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

Technology appraisal committee B [14 May 2026]

Contains [redacted] information

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

- ✓ **ACM1 recap and DG consultation responses**
- ❑ Key issues
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Summary

NICE National Institute for Health and Care Excellence

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 ➔ **Updated (reduced post ACM1)**

TA781 (March 2022): Sotorasib recommended in CDF within full MA

- Main uncertainties: unanchored ITC; utility and disutility values; treatment waning and EOL criteria
- Data collection: Primary trials CodeBreak100 and 200 and CAS RWE

ID6287: Managed access review (2025/2026)

- This appraisal has had a technical engagement stage
- ACM1 (February 2026): negative recommendation within the full MA

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; CDF: Cancer Drugs Fund; EOL: end of life; ITC: Indirect treatment comparison; KRAS: Kirsten ras sarcoma; MA: Marketing authorisation; MHRA: Medicines and Healthcare products Regulation Agency; NSCLC: Non-small cell lung cancer; PAS: Patient access scheme; PD-L1: Programmed cell death ligand 1

ACM1 key committee conclusions (1)

Issue	Committee conclusions	Resolved?
Clinical effectiveness evidence source	• It would consider the most appropriate evidence source (CAS RWE or CodeBreak 200) for each clinical efficacy input (OS, PFS, TTDD) • Requested more detail about company's approach to adjusting for treatment switching and propensity score analysis	No
Modelling OS	Requested analysis using CAS RWE baseline sotorasib OS curves and applying inverse crossover adjusted relative effect from CodeBreak 200 for docetaxel	No
Treatment effect waning	Because it had not decided on the approach to extrapolate OS, the committee could not conclude if treatment waning assumption was appropriate	No
Modelling PFS	Requested 2 analyses: 1. Use PFS from CodeBreak 200 to inform PFS directly 2. Explore relationship between PFS and TTNTD from CodeBreak 200 and use this to adjust CAS RWE sotorasib TTNTD curve (proxy for PFS). Apply inverse relative PFS efficacy from CodeBreak 200 to get docetaxel curve	No
Modelling TTDD	Requested additional analysis extrapolating TTDD data from CodeBreak 200	No

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; OS: Overall survival; PFS: Progression-free survival; TTDD: Time to treatment discontinuation or death; TTNTD, Time to next treatment or death

ACM1 key committee conclusions (2)

Issues	Committee conclusions	Resolved?
Utility values	• Requested MMRM that includes both progression and TTD covariates and TTD limited to 6 months before death • Alternatively, using treatment-independent utilities may be informative	No
QALY weightings for severity	Further analyses needed to determine appropriate evidence for clinical effectiveness and utility modelling, which will then inform the absolute and proportional shortfalls	No
Baseline characteristics	Prefer to use the CAS RWE baseline characteristics because they best reflect the populations in the NHS	Yes
Comparators	Docetaxel is the only relevant comparator for this evaluation	Yes
Administration costs	Use day case unit costs for the administration of docetaxel	Yes

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; MMRM: Mixed models for repeated measures; OS: Overall survival; QALY: Quality-adjusted life years; TTD: Time to death

ACM2: Key issues and questions for committee

#	Key issues	ICER impact
1	**Clinical effectiveness evidence source** • Which evidence source (CodeBreaK 200 or CAS RWE) should be used to inform OS, PFS and TTDD in the economic model?	Large
2	**Modelling OS** • What is the most appropriate approach to model OS?	Large
3	**Treatment effect waning** • Should an explicit treatment effect waning assumption be included in the economic model? • If so, should it occur between 3 - 5 or 2 - 5 years after treatment starting, or other?	Small
4	**Modelling PFS** • What is the most appropriate approach to model PFS?	Small
5	**Modelling TTDD** • What is the most appropriate approach to model TTDD?	Small
6	**Utility values** • What is the most appropriate approach to model utility values?	Small
7	**Severity modifier** • Is it appropriate to apply a QALY weighting for severity weight of x1.2 or x1.7?	Large

Appraisal committee meeting 2; CAS RWE: Cancer analysis system real world evidence; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life years; TTDD: Time to treatment discontinuation or death

Consultation responses summary (1)

- **Amgen (company)**
  - Provided additional information on treatment switching, propensity score analysis, KRAS mutation outcomes and QALY weightings for severity
  - Revised base case: Baseline characteristics, docetaxel day case cost, 2024/2025 NHS reference costs, utilities, modelling OS
  - Scenario analyses: OS modelling, PFS/TTNTD modelling, TTDD modelling, utilities
- **2 patient organisation – Oncogene cancer research and Roy Castle Lung Cancer Foundation**
- **1 web comment – The International Cancer Advocacy Network**
- **2 clinical expert**

OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life years; TTNTD: Time to next treatment or death

Consultation responses summary (2)

Patient organisations (Oncogene cancer research and Roy Castle lung cancer foundation):

