorasib improves OS and TTNTD (proxy for PFS)

Statistical analysis conducted

- Propensity score weighting used to balance covariates/baseline characteristics between groups using standard mortality ratio weighting (SMRW)
- Average treatment effect of the treated (ATT) estimand was presented
- No imputation performed for missing baseline data. Pragmatic approach preserves sample size but may introduce bias

Results

- **TTNTD HR**: 0.567 (95% CI: 0.49 to 0.66)
- Sotorasib improves TTNTD

- **OS HR**: 0.633 (95% CI: 0.54 to 0.75)
- Sotorasib improves OS

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; SMRW, standardised mortality ratio weighting; ATT, average treatment effect in the treated; TTNTD, time to next treatment or death; CAS RWE, Cancer Analysis System real world evidence; 2L+, second line treatment or later;

Key clinical study results summary

- CodeBreak 200 trial suggests smaller relative treatment effect (in terms of OS and PFS) compared to CAS RWE study (HRs are closer to 1)
- Relative OS treatment effect in CAS RWE aligns with Flatiron US RWE study

Study	Overall survival			Progression-free survival		
	Sotorasib N	Docetaxel N	HR (95% CI)	Sotorasib N	Docetaxel N	HR (95% CI)
CodeBreaK 200 (RCT, global dataset)	171	174	0.820 (0.32, 1.31) Adjusted for treatment switching	171	174	0.66 (0.51, 0.86)
CAS RWE study (Retrospective, England dataset)	394	1,271	0.633 (0.54, 0.75)	394	1,271	TTNTD (proxy for PFS): 0.567 (0.49, 0.64)*
Flatiron US RWE at 2L (Retrospective, US dataset)	164	116	0.65 (0.49, 0.87)	N/A		
	102	58	0.62 (0.41, 0.93) After SMRW + PSW			

* EAG corrected

See full summary of OS and PFS results

Abbreviations: 2L, second-line; CAS, Cancer Analysis System; CI, confidence interval; HR, hazard ratio; N/A, not applicable; NE, not estimable; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RWE, real-world evidence; SMRW, standardised mortality ratio weighting; PSW, propensity score weighting; TTNTD, time to next treatment or death;

Large impact

Key issue 2: Which study data to use in model (1/3)

The two key clinical evidence sources suggest different treatment effects and impacts CE results

Company: CAS RWE data should be used in economic model because:

CodeBreak 200 (RCT)	CAS RWE (retrospective study)
Smaller sample size (n=345) as patient enrolment was reduced. So, trial no longer powered to detect comparative OS	Larger sample size (n=757)
Shorter follow up duration – 24 months	Longer follow up duration – 39 months
Conducted in 149 centres globally (including UK)	Entirely UK based, reflecting UK standard practice
Treatment switching from docetaxel to sotorasib arm occurred (n=59, 34%) and may not be fully adjusted for. So, OS estimates may not be reliable	Exemplifies best practice in RWE generation. Study commissioned after TA781 managed access agreement with NICE/NHSE, to address uncertainties

2 main structural limitations of CAS RWE:

1) Unknown KRAS mutation status - Clinical experts noted that mutation status may have prognostic influence, but is confounded by smoking history, co-mutation patterns and comorbidities. So KRAS-unknown docetaxel group remains an acceptable comparator. See KM by mutation status.

2) Smoking history not recorded and has potential to be unmeasured confounder. There is no evidence of smokers/non-smokers having different outcomes with docetaxel and sotorasib. Subgroup analysis of PFS (CB200) suggest no difference between former and current smokers. See forest plot of subgroup analysis

Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; RCT, randomised control trial; OS, overall survival; PFS, progression-free survival; TTNTD, Time to next treatment or death; NHSE, National Health Service England; MA, managed access

Large impact

Key issue 2: Which study data to use in model (2/3)

EAG comments: Prefers CB200 data for OS, PFS and TTDD but there are several further considerations:

CodeBreak 200 (RCT)	CAS RWE (retrospective study)
Randomised study and baseline characteristics align between treatment arms	Non-randomised – risk of selection bias and confounders. Efforts were made through recruitment, statistical and sensitivity analysis to ensure populations receiving each treatment were similar, that differences were adjusted for, and impact was tested
High rate of withdrawal from docetaxel arm compared to sotorasib (n= 39 vs 12)	ROBINS-1 assessment result: Serious risk of bias. Result driven by domains “Missing data” and potentially “Confounding”
Provides a direct source of PFS, which is unaffected by treatment switching	Concerns about using TTNTD as proxy for PFS
Alignment of sources used in economic model (characteristics, OS, PFS and TTDD)	Misalignment of sources in economic model for baseline characteristics (CB200) and OS, PFS and TTDD (CAS RWE)
Survival curves may suggest no clear difference in results by KRAS mutation status, though sample size is probably too small for any confidence in this conclusion	No information about key prognostic factors: KRAS mutation status unknown in [redacted] and [redacted] of docetaxel and sotorasib patients, although impact of mutation status on outcomes unclear. No brain metastasis status in [redacted] and [redacted] of docetaxel and sotorasib patients

Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; RCT, randomised control trial; OS, overall survival; PFS, progression-free survival; TTDD, time to treatment discontinuation or death; TTNTD, Time to next treatment or death; KRAS, Kirsten rat sarcoma virus;

Large impact

Key issue 2: Which study data to use in model (3/3)

The two key clinical evidence sources suggest different treatment effects and impacts CE results

Technical engagement clinical expert comments

- RWE is large and probably more relevant as it represents what clinicians with expertise are doing, based on their knowledge and skillset
- 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

Technical engagement patient expert comments

- KRAS is generally considered to be a poor prognostic indicator so would anticipate a known population with KRAS mutations to have worse outcomes
- The most meaningful comparative analysis is one that reflects routine NHS care and outcomes

- Should OS, PFS and TTDD be informed by the same evidence source?
- Which evidence source (CB200 or CAS RWE) should be used to inform OS, PFS and TTDD in the economic model?

Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; Kirsten rat sarcoma; CE, cost effestiveness;

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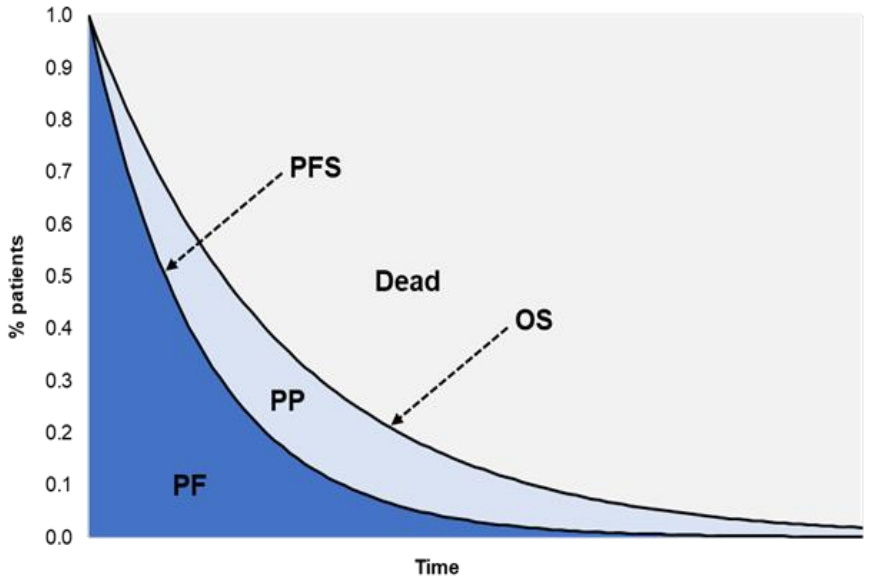
Company's model overview