- KRAS G12C lung cancer is devastating and life-limiting with patients having rapid disease progression, severe symptoms and a heavy treatment burden
- High unmet need population ➔ removing access to sotorasib (only targeted treatment) would be a setback for KRAS G12C lung cancer, undermining precision medicine and the value of identifying this mutation
- Patients value even small survival benefits ➔ modelling uncertainty should not outweigh disease severity and lack of alternatives
- As an oral, at-home treatment, sotorasib offers clear advantages over intravenous chemotherapy, with fewer hospital visits, less toxicity, and greater independence
- Quality of life gains are substantial, including reduced treatment burden, improved dignity, and better mental wellbeing
- Real-world evidence support sotorasib's meaningful benefit – improving tolerability, convenience and quality of life
- Some patients may decline further chemotherapy, leaving sotorasib as the only active treatment option

KRAS: Kirsten ras sarcoma

Consultation responses summary (3)

Web comment (The International Cancer Advocacy Network)

- Substantial clinical, real-world, and patient-reported evidence shows sotorasib is superior to docetaxel in PFS, OS, tolerability, and quality of life, particularly due to sotorasib's oral administration and fewer, more manageable side effects
- Uncertainty in the analysis of clinical effectiveness evidence and modelling supports further evidence collection and model refinement but not denying access to sotorasib

Clinical experts

- Unmet need for effective and well tolerated treatment option for people with KRAS G12C-positive advanced NSCLC who progress after chemo-immunotherapy and have very limited options
  - ➢ Treatment with docetaxel is commonly avoided due to risk of toxicity and reduced quality of life
- For people with limited alternatives, sotorasib has provided meaningful benefits in terms of disease control, quality of life and survival and tolerability
- Economic modelling may underestimate sotorasib's real-world clinical value ➔ May not capture highly meaningful factors including disease control, acceptable tolerability, improved quality of life, and hope
- While CodeBreaK 200 trial data are important, real-world evidence from the managed access period should carry substantial weight as it better reflects NHS patient populations and routine clinical practice

KRAS: Kirsten ras sarcoma; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; QALYs: Quality-adjusted life years

Equalities issues raised

Committee ACM1 considerations

- Noted some people may struggle to self-administer sotorasib due to cognitive impairments or disabilities, but this was not something that could be addressed in its recommendation
- Potential inequalities from inconsistent KRAS mutation testing across NHS ➔ As its recommendation does not restrict access to treatment for specific groups, this was not an equalities issue

DG consultation responses – Oncogene cancer research:

- **Equalities:**
  - ➢ Even if recommendations apply equally to all patients, its impact is not experienced equally. Committee should consider how real-world impact of recommendation may differ across patient groups
- **Health inequalities:**
  - ➢ Inconsistent KRAS testing may already create inequalities in access to targeted treatments, and removing sotorasib risks worsening this by limiting options even when a mutation is identified
  - ➢ Restricting access risks widens inequalities and conflicts with UK priorities on personalised cancer care
  - ➢ If sotorasib is not routinely available on the NHS, some patients may seek it privately or abroad, risking a two-tier system where access depends on financial means rather than clinical need

NICE tech team: No robust quantitative or qualitative evidence has been provided by company or stakeholders on the impact of sotorasib upon health inequalities

Are there any equality or health inequality considerations that can be addressed by the committee in this appraisal?

ACM1: Appraisal committee meeting 1; KRAS: Kirsten ras sarcoma

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

- ❑ ACM1 recap and DG consultation responses
- ✓ **Key issues**
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Summary

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Key issue 1: Clinical effectiveness evidence source (1)

Large impact

ACM1 considerations

- **Company:** Prefer CAS RWE → has larger sample size, longer follow-up, England-based data, and have concerns about CodeBreaK 200 treatment switching and reduced OS power
- **EAG:** Prefer CodeBreaK 200 → CAS RWE is non-randomised, at serious risk of bias and subject to residual confounding (unknown KRAS mutation status and presence of brain metastases)
- **Committee consideration:**
  - Requested more detail about company's treatment switching adjustment and propensity score analysis
  - It would consider the most appropriate evidence source for each clinical efficacy input

Company DG consultation response

- Base case still uses CAS RWE to inform OS, PFS and TTDD - most consistent and clinically relevant data

Treatment switching in CodeBreaK 200:

- Two-stage crossover adjustment most appropriate because of trial design (switch only after progression), and covariate adjustment (disease status and patient characteristics at progression)
  - Residual risk of unmeasured confounding limited, given structured clinical input and available trial data
- OS estimates with and without adjustment are unstable due to 1) confounding in docetaxel arm limits ability to apply effective adjustment and 2) unadjusted results heavily influenced by crossover

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; DG: Draft guidance; DSU: Decision support unit; KRAS: Kirsten ras sarcoma; OS: Overall survival; PFS: Progression-free survival; TTDD: Time to treatment discontinuation or death