Model structure

- Partitioned survival model
- Lifetime (20-year) time horizon
- Weekly cycle length
- State occupancy informed by CAS RWE study
- TTNTD data as a proxy for PFS



Treatment affects QALYs by:

- Increasing QALYs due to improvements in OS and TTNTD in sotorasib arm compared to docetaxel
- Size of QALY change dependent on clinical evidence source

Treatment affects costs by:

- Increasing costs, mostly driven by drug acquisition costs

Assumptions with greatest impact:

- Source of clinical data in economic model (CB200 or CAS RWE studies)
- Modelling approach of time to treatment discontinuation
- Severity QALY weighting

Abbreviations: PF, progression free; PP, post-progression; PFS, progression free survival; OS, overall survival; TTNTD, time to next treatment or death; CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; QALY, quality adjusted life year

Large impact

Key issue 3: CB200 OS model selection (1/2)

EAG and company use different models to estimate long-term OS

Only relevant if CB200 is preferred data source

Company

- Uses CB200 data in scenario analysis (as prefers using CAS RWE data in base case). In scenario analysis:
  - Sorotasib OS: independent lognormal has best statistical fit and visual fit to observed hazards
  - Docetaxel OS: independent Weibull preferred but gamma is logical alternative

EAG comments

- Uses CB200 data in base case. Prefers independent gamma for sotorasib and docetaxel as long-term estimates align with EAG clinical expert estimates. For docetaxel, Weibull underestimates OS
- Company's validation of OS extrapolations is limited and does not align with EAG clinical expert estimates

Stakeholder	Sotorasib			Docetaxel		
	OS model	3-year OS	5-year OS	OS model	3-year OS	5-year OS
Company (scenario with CB200)	Lognormal	[redacted]	[redacted]	Weibull	[redacted]	[redacted]
EAG base case	Gamma	[redacted]	[redacted]	Gamma	[redacted]	[redacted]
EAG clinical expert	-	7%	2%	-	5%	2%
EAG (scenario analysis)	Log-logistic	[redacted]	[redacted]	Gamma	[redacted]	[redacted]
Company base case (with CAS RWE)	Jointly-fitted gen. gamma	[redacted]	[redacted]	Jointly-fitted gen. gamma	[redacted]	[redacted]
See other OS model estimates						

NICE Abbreviations: OS, overall survival; CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; gen. gamma, generalised gamma;

Large impact

Key issue 3: CB200 OS model selection (2/2)

EAG and company use different models to estimate long-term OS

Only relevant if CB200 is preferred data source

Survival plots with observed KMs and survival models

- Should sotorasib OS be modelled using independent log-normal or gamma?
- Should docetaxel OS be modelled using independent Weibull or gamma?

See PFS survival plots

Abbreviations: OS, overall survival; PFS, progression free survival; CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence;

Small impact

Key issue 4: CAS RWE OS model selection (1/2)

Only relevant if CAS RWE is preferred data source

EAG and company use different models to estimate long-term OS

Company

- Company base case uses jointly fitted generalised gamma to model OS
- Justification: most plausible extrapolations, good visual fit and second-best statistical fit

EAG comments

Prefers to use CB200 data to inform OS in base case. But in scenario where CAS RWE data is used:

- Long-term OS estimates from company's models do not align with EAG clinical expert estimates
- Jointly fitted gamma curves have worse visual and statistical fit to observed data. But long-term estimates are more aligned with EAG expert opinion
- So, jointly fitted gamma may be more suitable for OS. However, clinical expert opinions may differ and should be taken with caution

Estimates	Company model		EAG model		EAG clinical expert	
	Sotorasib	Docetaxel	Sotorasib	Docetaxel	Sotorasib	Docetaxel
3-year OS	[redacted]	[redacted]	[redacted]	[redacted]	7%	5%
5-year OS	[redacted]	[redacted]	[redacted]	[redacted]	2%	2%

Should OS be modelled using jointly fitted generalised gamma or gamma?

NICE

Abbreviations: OS, Overall survival; CAS RWE, Cancer Analysis system real world evidence; CB200, CodeBreak 200

Small impact

Key issue 4: CAS RWE OS model selection (2/2)

EAG and company use different models to estimate long-term OS

Only relevant if CAS RWE is preferred data source

Company's preferred model

[redacted]

EAG's preferred model

[redacted]

See TTNTD (proxy for PFS) survival plots

Abbreviations: OS, Overall survival; TTNDT, time to next treatment or death; PFS, progression free survival; CAS RWE, Cancer Analysis system real world evidence;

Small/ unknown impact

Key issue 5: Suboptimal approach to estimating utilities

Company's arguments for not providing requested analysis insufficiently justified and approach can be improved

Background – TA781: committee recognised uncertainty with time-to-death (TTD) approach. Progression-based (PB) approach also plausible

Company

- TTD approach preferred as Hatswell et al, (2010) showed TTD better reflects deterioration in QoL than PB approach. Explored different mixed models (MMRMs).
- Scenario analysis using PB approach (in original submission, prior to age- and sex- matched and no capping at UK general population values, using van Hout mapping function) had small impact on ICER

EAG comments

- Accepts incorporating TTD, but this should complement a health-state progression-based approach
- Company did not provide requested MMRM (that included both progression and TTD covariates)
- Alternatively, incorporating other assumptions into company model would improve approach
- In absence of requested analysis, EAG adopts company approach (continuous TTD with same transformation), but also uses NICE reference case EQ-5D mapping function (supplementary slides)

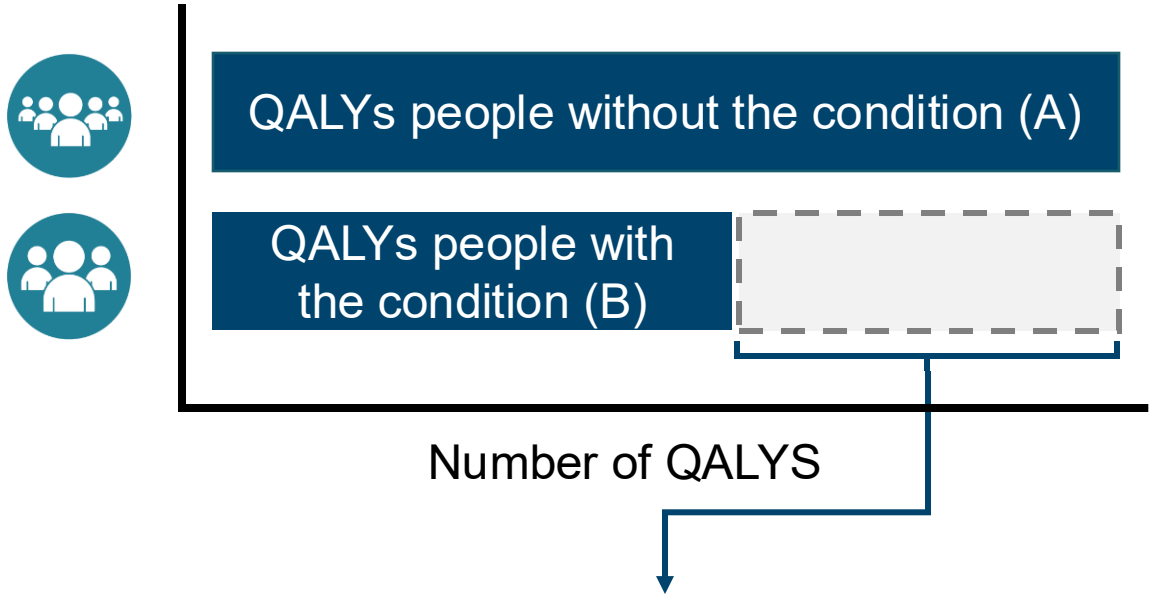
Is the company's or EAG's approach to modelling utilities more appropriate for decision-making?