Large impact

Key issue 1: Clinical effectiveness evidence source (2)

Company DG consultation response (continued)

Propensity score analysis on CAS RWE data:

- SMR propensity score weighting used to address confounding and balance baseline characteristics
- Included broad, clinically informed set of baseline covariates, with balance assessed using standardised mean differences and extreme weights truncated per NICE guidance
- Good post-weighting balance and effective sample sizes - only BMI still imbalanced, supporting robustness

Unknown KRAS G12C mutation status in the CAS RWE docetaxel cohort

- Missing KRAS mutation status in docetaxel cohort is a limitation, but unlikely to significantly bias results
  - Reflects historical NHS practice when testing and targeted therapies like sotorasib were not available
  - Current practice: KRAS G12C positive patients would have available targeted therapy over docetaxel
- Evidence suggests KRAS mutation status is not a strong prognostic factor for people having docetaxel:
  - Exploratory analysis: KRAS status showed no OS, TTD, or TTNT differences in docetaxel patients
  - ASCO 2022: similar survival outcomes between KRAS-mutant and wild-type across treatment classes
  - 7 UK clinical experts: expect no materially different survival outcomes by KRAS status in this setting

See: Propensity score diagnostics, OS KM stratified by KRAS mutation status and ASCO 2022 data

ASCO: American Society of Clinical Oncology; BMI: Body mass index; CAS RWE: Cancer analysis system real world evidence; DG: Draft guidance; KRAS: Kirsten ras sarcoma; OS: Overall survival; SMR, standardised mortality ratio

Large impact

Key issue 1: Clinical effectiveness evidence source (3)

EAG critique

- Considers the two-stage adjustment method to be valid
- Company acknowledge that post-progression switching likely improves survival, but has not explained why the two-stage adjustment fails to fully address the bias
  - ➢ This may be due to missing confounder data causes insufficient adjustment or because most of sotorasib's survival benefit occurs pre-progression
- Agree that covariate balance was generally achieved but there might still be bias due to missing data on confounders
  - ➢ No clear evidence that mutation status affects prognosis with docetaxel, but evidence is limited
  - ➢ Potential residual bias remains as key confounders (KRAS status, brain metastases) were not adjusted for
- Acknowledge that CAS RWE may better reflect absolute OS for sotorasib, but continues to prefer randomised comparisons for estimates of relative treatment effects

See appendix: Clinical effectiveness evidence recap

KRAS: Kirsten ras sarcoma; OS: Overall survival; PFS: Progression-free survival; TTDD: Time to treatment discontinuation or death

Large impact

Key issue 2: Modelling OS (1)

ACM1 considerations

- **Company:** uses CAS RWE data and prefers jointly fitted generalised gamma model
- **EAG:** uses CodeBreaK 200 data and prefers independently fitted gamma model for both arms
- **Committee consideration:**
  - CAS RWE best reflected sotorasib absolute OS benefits, but not relative benefit compared to docetaxel
  - CodeBreaK 200 relative treatment effect adjusted for treatment switching may be more plausible
  - Requested analysis: apply inverse crossover adjusted relative treatment effect from CodeBreak 200 to the baseline OS curves of sotorasib from CAS RWE to generate docetaxel curves

Company DG consultation response

- Revised base case: CAS RWE data with independently fitted log logistic model for sotorasib and docetaxel
- Provided committee requested scenario
  - CodeBreaK 200 OS estimates (pre/post-adjustment) are unreliable due to crossover and design issues
  - Docetaxel OS estimates exceed clinical expectation and CAS RWE – lack external validity
  - Applying CodeBreaK 200 HR to CAS RWE assumes comparability across very different populations and settings ➔ approach introduces additional structural uncertainty