See utilities by TTD and progression-based approach

Abbreviations: TTD, time-to-death; PB, progression-based; EAG, external assessment group; MMRM, mixed model for repetitive measurements; EQ-5D-5L, EuroQol 5-Dimension 5 level; AIC, Akaike information criterion; PF, progression-free; PD, progressed disease;

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Different QALY weights are applied depending on the absolute or proportional QALY shortfall:

QALY weight	Absolute QALY shortfall	Proportional QALY shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A

Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

Abbreviations: QALY, quality-adjusted life year

Large impact

Key issue 6: QALY weightings for severity

Company and EAG suggest different severity QALY weighting should be applied

Background

- TA781: committee agreed sotorasib meets the short life expectancy criterion
- In terminated appraisal TA1076, EAG applied a x1.7 weighting for adagrasib in the same indication

Company: A severity weighting of 1.7 should be applied

EAG comments

- In company base case, sources used for baseline characteristics and treatment effectiveness are misaligned, despite baseline characteristics from CAS RWE being available for shortfall calculation
- Following updates to company's approach to estimating utility, shortfall calculations are sensitive to rounding of age (63 vs 64 years). Median age = 64 years. Mean age of sotorasib = 63.4. Mean age of docetaxel = 63.6.

Severity weightings calculated using different sources:	Absolute shortfall (must be >12 or >18)	Proportional shortfall (must be >0.85 or >0.95)	Severity weighting
Company BC: Age (63); Characteristics (CB200); Efficacy (CAS RWE)	11.07	**0.9510**	x 1.7
Company BC: Age (64); Characteristics (CB200); Efficacy (CAS RWE)	10.71	**0.9495**	x 1.2
EAG BC: Age (64); Characteristics (CB200); Efficacy (CB200)	10.6	**0.9397**	x 1.2

Is it appropriate to apply a QALY severity weighting of x1.2 or x1.7?

Abbreviations: QALY, Quality adjusted life years; BC, base case; EA, exploratory analysis; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence;

Summary of company and EAG base case assumptions

Key issue/ assumption	Company base case	EAG base case	ICER Impact
Baseline characteristics source	CB200	CB200	**N/A**
Data source for OS/PFS/TTDD	CAS RWE	CB200	**Large**
How to model OS, PFS/ TTNTD and TTDD	(Preferred survival models, by data source, on next slide)		
EQ-5D mapping function	Van Hout approach	Hernandez-Alava approach	**Small**
Estimating utilities	Time-to-death approach	In absence of requested analysis adopts company's TTD approach	**Unknown**
Treatment effect waning	No waning	Gradual waning between 2 to 5 years after treatment initiation	**Small**
Severity QALY weighting	1.7	1.2	**Large**

Abbreviations: QALY, Quality adjusted life years; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; PFS, progression free survival; TTNTD, time to next treatment or death; TTDD, time to treatment discontinuation or death; TTD, time to death; HR, hazard ratio; EQ-5D, EuroQol 5-Dimension; gen. gamma, generalised gamma;

Summary of company's and EAG's preferred assumptions informing efficacy depending on evidence source used

Assumption	Key issue	Company preference	EAG preference	ICER impact
CB200 or CAS RWE	Which study data to use	CAS RWE	CB200	Large
If CAS RWE data source is used	How to model OS	Jointly fitted gen. gamma	Jointly fitted gamma	Small
	How to model TTNTD (proxy for PFS)	Jointly fitted gen. gamma	Jointly fitted Weibull	Small
	How to model TTDD	Independent gen. gamma for both arms	S: Independent log-logistic D: Independent gamma	Small
If CB200 data source is used	How to model OS	S: independent log-normal D: independent Weibull	Independent gamma for both arms	Large
	How to model PFS	S: independent exponential D: independent log-logistic	Independent log-logistic for both arms	Small
	How to model TTDD	Proportion-based approach	Prefer to fit curves to observed TTDD. Analyses not provided, so aligned with company	Unknown

Abbreviations:CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; PFS, progression free survival; TTNTD, time to next treatment or death; TTDD, time to treatment discontinuation or death; S, sotorasib; D, docetaxel; HRs, gen. gamma, generalised gamma; SA, scenario analysis; HR, hazard ratio;

Company base case results

- * Company base case assumes a QALY severity weighting of 1.7
- Uses CAS RWE data to inform OS, TTNTD (proxy for PFS) and TTDD
- These results include PAS prices

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Severity weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£39,911
				1.7	[redacted]	£28,172 *

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Severity weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£40,509
				1.7	[redacted]	£28,595 *

Abbreviations: PAS, patient access scheme; QALYs, quality adjusted life years; ICER, incremental cost effectiveness ratio; NHB, net health benefit;

EAG base case results

- * EAG base case assumes a QALY severity weighting of 1.2
- Uses CB200 data to inform OS, PFS and TTDD
- These results include PAS prices

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Severity weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£48,623*
				1.7	[redacted]	£34,322

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Severity weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£51,422*
				1.7	[redacted]	£36,298

Abbreviations: PAS, patient access scheme; QALYs, quality adjusted life years; ICER, incremental cost effectiveness ratio; NHB, net health benefit;

Using CAS RWE: Company's deterministic base case and EAG's preferred assumptions (1/2)

How EAG's preferred assumptions individually impact company base case

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY
Company base-case (using CAS RWE for efficacy data)						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£39,911
				1.7	[redacted]	£28,172
CAS RWE: OS – EAG prefers jointly fitted gamma						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£46,862
				1.7	[redacted]	£33,079
CAS RWE: TTNTD (proxy for PFS) – EAG prefers jointly fitted Weibull (small impact so excluded as key issue)						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£39,842
				1.7	[redacted]	£28,124

Abbreviations: QALY, Quality adjusted life years; ICER, incremental cost effectiveness ratio; NHB, net health benefit; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival;

Using CAS RWE: Company's deterministic base case and EAG's preferred assumptions (2/2)

How EAG's preferred assumptions individually impact company base case

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY
CAS RWE: TTDD – EAG prefers sotorasib: independent log-logistic, docetaxel: independent gamma						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£44,395
				1.7	[redacted]	£31,337
CAS RWE: EAG prefer gradual treatment effect waning 2-5 years after treatment initiation						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£42,022
				1.7	[redacted]	£29,663
EAG cumulative scenario if CAS RWE data were used (includes all above assumptions)*						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£54,121
				1.7	[redacted]	£38,203

* EAG cumulative scenario does not include using Hernandez-Alava mapping function.
Scenario analysis results of using Hernandez-Alava mapping function on next slide

Abbreviations: QALY, Quality adjusted life years; ICER, incremental cost effectiveness ratio; NHB, net health benefit; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; PFS, progression free survival; TTDD, time to treatment discontinuation or death;

EAG deterministic scenario analysis (on company base case)

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY
Company base-case (using CAS RWE for efficacy data)						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£39,911
				1.7	[redacted]	£28,172
Scenario analysis: EAG prefer using Hernandez-Alava function to map EQ-5D-5L to -3L						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£37,829
				1.7	[redacted]	£26,703

Abbreviations: QALY, Quality adjusted life years; ICER, incremental cost effectiveness ratio; NHB, net health benefit; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; RDI, relative dose intensity; EQ-5D, EuroQol 5-Dimension 5 level

Using CB200: EAG deterministic base case and company's preferred assumptions

How company's preferred assumptions (when using CB200 data) individually impact EAG's base case

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY
EAG base-case (using CB200 data for OS, PFS and TTDD)						
Docetaxel	[redacted]	[redacted]	-			
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£48,623
				1.7	[redacted]	£34,322
CB200: OS – Company prefer sotorasib: independent log-normal, docetaxel: independent Weibull						
Docetaxel	[redacted]	[redacted]	-			
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£35,875
				1.7	[redacted]	£25,323
CB200: PFS – Company prefer sotorasib: independent exponential. EAG and Company agree docetaxel: independent log-logistic						
Docetaxel	[redacted]	[redacted]	-			
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£45,448
				1.7	[redacted]	£32,081

Abbreviations: QALY, Quality adjusted life years; ICER, incremental cost effectiveness ratio; NHB, net health benefit; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; Progression free survival; TTDD, time to next treatment or death;

EAG deterministic scenario analysis (on EAG base case)

Technology	Total costs	Total QALYs	Incremental costs (£)	Severity modifier	Incremental QALYs	ICER £/QALY
Scenario analysis 1: Median RDI from CB200 for sotorasib and docetaxel						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£56,153
				1.7	[redacted]	£39,637
Scenario analysis 2: CB200, Sotorasib OS: independent log-logistic						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.2	[redacted]	£37,357
				1.7	[redacted]	£26,370

- **Scenario analysis 1:** RDI data is skewed so using mean or median RDI impacts cost-effectiveness results. Company and EAG base case uses means. See further information
- **Scenario analysis 2:** EAG believes fitting independent log-logistic models to sotorasib OS is also plausible (as well as independent gamma, which was used in EAG base case)

Abbreviations: QALY, Quality adjusted life years; ICER, incremental cost effectiveness ratio; NHB, net health benefit; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; RDI, relative dose intensity

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues for discussion

Link	Key issue	ICER impact
1	Is docetaxel the only relevant comparator?	Unknown
2	• Should OS, PFS and TTDD be informed by the same evidence source? • Which evidence source (CB200 or CAS RWE) should be used to inform OS, PFS and TTDD in the economic model?	Large
3	If CB200 trial is used as clinical efficacy source: • Sotorasib: should OS be modelled using independent log-normal or gamma? • Docetaxel: should OS be modelled using independent Weibull or gamma?	Large
4	If CAS RWE study is used as clinical efficacy source: • Should OS be modelled using jointly fitted generalised gamma or gamma?	Small
5	Is the company's approach to modelling utilities appropriate for decision-making?	Small/ unknown
6	Is it appropriate to apply a QALY severity weighting of x1.2 or x1.7?	Large

Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer Analysis System real world evidence; OS, overall survival; PFS, progression free survival; TTNTD, time to next treatment or death; TTDD, time to treatment discontinuation or death; QALY quality adjusted life year; RDI, relative dose intensity;

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

Supplementary appendix

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Supplementary appendix

Link	Contents	ICER impact
1	Baseline characteristics in CB200 and CAS RWE	N/A
2	CB200 OS Kaplan-Meier, FAS without crossover adjustment	N/A
3	Unweighted KM plot for docetaxel OS by KRAS mutation status (CAS RWE data)	N/A
4	Subgroup analysis of PFS (CB200 data)	N/A
5	Survival model selected for OS from CB200	Large
6	Survival model selected for PFS from CB200	Small
7	Survival model selected for OS and TTNTD from CAS RWE	Small
8	Evidence source for modelling TTDD	Large
9	Modelling treatment effect waning	Small
10	Lack of subgroup analysis	Unknown
11	Incorrect mapping of EQ-5D-5L to -3L	Small
12	Estimating utilities using time-to-death approach	Unknown
13	Using mean or median RDI in economic model	Large
14	Decision problem	N/A
15	Key clinical study results summary	Large

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Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer Analysis System real world evidence; OS, overall survival; PFS, progression free survival; TTNTD, time to next treatment or death; EQ-5D-5L / 3L, EuroQol 5-Dimension 5 level / 3 level; QALY quality adjusted life year;

Baseline characteristics

* ECOG/age at index for CAS RWE study.
Full baseline characteristics available in CS

	CodeBreak 200		CAS RWE	
	Docetaxel (n=174)	Sotorasib (n=171)	Docetaxel (n=1,271)	Sotorasib (n=394)
Age mean (median)*	63.6 (64)	63.4 (64)	[redacted]	[redacted]
Male n (%)	95 (54.6)	109 (63.7)	[redacted]	[redacted]
ECOG at screening* 0 n (%)	59 (33.9)	59 (34.5)	[redacted]	[redacted]
ECOG at screening* 1 n (%)	115 (66.1)	112 (65.5)	[redacted]	[redacted]
ECOG at screening* 2 n (%)	0	0	[redacted]	[redacted]
Missing	-	-	[redacted]	[redacted]
Squamous n (%)	7 (4.0)	1 (0.6)	[redacted]	[redacted]
Non-squamous n (%)	165 (94.8)	169 (98.8)	[redacted]	[redacted]
Unspecified	-	-	[redacted]	[redacted]
Other n (%)	2 (1.1)	1 (0.6)	[redacted]	[redacted]
Locally adv. + unresectable n (%)	8 (4.6)	9 (5.3)	-	-
Metastatic n (%)	166 (95.4)	162 (94.7)	-	-
PD-L1 <1% n (%)	55 (31.6)	57 (33.3)	-	-
PD-L1 ≥1 to <50% n (%)	70 (40.2)	46 (26.9)	-	-
PD-L1 ≥50% n (%)	40 (23.0)	60 (35.1)	-	-
KRAS G12C Mutated n (%)	In eligibility criteria	In eligibility criteria	[redacted]	[redacted]
KRAS G12C Not mutated n (%)	In eligibility criteria	In eligibility criteria	[redacted]	[redacted]
No record n (%)	In eligibility criteria	In eligibility criteria	[redacted]	[redacted]

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Abbreviations: ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten ras sarcoma; PD-L1, programmed cell death ligand 1; adv, advanced; CS, Company submission