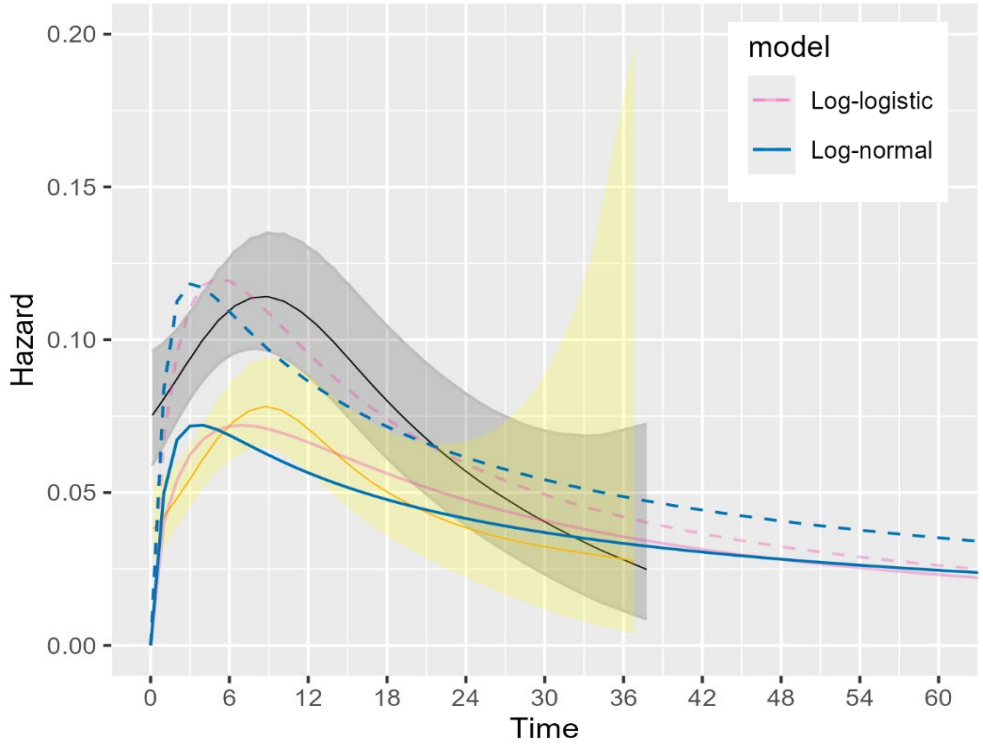
ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; DG: Draft guidance; HR: Hazard ratio; OS: Overall survival

Large impact

Key issue 2: Modelling OS (2)

Company DG consultation response

Modelled hazards versus smoothed CAS OS observed hazards



Independently fitted log logistic models versus CAS RWE OS Kaplan-Meier

- Only the log logistic and log normal closely approximate the profiles observed in CAS for both arms
- Log logistic better approximates CAS RWE relative survival benefit with hazard rates converging over time
- Log logistics model provides a good visual fit to the Kaplan-Meier data

NICE

CAS RWE: Cancer analysis system real world evidence; OS: Overall survival

See appendix: Modelled versus observed hazards and Goodness-of-fit statistics

Large impact

Key issue 2: Modelling OS (3)

EAG critique

- Company's log logistic model fit the data well, but the EAG considers it overestimates long-term survival
- Maintains preference for randomised CodeBreaK 200 data for relative treatment effects due to risks of confounding in observational CAS RWE data (unknown KRAS mutation and presence of brain metastases)
- Revised base case:
  - Docetaxel: inverse crossover adjusted HR from CodeBreak 200 to baseline CAS RWE sotorasib OS curves
  - Sotorasib: independent generalised gamma model - better aligns with clinical expectations

		Sotorasib			Docetaxel		
		Model	3-year OS	5-year OS	Model	3-year OS	5-year OS
Clinical expert (aligned with company base case at ACM1)		-	[redacted]	[redacted]	-	[redacted]	[redacted]
EAG clinical expert		-	7%	2%	-	5%	2%
Company (CAS RWE)	Base case	Log logistic	[redacted]	[redacted]	Log logistic	[redacted]	[redacted]
	Scenario	Log logistic	[redacted]	[redacted]	Inverse HR (CB200)	[redacted]	[redacted]
EAG*	Base case	Gen Gamma (CAS RWE)	[redacted]	[redacted]	Inverse HR (CB200)	[redacted]	[redacted]
	Scenario	Log logistic (CAS RWE)	[redacted]	[redacted]	Inverse HR (CB200)	[redacted]	[redacted]

* Includes gradual treatment effect waning of sotorasib between 2 – 5 years after starting treatment

What is the most appropriate approach to model OS?

NICE

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; CB200: CodeBreaK 200; HR: Hazard ratio; KRAS: Kirsten ras sarcoma; OS: Overall survival

Small impact

Key issue 3: Treatment effect waning

ACM1 considerations

- **Company:** No treatment effect waning included
- **EAG:** Gradual waning between 2 to 5 years after treatment initiation
- **Committee consideration:** Because it had not decided on the approach to extrapolate OS, the committee could not conclude if treatment waning assumption was appropriate

Company comments at ACM1

- 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 at ACM1

- 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?
- If so, should it occur between 3 - 5 or 2 - 5 years after treatment starting, or other?

NICE

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; CB200: CodeBreak200; ICER: Incremental cost effectiveness ratio; OS: Overall survival; TA781: Technology appraisal 781; TEW: Treatment effect waning

Small impact

Key issue 4: Modelling PFS (1)

ACM1 considerations

- **Company:** CAS RWE data, use TTNTD as proxy for PFS and prefer jointly fitted generalised gamma model
- **EAG:** CodeBreaK 200 data and prefer independent log logistic model for both arms
- **Committee ACM1 consideration:**
  - Using TTNTD as proxy for PFS is a strong assumption given CodeBreak 200 PFS results were very different to CAS RWE TTNTD results, and because PFS is likely shorter than TTNTD
  - Requested 2 additional analyses as follows:
    1. Use PFS from CodeBreak 200 to inform PFS directly
    2. Explore the relationship between PFS and TTNTD from CodeBreak 200 and use this to adjust CAS RWE sotorasib TTNTD curve (proxy for PFS). Apply inverse relative PFS efficacy from CodeBreak 200 to get the docetaxel curve