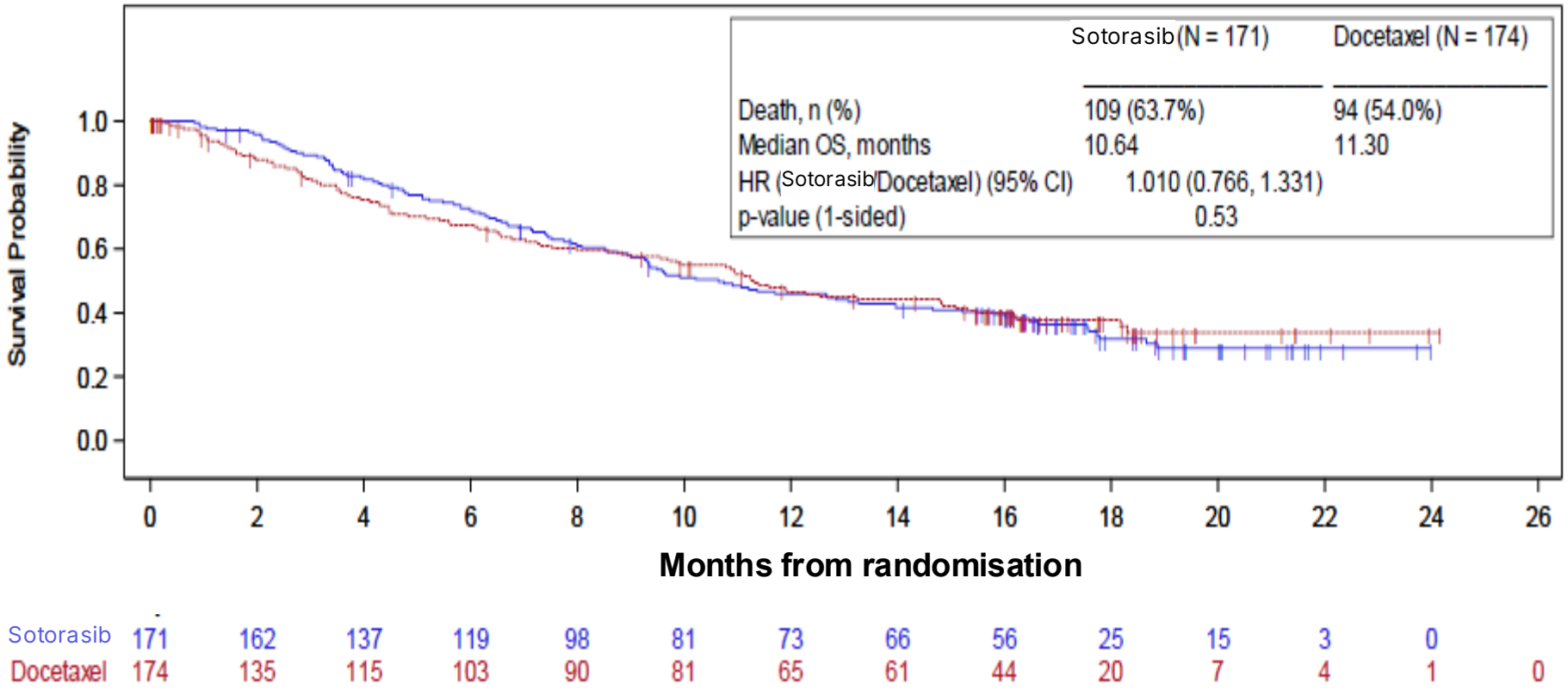
Return to main deck

Key clinical trial results: CodeBreak 200 – FAS without crossover adjustment

Return to main deck

No significant difference in survival before crossover analysis

Kaplan-Meier curve for overall survival (Full analysis set)



Abbreviations: FAS, Full analysis set; PFS, progression-free survival; OS, overall survival; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio

Large impact

Key issue 2: Which study data to use in model (1/2)

The two key clinical evidence sources suggest different treatment effects and impacts CE results

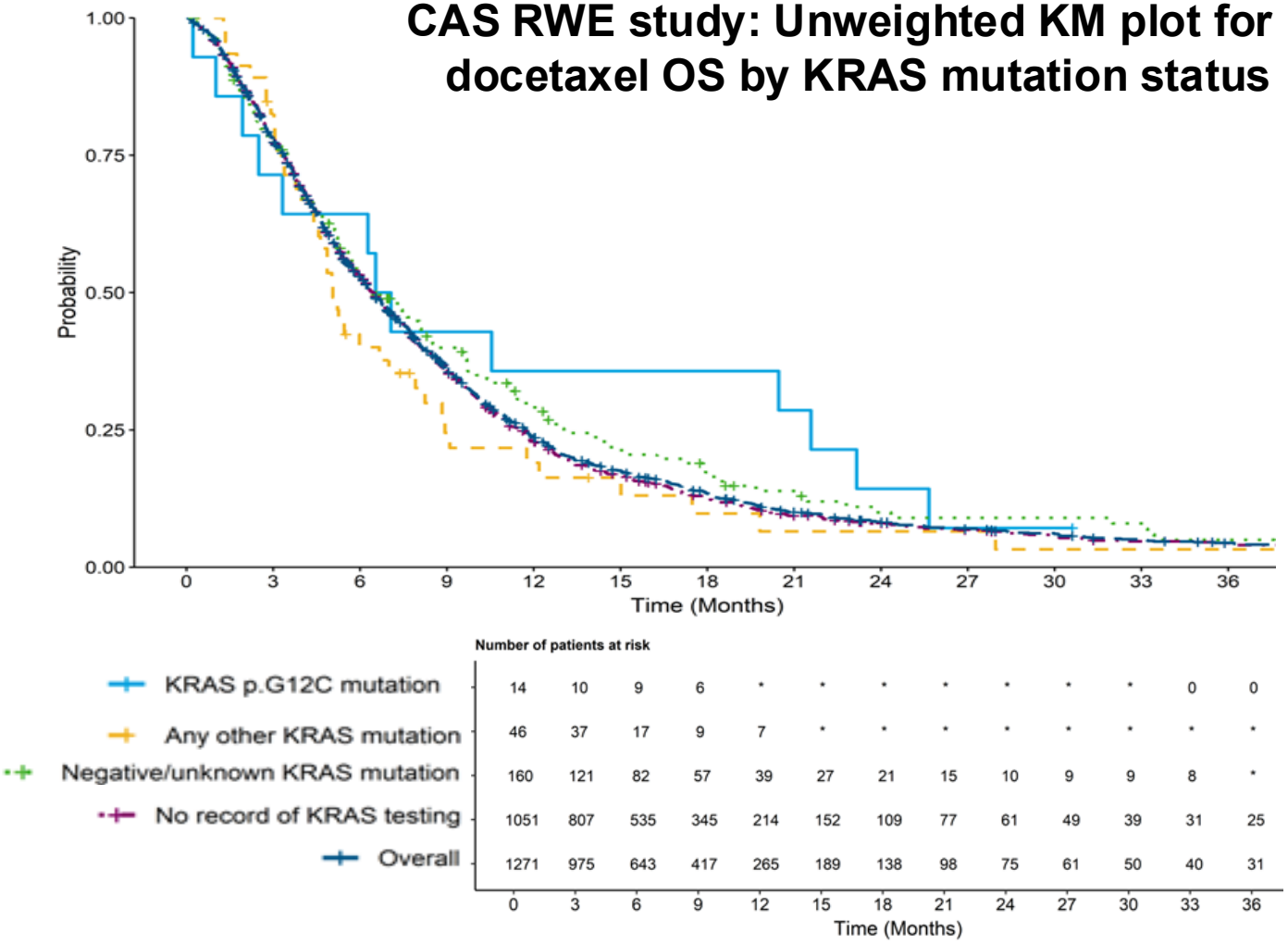
Company

- Structural limitation of CAS RWE: KRAS mutation status is unknown in [redacted] and [redacted] of patients receiving docetaxel and sotorasib respectively
- But relative efficacy of non-targeted therapies (such as docetaxel) in KRAS mutant positive patients is unclear (as shown in figure)

EAG

- Agree results do not show clear difference by mutation status
- but sample size of subgroups (by KRAS mutation status) is small so confidence in conclusion is uncertain

CAS RWE study: Unweighted KM plot for docetaxel OS by KRAS mutation status



Return to main deck

Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; RCT, randomised control trial; OS, overall survival; PFS, progression-free survival; TTNTD, Time to next treatment or death; NHSE, National Health Service England;

Large impact

Key issue 2: Which study data to use in model (2/2)