Company DG consultation response

- Base case unchanged: CAS RWE data, TTNTD as PFS proxy and jointly fitted generalised gamma model

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; DG: Draft guidance; HR: Hazard ratio; PFS: Progression-free survival; TTNTD: Time to next treatment or death

Small impact

Key issue 4: Modelling PFS (2)

PFS Model selection and CodeBreaK 200 sotorasib KM for PFS/TTNTD

Company DG consultation response (continued)

- Provided committee requested scenario analyses:
  1. Independently fitted exponential (sotorasib) and log-logistic model (docetaxel) to CodeBreaK 200 PFS
  2. Inappropriate to apply different HR to one arm of jointly fitted model, so fitted independent log logistic model for sotorasib arm (log-logistic has best statistical fit but all models underestimate KM tail)
     - Post-hoc CodeBreaK 200 TTNTD/PFS analysis: HR - [redacted] (95% CI = [redacted]

EAG critique

- **Base case unchanged**: CodeBreaK 200 data and fitted independent log logistic model for both arms
- Using different evidence sources to inform the sotorasib baseline PFS (CodeBreak 200) and OS (CAS RWE) curves may be suboptimal
  - Company's TTNTD scenario using TTNTD relationship is conditional on the questionable assumption that the relationship between PFS and TTNTD would be similar in CodeBreaK 200 and CAS RWE
  - Company's TTNTD scenario had relatively small impact on company's base-case but substantially increased EAG base-case ICER

What is the most appropriate approach to model PFS?

CAS RWE: Cancer analysis system real world evidence; CI: Confidence interval; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; KM: Kaplan Meier; OS: Overall survival; PFS: Progression-free survival; TTNTD: Time to next treatment or death

Key issue 5: Modelling TTDD

TTDD Model selection

Small impact

ACM1 considerations

- **Company:** prefer CAS RWE data and fitted independent generalised gamma models to both arms
- **EAG:** In absence TTDD parametric model analysis, used time-varying HRs from CodeBreaK 200
- **Committee consideration:** Requested company to provide extrapolation of CodeBreaK 200 TTDD data

Company DG consultation response

- Base case unchanged ➔ CAS RWE fitted with independent generalised gamma models to both arms
- Scenario (extrapolate CodeBreaK 200 data): log-normal model (sotorasib) and Weibull model (docetaxel)
  - Weibull had good statistical fit but resulted in <1% on treatment at 2 years and none at 3.5 years ➔ still significantly longer than CAS RWE, highlighting its generalisability for sotorasib and docetaxel

EAG critique

- Still question suitability of using CAS RWE to inform TTDD ➔ prefer CodeBreaK observed TTDD data
- Company did not provide sufficient model-selection justification (e.g. per NICE DSU TSD 19) for EAG to assess most appropriate extrapolation ➔ could not independently evaluate alternative parametric models.
- Revised base case: in absence of details, adopt company's TTDD scenario analysis

What is the most appropriate approach to model TTDD?

NICE

ACM1: Appraisal committee meeting 1; CAS RWE: Cancer analysis system real world evidence; DG: Draft guidance; DSU TSD 19: Decision support unit technical support document 19; HRs: Hazard ratios; TTDD: Time to treatment discontinuation or death

Small impact

Key issue 6: Utility values (1)

ACM1 considerations

- **Company:** prefer TTD approach and to use Van Hout mapping function
- **EAG:** prefer progression-based approach, but in absence of requested analyses, adopted company approach, but use NICE reference case mapping function (Hernandez-Alava)
- **Committee consideration:**
  - Prefer to use the Hernandez-Alava mapping function as stipulated in NICE reference case.
  - Requested: MMRM with progression and TTD covariates, TTD limited to 6 months before death
    - If no MMRM available, treatment-independent utilities may be informative