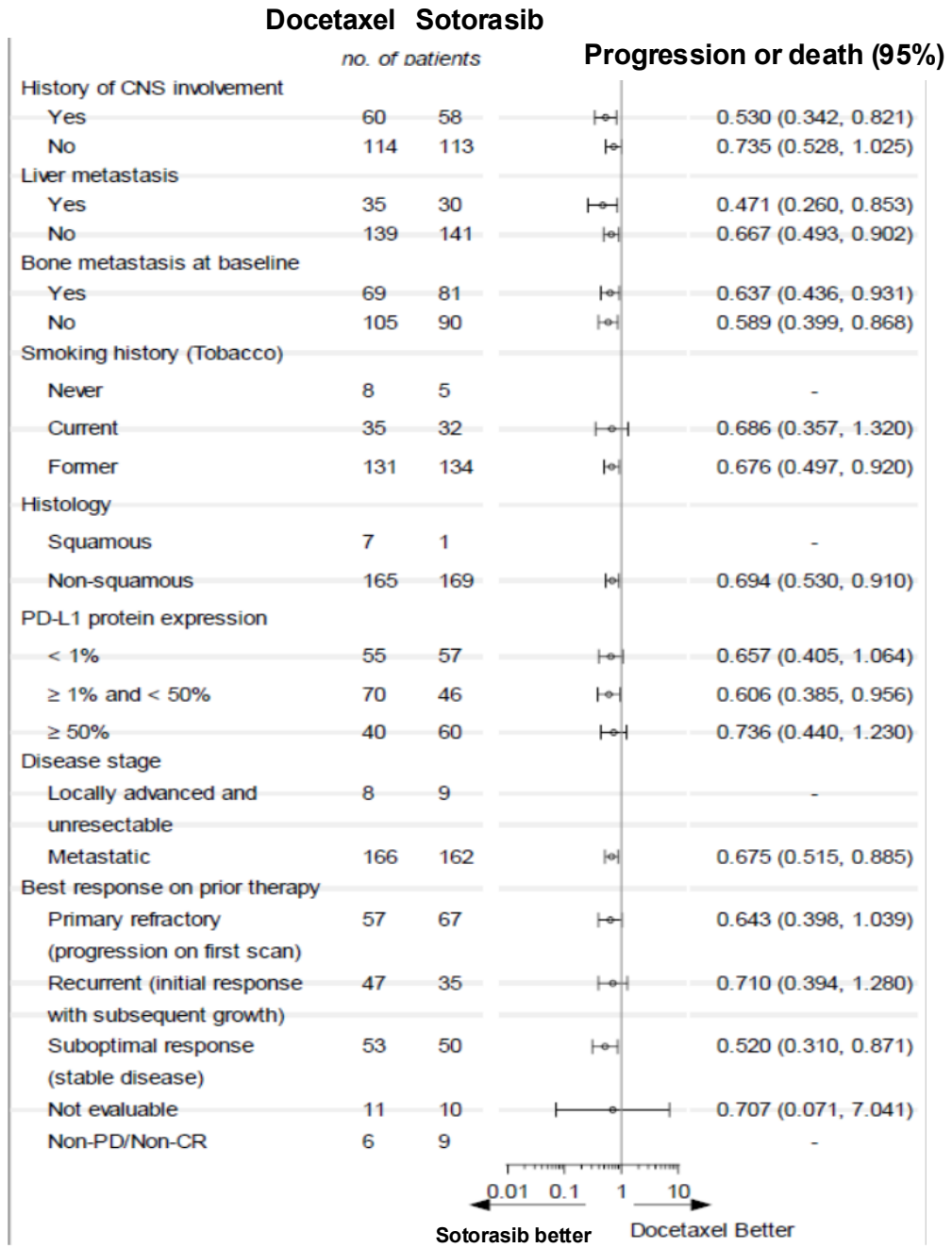
The two key clinical evidence sources suggest different treatment effects and impacts CE results

Company

- Structural limitation of CAS RWE: Smoking history not recorded in CAS RWE data and has potential to be unmeasured confounder
- But no evidence of smokers/non-smokers having different outcomes with docetaxel and sotorasib
- Subgroup analysis of PFS (using CB200 data) suggests no difference between former and current smokers
- Too few patients in the “never” smoked category to analyse (n=13)

Return to main deck

CodeBreak 200 trial: Subgroup analysis of PFS showing HR for disease



Abbreviations: CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; PFS, progression-free survival; CNS, central nervous system; PD-L1, Programmed Death-Ligand 1;

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Large impact

Key issue 3: CB200 OS model selection (1/3)

EAG and company use different models to estimate long-term OS

Only relevant if CB200 is preferred data source

Landmark 3- and 5- year OS estimates using different survival models

Stakeholder	Sotorasib			Docetaxel		
	Preferred OS model	3-year OS	5-year OS	Preferred OS model	3-year OS	5-year OS
Company	Log-normal	[redacted]	[redacted]	Weibull	[redacted]	[redacted]
EAG	Gamma	[redacted]	[redacted]	Gamma	[redacted]	[redacted]
EAG clinical expert	-	7%	2%	-	5%	2%
EAG scenario analysis	Log-logistic	[redacted]	[redacted]	Gamma	[redacted]	[redacted]
Company base case (using CAS RWE)	-	[redacted]	-	-	[redacted]	-
Other model estimates (using CB200)	Exponential	[redacted]	[redacted]	Exponential	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	Gompertz	[redacted]	[redacted]
	Gen. gamma	[redacted]	[redacted]	Gen. gamma	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	Log-normal	[redacted]	[redacted]

Return to key issue

Abbreviations: OS, Overall survival; PFS, progression-free survival; CB200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; Gen, generalised;

Key issue 3: CB200 OS model selection (2/3)

Large impact

Only relevant if CB200 is preferred data source

EAG and company use different models to estimate long-term OS

Hazard plot: Sotorasib OS

Hazard plot: Docetaxel OS

Company's preferred OS model: Sotorasib = individual lognormal, docetaxel = individual Weibull
EAG's preferred OS model: Sotorasib = individual gamma, docetaxel = individual gamma

Return to key issue

 Abbreviations: OS, Overall survival; PFS, progression-free survival; CB200, CodeBreak 200;

Large impact

Key issue 3: CB200 OS model selection (3/3)

EAG and company use different models to estimate long-term OS

Only relevant if CB200 is preferred data source

Statistical fit of individually fitted survival models to OS data

Distribution	Sotorasib		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]

Key

Company's preferred model

EAG's preferred model

Return to key issue

Abbreviations: OS, Overall survival; PFS, progression-free survival; CB200, CodeBreak 200; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion;

CB200 PFS model selection (1/3)

Small impact

Only relevant if CB200 is preferred data source

EAG and company use different models to estimate long-term PFS of sotorasib

Survival plots with observed KMs and PFS models

Company

- Sorotasib: independent exponential – conservative estimate, best visual fit but poor statistical fit.
- Docetaxel: independent log-logistic – best statistical fit and long-term estimates

EAG comments

- Prefers independent log-logistic models for sotorasib and docetaxel as they provide best statistical fit and long-term estimates align with EAG expert opinion

Abbreviations: PFS, progression-free survival; CB200, CodeBreak 200;

Return to key issue

Small impact

CB200 PFS model selection (2/3)

Only relevant if CB200 is preferred data source

EAG and company use different models to estimate long-term PFS of sotorasib

Hazard plot: Sotorasib PFS

Hazard plot: Docetaxel PFS

Company's preferred PFS model: Sotorasib = individual exponential, Docetaxel = individual log-logistic
EAG's preferred PFS model: Sotorasib = individual log-logistic, Docetaxel = individual log-logistic

 Abbreviations: OS, Overall survival; PFS, progression-free survival; CB200, CodeBreak 200;

Small impact

CB200 PFS model selection (3/3)

Only relevant if CB200 is preferred data source

EAG and company use different models to estimate long-term PFS of sotorasib

Statistical fit of individually fitted survival models to PFS data

Distribution	Sotorasib		Docetaxel	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]

Key

Company's preferred model

EAG's preferred model

Return to key issue

Abbreviations: OS, Overall survival; PFS, progression-free survival; CB200, CodeBreak 200; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CB200, Codebreak 200;

Small impact

CAS RWE: TTNTD (proxy for PFS) model selection (1/2)

EAG and company use different models to estimate long-term TTNTD

Only relevant if CAS RWE is preferred data source

Company

- Company base case uses TTNTD (proxy for PFS) – jointly fitted generalised gamma
- Justification: most plausible extrapolations, good visual fit and second-best statistical fit

Estimates	Company model		EAG model		EAG clinical expert	
	Sot	Doc	Sot	Doc	Sot	Doc
3-year TTNTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Long-term TTNTD estimates from company's models do not align with EAG clinical expert estimates
- Jointly fitted Weibull curves have worse visual and statistical fit to observed data. But long-term estimates are more aligned with EAG expert opinion
- So, jointly fitted Weibull may be more suitable for TTNTD However, clinical expert opinions may differ and should be taken with caution

Should TTNTD (proxy for PFS) be modelled using jointly fitted generalised gamma or Weibull?