Company DG consultation response

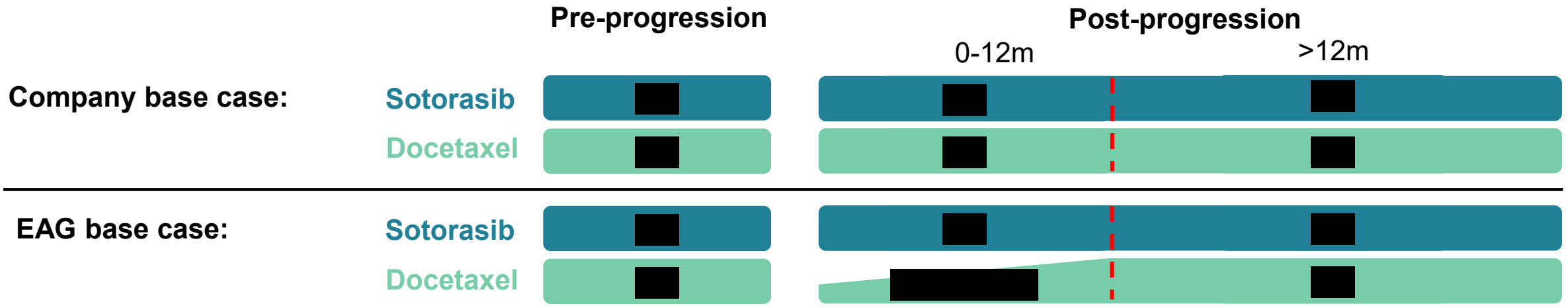
- Revised base case: utilities estimated from MMRM with treatment and progression covariates
  - Using Hernandez-Alava mapping function to map EQ-5D-5L to -3L
  - Clear evidence to support treatment-specific utility values within CodeBreaK 200
- Explored 3 additional scenario analyses:
  1. Base case + docetaxel post-progression utility waning (increase over 12 months to equal sotorasib)
     - Reflects that docetaxel AEs may cause post-progression QoL decrement, but improves over time
  2. MMRM including both progression status and TTD covariates
     - Does not consider any treatment difference so AE and IV infusion utility decrements included
  3. Progression-based model with treatment independent utilities
     - Model has poor statistical fit and ignores and underestimates sotorasib's utility benefits

ACM1: Appraisal committee meeting 1; AE: Adverse event; DG: Draft guidance; HRQoL: Health-related quality of life; IV: Intravenous infusion; MMRM: Mixed models for repeated measures; TTD: Time to death

Key issue 6: Utility values (2)

EAG critique

- Revised base case: utilities from MMRM by progression and treatment arm (company base case) + 12-month linear waning of docetaxel post-progression utility decrement
  - ➢ Company base-case MMRM shows best statistical fit, but only marginally better than simpler models
  - ➢ ACM1 clinical experts suggest docetaxel's toxicity may persist after progression but should not cause long-term differences once side effects resolve
  - ➢ Company provide limited justification for base case approach (e.g. no full model specification or diagnostics) ➔ Difficult to assess robustness of underlying MMRM
- MMRM including progression status and TTD covariates scenario is suboptimal, as dataset limitations reduce confidence in the estimated utility values
- Agree treatment-dependent utilities are appropriate for PFS state, but use post-progression is uncertain



What is the most appropriate approach to modelling utility values?

ACM1: Appraisal committee meeting 1; MMRM: Mixed models for repeated measures; SE: Standard error; TTDD: Time to death

Large impact

Key issue 7: Severity modifier

Committee ACM1 considerations

- Prefer CAS RWE baseline characteristics for absolute and proportional shortfall calculations because they best reflect populations in the NHS
- In adagrasib (TA1076), OS data was immature and so results and QALYs gained were uncertain

QALY weight	AS	PS
1	< 12	< 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	≥18	≥0.95

	Age (CAS RWE)	Sex (CAS RWE)	SoC QALYs	AS	PS	QALY weight
Company	[redacted]	[redacted]	[redacted]	10.7	93.5	1.2*
EAG	[redacted]	[redacted]	[redacted]	10.6	92.8	1.2

Company DG consultation response

- *1.7 modifier best reflects high unmet need and poor prognosis and ensures fair, consistent decision making
  - Shortfall highly sensitive to modelling assumptions e.g., age and several plausible analyses are close to threshold (NICE note: need SoC QALY ≤0.57 to meet 1.7 weight – not met in any ACM2 scenarios)
  - Reliance on point estimates does not reflect range of plausible outcomes - NICE previously been pragmatic where results fall near cutoffs
- Adagrasib (TA1076) in same population met 1.7 modifier ➔ disease context and prognosis not changed
  - Differences in classification likely reflect methodological choices than change in disease burden
  - Consistency is important to ensure transparent and predictable decision making

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

ACM: Appraisal committee meeting; AS: absolute shortfall; CAS RWE: Cancer analysis system real world evidence; DG: Draft guidance; PS: Proprotional shortfall; SoC: Standard of care; QALY: Quality-adjusted life years

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- ❑ Summary

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Summary of company and EAG base case assumptions

	Company base case at ACM2	EAG base case at ACM2
Baseline characteristics	CAS RWE	CAS RWE
Modelling OS	CAS RWE S&D: independent log logistic	S: independent gen gamma (CAS RWE) D: inverse HR from CodeBreaK 200
Treatment effect waning	No waning	Gradual waning between 2 to 5 years after treatment initiation
Modelling PFS/TTNTD	CAS RWE (TTNT proxy) S&D: jointly fitted gen gamma	CodeBreaK 200 (PFS) S&D: independent log logistic
Modelling TTDD	CAS RWE S&D: independent gen gamma	CodeBreaK 200 S: independent log normal D: independent Weibull
Mapping function	Hernandez-Alava approach	
Utilities	MMRM by treatment and progression	Company base case + 12-month linear waning of docetaxel post-progression utility decrement
Severity weight	1.7*	1.2

* Company's base case model produces a severity weight of x1.2

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ACM2: Appraisal committee meeting 2; CAS RWE: Cancer analysis system real world evidence; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; TTDD: Time to treatment discontinuation or death; TTNTD, Time to next treatment or death

Results include revised reduced PAS

Company base case results at ACM2

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	QALY weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£59,351
				1.2	[redacted]	£49,459
				1.7	[redacted]	£34,912

Company ACM2 base case

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	QALY weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£59,869
				1.2	[redacted]	£49,891
				1.7	[redacted]	£35,217

Company ACM2 base case

NICE

ICER: Incremental cost effectiveness ratio; PAS: Patient access scheme; QALYs: Quality adjusted life years

Results include revised reduced PAS

EAG base case results at ACM2

Deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	QALY weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£127,824
				1.2	[redacted]	£106,520
				1.7	[redacted]	£75,190

→ EAG ACM2 base case

Probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	QALY weighting	Incremental QALYs	ICER (£/QALY)
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	£123,023
				1.2	[redacted]	£102,519
				1.7	[redacted]	£72,367

→ EAG ACM2 base case

NICE

ICER: Incremental cost effectiveness ratio; PAS: Patient access scheme; QALYs: Quality adjusted life years

Results include revised reduced PAS

EAG probabilistic scenario analysis

Technology	Total costs	Total QALYs	Inc costs (£)	QALY weight	Inc QALYs	ICER £/QALY
EAG base case approach						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£123,023**
				1.2	[redacted]	**£102,519**
				1.7	[redacted]	**£72,367**
Scenario analysis 1: Use independently fitted log-logistic from CAS RWE to inform sotorasib OS						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£98,730**
				1.2	[redacted]	**£82,275**
				1.7	[redacted]	**£58,076**
Scenario analysis 2: use the adjusted TTNTD from CAS RWE to inform sotorasib PFS, and use the inverse HR from CodeBreaK 200 to inform docetaxel PFS						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£151,872**
				1.2	[redacted]	**£126,560**
				1.7	[redacted]	**£89,337**

NICE

CAS RWE: Cancer analysis system real world evidence; HR: Hazard ratio; ICER: Incremental cost effectiveness ratio; OS: Overall survival; PAS: Patient access scheme; PFS: Progression-free survival; QALYs: Quality adjusted life years; TTNTD: Time to next treatment or death

Results include revised reduced PAS

Company deterministic scenario analysis (1)

Technology	Total costs	Total QALYs	Inc costs (£)	QALY weight	Inc QALYs	ICER £/QALY
Company base case approach						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£59,351**
				1.2		**£49,459**
				1.7		**£34,912**
Scenario analysis 1: apply CodeBreaK 200 inverse crossover adjusted HR to baseline CAS RWE sotorasib OS curves to generate the docetaxel curves						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£85,985**
				1.2		**£71,654**
				1.7		**£50,579**
Scenario analysis 2: using PFS from CodeBreaK 200 to inform PFS directly						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£61,114**
				1.2		**£50,928**
				1.7		**£35,949**
Scenario analysis 3: use adjusted CAS RWE TTNTD to inform sotorasib PFS, and use inverse HR from CodeBreaK 200 to inform docetaxel PFS						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£60,259**
				1.2		**£50,216**
				1.7		**£35,447**

NICE CAS RWE: Cancer analysis system real world evidence; HR: Hazard ratio; ICER: Incremental cost effectiveness ratio; PAS: Patient access scheme; PFS: Progression-free survival; QALYs: Quality adjusted life years; TTNTD: Time to next treatment or death

Company deterministic scenario analysis (2)

Results include revised reduced PAS

Technology	Total costs	Total QALYs	Inc costs (£)	QALY weight	Inc QALYs	ICER £/QALY
Company base case approach						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£59,351**
				1.2		**£49,459**
				1.7		**£34,912**
Scenario analysis 4: extrapolating TTDD data from CodeBreaK 200						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£59,862**
				1.2		**£49,885**
				1.7		**£35,213**
Scenario analysis 5: MMRM by treatment and progression + waning of docetaxel post-progression utility decrement						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£60,959**
				1.2		**£50,799**
				1.7		**£35,858**
Scenario analysis 6: MMRM by progression and TTD						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£61,716**
				1.2		**£51,430**
				1.7		**£36,303**
Scenario analysis 7: progression-based treatment independent utilities						
Docetaxel	[redacted]	[redacted]	-		-	-
Sotorasib	[redacted]	[redacted]	[redacted]	1.0	[redacted]	**£67,429**
				1.2		**£56,191**
				1.7		**£39,664**

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ICER: Incremental cost effectiveness ratio; MMRM: Mixed models for repeated measures; PAS: Patient access scheme; QALYs: Quality adjusted life years; TTD: Time to death; TTDD: Time to discontinuation or death