Back to OS model selection key issue

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

Small impact

CAS RWE: TTNTD (proxy for PFS) model selection (2/2)

EAG and company use different models to estimate long-term TTNTD

Only relevant if CAS RWE is preferred data source

Company's preferred models

[redacted]

EAG's preferred models

[redacted]

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

Small impact

CAS RWE: OS and TTNTD model selection

EAG and company use different models to estimate long-term OS and TTNTD

Only relevant if CAS RWE is preferred data source

Statistical fit of jointly-fitted survival models to OS data

Distribution	Jointly fitted OS	
	AIC	BIC
Exponential	3823.07	3832.33
Gamma	3812.61	3826.50
Generalised gamma	3793.61	3812.13
Gompertz	3823.02	3836.91
Log-normal	3807.09	3820.98
Log-logistic	3779.10	3792.98
Weibull	3819.20	3833.09

Statistical fit of jointly-fitted survival models to TTNTD data

Distribution	Jointly fitted TTNTD	
	AIC	BIC
Exponential	3826.41	3835.67
Gamma	3787.98	3801.86
Generalised gamma	3774.49	3793.00
Gompertz	3827.82	3841.71
Log-normal	3794.77	3808.66
Log-logistic	3761.95	3775.84
Weibull	3801.01	3814.90

Key

Company's preferred model

EAG's preferred model

Return to key issue

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Abbreviations: OS, Overall survival; PFS, progression-free survival; TTNTD, time to next treatment or death; CB200, CodeBreak 200; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CAS RWE, Cancer analysis system real world evidence;

Large impact

Evidence source for modelling TTDD (1/3)

Company and EAG use different source to inform time-to-treatment-discontinuation (TTDD)

Dependent on preferred data source for OS/PFS

Approach	Company	EAG
Using CAS RWE: Company's preference	Some misclassification of TTDD expected as treatment end dates not recorded. But low risk due to start dates and cycle number enabling calculation of treatment duration. Enables alignment of sources used for OS/TTNTD.	• Questions extent of misclassification. Impact on estimated TTDD unclear. • If CAS RWE data informed OS/TTNTD, it would be reasonable to use CAS RWE to inform TTDD
Using CB200: EAG's preference	CB200 allowed patients to continue after disease progression – does not reflect UK practice. Disagree with EAG's approach as it suggests patients continue treatment after disease progression (implausible)	In CB200, treatment continued after progression, so may be reasonable to model TTDD consistently with clinical efficacy. TTDD is capped at PFS to prevent suggested implausible outcome. Enables alignment of sources used for OS/PFS
Company's SA	Used CB200 (but with different modelling approach to EAG)	SA methods in clarification vs technical engagement response are inconsistent and arbitrary
Base case	TTDD modelled using CAS RWE	In absence of requested TTDD parametric model analysis, time-varying HRs from CB200 used

Patient expert comments: Patients may stop/pause treatment for variety of reasons, allowing patients to stay on therapy and maintain QoL. It is important the model reflects this real-world experience

Abbreviations: TTDD, time to treatment discontinuation or death; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; PFS, progression free survival; TTNTD, time to next treatment or death; SA, scenario analysis; HRs, hazard ratios; QoL, quality of life; gen. gamma, generalised gamma;

Large impact

Evidence source for modelling TTDD (2/3)

Company and EAG use different source to inform time-to-treatment-discontinuation (TTDD)

Dependent on preferred data source for OS/PFS

TTDD curves used in economic models

[redacted]

Quantile	Docetaxel duration of treatment (months)				Sotorasib duration of treatment (months)			
	CAS RWE data	CB200 data	Company BC	EAG BC	CAS RWE data	CB200 data	Company BC	EAG BC
25%	[redacted]							
50% (median)	[redacted]							
75%	[redacted]							

Should TTDD be modelled using CAS RWE or CB200?

NICE

Abbreviations: TTDD, time to treatment discontinuation or death; CB200, CodeBreak 200; CAS RWE, Cancer Analysis System Real World Evidence; OS, overall survival; PFS, progression free survival; SA, scenario analysis; BC, base case; QoL, quality of life

Small impact

Modelling of relative treatment effect waning

Unclear if an explicit relative treatment effect waning assumption should be included in economic model

Background

- TA781: committee concluded waning assumptions of 3 and 5 years after starting treatment plausible

Company

- Waning assumption is not applied as CAS RWE data indicates sufficient follow-up and completeness to capture any relative waning already:
  - Sotorasib arm: Median follow up = 8.62 months. 61% had died and 19% had started next treatment
  - Docetaxel arm: Median follow up = 6.11 months. 89% had died and 18% had started next treatment
- EAG scenario analysis with waning assumption had a minor impact on ICER

EAG comments

- It is a strong assumption that TEW is captured in CAS RWE data
- Converging cumulative and smoothed hazards for OS (CB200) may suggest TEW
- Prefers to assume gradual TEW of sotorasib between 2 – 5 years after starting treatment – aligns with EAG's preference in TA781

CB200: OS log-cumulative hazard plot

- Should an explicit treatment effect waning assumption be included in the economic model?
- Should it occur between 3 - 5 or 2 - 5 years after treatment starting, or other?

Abbreviations: TEW, treatment effect waning; CAS RWE, Cancer analysis system real world evidence; CB200, CodeBreak200; ICER, incremental cost effectiveness ratio

Lack of subgroup analysis (1/2)

Subgroup analysis may show differences in efficacy and appears possible but not presented by company

Background

- Factors that may impact efficacy include number of prior lines of treatment, disease stage, histology and newly diagnosed or recurrent distant metastatic disease

Company

- Subgroup analysis was not performed as there were no subgroups observed with substantially different efficacy to the whole population in CAS RWE
- It is not possible to re-analyse CAS RWE as the company does not have access to PLD
- After technical engagement, the company uphold that their clinical experts did not consider any additional subgroups relevant or necessary for the appraisal

EAG comments

- Justification for not performing subgroup analyses insufficient
- The absence of variation in efficacy not clearly demonstrated, and variation is evidenced (next slide):
  - Company states that prior record of brain metastasis impacts relative efficacy in CAS RWE
  - Variation in efficacy evidenced in CB200 in patients with liver and CNS involvement
- Subgroup analysis of CB200 data appears possible and could be useful

Does the data suggest that subgroup analysis could be useful for decision making?

Abbreviations: PLD, patient level data; Cb200, CodeBreak 200; CAS RWE, Cancer analysis system real world evidence; CNS, central nervous system;

Unknown impact

Lack of subgroup analysis (2/2)

Subgroup analysis of PFS suggests efficacy differs depending on CNS involvement, liver metastasis and prior lines of treatment

CB200 subgroup analysis of PFS	Number of patients		HR for disease progression or death (95% CI)	Difference from all randomised subjects
	Docetaxel	Sotorasib		
All randomised subjects	174	171	0.663 (0.509, 0.864)	-
History of CNS involvement	60	58	0.530 (0.342, 0.821)	-0.133
No history of CNS involvement	114	113	0.735 (0.528, 1.025)	+0.072
History of liver metastasis	35	30	0.471 (0.260, 0.853)	-0.192
1 prior line of therapy in advanced disease	78	77	0.695 (0.466, 1.036)	+0.032
2 prior lines of therapy in advanced disease	69	65	0.608 (0.399, 0.924)	-0.055
>2 prior lines of therapy in advanced disease	27	29	0.740 (0.374, 1.463)	+0.077

Does the data suggest that subgroup analysis could be useful for decision making?

NICE

Abbreviations: PLD, patient level data; HR, hazard ratio; CB200, CodeBreak 200; PFS, progression free survival; CNS, central nervous system; CI, confidence interval; QoL, quality of life;

Small impact

Mapping of EQ-5D-5L results to -3L (1/3)

Company base case uses mapping method that deviates from reference-case

Background

- EQ-5D-5L results collected during CB200 need to be mapped to -3L
- TA781: Van Hout (VH) mapping function was used
- NICE reference case states the Hernandez-Alava (HA) mapping function should be used

Company

- Prefers VH method because the HA method produces higher utilities that are inconsistent with experience of patients. This is supported by Maervoet and Bergemann (2024), which reported that HA function resulted in consistently higher (0.01 to 0.09) utility values
- HA method results in pre-progression utility values for sotorasib arm that are higher than values for the general population (age and sex-matched)

EAG comments

- The HA mapping function should be used as per the NICE reference case
- To overcome the issue of utility values exceeding general population values, utilities are capped to general population levels in the economic model

Should the VH or HA (NICE reference case) mapping function be used in the economic model?

Abbreviations: VH, Van Hout mapping function; HA, Hernandez-Alava mapping function; EQ-5D-5L / 3L, EuroQol 5-Dimension 5 level / 3 level; CB200, CodeBreak 200;

Small impact

Utilities by mapping function (2/3)

Utilities by progression status – utilities estimated using the Hernandez-Alava function are higher

Treatment arm	Progression status	Mean (SE)		Difference (HA-VH)
		Van Hout	Hernandez-Alava	
Sotorasib	Pre-progression	[redacted]	[redacted]	+ 0.065
	Post-progression	[redacted]	[redacted]	+ 0.077
Docetaxel	Pre-progression	[redacted]	[redacted]	+ 0.065
	Post-progression	[redacted]	[redacted]	+ 0.056

NICE

Abbreviations: SE, standard error; VH, Van Hout mapping function; HA, Hernandez-Alava mapping function;

Small impact

Utilities my mapping function (3/3)

Utilities by time-to-death – utilities estimated using the Hernandez-Alava function are higher

Treatment arm	Time-to-death – treatment (months)	Mean (SE)		Difference (HA-VH)
		Van Hout	Hernandez -Alava	
Sotorasib	≥ 6	[redacted]	[redacted]	+ 0.071
	3 – 6	[redacted]	[redacted]	+ 0.075
	1 – 3	[redacted]	[redacted]	+ 0.092
	< 1	[redacted]	[redacted]	+ 0.071
Docetaxel	≥ 6	[redacted]	[redacted]	+ 0.074
	3 – 6	[redacted]	[redacted]	+ 0.082
	1 – 3	[redacted]	[redacted]	+ 0.072
	< 1 month	[redacted]	[redacted]	+ 0.09

NICE Abbreviations: SE, standard error; VH, Van Hout mapping function; HA, Hernandez-Alava mapping function;

Large impact

Estimating RDIs using means or medians

Relative dose intensity (RDI) data is skewed, so use of means or medians impacts cost-effectiveness results

Background
TA781: used CodeBreak 100 as source for RDI

Company
- RDI informed by mean values of RDI from CB200

RDI	Company approach (means)	EAG scenario analysis (medians)
Sotorasib	86.4%	100.0%
Docetaxel	90.4%	94.8%

EAG comments
- Clinical expert agrees that company's means seem plausible based on known discontinuation and dose modification rates for both treatments
- But uncertain if mean values are appropriate because of left skewness of RDI data
- In scenario analysis, explored using median values instead of means
  - Deterministic results: using medians increased ICER (see results)
  - Probabilistic results: significantly different to deterministic and appear implausible. Likely because RDI for sotorasib is capped at 100% (which is equal to median point estimate). EAG was unable to adjust standard errors to improve probabilistic results

Should mean or median RDI estimates be used in the model?

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Abbreviations: RDI, relative dose intensity; ICER, incremental cost effectiveness ratio; CB200, Codebreak 200; CB100, Codebreak 100;

Decision problem

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	Final scope	Company	EAG comments
Population	Adults with previously treated KRAS G12C-mutated, locally advanced or metastatic NSCLC	Adults 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. (As per conditional MA)	-
Intervention	Sotorasib	As per scope	-
Comparators	• Docetaxel • Docetaxel with nintedanib • Adagrasib (subject to NICE appraisal)	Docetaxel is considered the only relevant comparator	Excluding adagrasib reasonable. Excluding docetaxel with nintedanib has some merit as a small % may be used
Outcomes	OS, PFS, response rates, TTD, AEs of treatment, HRQoL	OS. PFS not captured in CAS RWE so TTNTD as proxy. TTD not captured so derived from treatment start date and number of treatment cycles received	Outcomes largely in line with scope. Concerns for approach to deriving TTD and TTNTD.

Abbreviations: KRAS, Kristen ras; NSCLC, non-small cell lung cancer; PD, programmed cell death; OS, overall survival, PFS, progression free survival; TTD, time to treatment discontinuation; AE, adverse event; HRQoL, health related quality of life; RWE, real world evidence; MA, marketing authorisation; TTNTD, time to next treatment or death

Key clinical study results summary

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1) OS outcomes for docetaxel and relative treatment effect in CAS RWE align with Flatiron US RWE study

2) CodeBreak 200 RCT suggests smaller relative treatment effect (in terms of OS and PFS) compared to CAS RWE (HRs are closer to 1)

Study	Overall survival					Progression-free survival				
	Sotorasib		Docetaxel		HR (95% CI)	Sotorasib		Docetaxel		HR (95% CI)
	N	OS, months (95% CI)	N	OS, months (95% CI)		N	PFS, months (95% CI)	N	PFS, months (95% CI)	
CodeBreaK 200 (RCT)	171	10.64 (8.94, 13.96)	174	11.3 (9.00, 14.85)	0.820 (0.32, 1.31)¶	171	5.62 (4.27, 7.75)	174	4.47 (3.02, 5.68)	0.663 (0.509, 0.864)
CodeBreaK 100 (Single arm)	174	12.5 (10.0, NE)	N/A			174	6.8 (5.1, 8.2)	N/A		
CAS RWE study (Retrospective, England dataset)	394	10.18 (9.10, 12.02) After SMRW	363	6.87 (6.01, 7.82) After SMRW	0.633 (0.54, 0.75)	394	8.51 (7.33, 9.43) § After SMRW	363	5.62 (5.06, 6.18) § After SMRW	0.567; (0.49, 0.64), §*
Flatiron US RWE At 2L (Retrospective, US dataset)	164	10.2 (8.0, 14.6)	116	7.2 (5.1, 10.6)	0.65 (0.49, 0.87)	N/A				
	102	10.2 (7.6, 16.3) §§ After SMRW	58	6.0 (4.2, 11.0) §§ After SMRW	0.62 (0.41, 0.93) §§ After SMRW					

* EAG corrected. § TTNTD used as a proxy for PFS. §§ After propensity score weighting. ¶ After adjusting for treatment switching

Abbreviations: 2L, second-line; CAS, Cancer Analysis System; CI, confidence interval; HR, hazard ratio; N/A, not applicable; NE, not estimable; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RWE, real-world evidence; SMRW, standardised mortality ratio weighting; TTNTD, time to next treatment or death;