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

- ❑ ACM1 recap and DG consultation responses
- ❑ Clinical effectiveness evidence
- ❑ Cost effectiveness evidence
- ❑ Base case assumptions and cost-effectiveness results
- ✓ **Summary**

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ACM2: Key issues and questions for committee

#	Key issues	ICER impact
1	**Clinical effectiveness evidence source** • Which evidence source (CodeBreaK 200 or CAS RWE) should be used to inform OS, PFS and TTDD in the economic model?	Large
2	**Modelling OS** • What is the most appropriate approach to model OS?	Large
3	**Treatment effect waning** • Should an explicit treatment effect waning assumption be included in the economic model? • If so, should it occur between 3 - 5 or 2 - 5 years after treatment starting, or other?	Small
4	**Modelling PFS** • What is the most appropriate approach to model PFS?	Small
5	**Modelling TTDD** • What is the most appropriate approach to model TTDD?	Small
6	**Utility values** • What is the most appropriate approach to model utility values?	Small
7	**Severity modifier** • Is it appropriate to apply a QALY weighting for severity weight of x1.2 or x1.7?	Large

Appraisal committee meeting 2; CAS RWE: Cancer analysis system real world evidence; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life years; TTDD: Time to treatment discontinuation or death

Decision making framework (1)

What are committee's preferred assumptions?	Options	
Which evidence source should be used to inform OS, PFS and TTDD in the economic model?	CodeBreaK 200 or CAS RWE	
What is the most appropriate approach to model OS?	Company BC	CAS RWE S&D: independent log logistic
	EAG BC	S: independent gen gamma (CAS RWE) D: inverse HR from CodeBreaK 200
	Other	S: independent log logistic (CAS RWE) D: inverse HR from CodeBreaK 200
What is the most appropriate approach to model PFS?	Company BC	CAS RWE (TTNTD proxy) S&D: jointly fitted gen gamma
	EAG BC	CodeBreaK 200 (PFS) S&D: independent log logistic
	Other	PFS directly from CodeBreaK 200 Sotorasib: independent exponential Docetaxel: independent log logistic
		Adjusted TTNTD from CAS RWE for sotorasib PFS + inverse HR from CodeBreaK200 to inform docetaxel PFS

BC: Base case; CAS RWE: Cancer analysis system real world evidence; D: Docetaxel; HR: hazard ratio; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life years; S: Sotorasib; TTNTD: Time to next treatment or death

Decision making framework (2)

What are committee's preferred assumptions?	Options	
What is the most appropriate approach to model TTDD?	Company BC	CAS RWE S&D: independent gen gamma
	EAG BC	CodeBreaK 200 S: independent log normal D: independent Weibull
	Other	TTDD directly from CodeBreaK 200
Should an explicit treatment effect waning assumption be included in the model? Should it occur between 3 - 5 or 2 - 5 years after treatment starting, or other?	Company BC	No waning
	EAG BC	Gradual waning between 2 to 5 years
	Other	Gradual waning between 3 to 5 years
What is the most appropriate approach to modelling utility values?	Company BC	MMRM by treatment and progression
	EAG BC	Company base case + docetaxel post-progression utility decrement waning
	Other	Progression status and a decrement related to TTD within 6 months of death
		Progression based, treatment independent utilities
Is it appropriate to apply a QALY weighting for severity weight of x1.2 or x1.7?	Company BC	1.7
	EAG BC	1.2

BC: Base case; D: Docetaxel; ICER: Incremental cost-effectiveness ratio; MMRM: Mixed models for repeated measures; QALY: Quality-adjusted life years; S: Sotorasib; TTD: Time to death; TTDD: Time t0 treatment discontinuation or death

Decision making framework (3)

What are committee's preferred assumptions?	Options
What is the committee's preferred ICER threshold?	Range: £25,000 to £35,000
What is the committee's preferred ICER?	
Is the ICER below the preferred ICER threshold?	
What, if any, are the key remaining uncertainties?	
Equality considerations	
Uncaptured benefits	

ICER: Incremental cost-effectiveness ratio

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

Supplementary appendix

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Key clinical studies: overview

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		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
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	EAG base case	Company and EAG base case

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

AE: Adverse event; CAS: Cancer Analysis System; FAS: Full analysis set; HRQoL: Health-related quality of life; KM: Kaplan-Meier; KRAS: Kristen ras; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; TTDD: Time to treatment discontinuation or death; TTNTD: Time to next treatment or death

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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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adv: Advanced; CAS RWE: Cancer analysis system real world evidence; CS: Company submission; ECOG: Eastern Cooperative Oncology Group; KRAS: Kirsten ras sarcoma; PD-L1: Programmed cell death ligand 1

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Key clinical study results summary

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- CodeBreak 200 trial suggests smaller relative treatment effect (in terms of OS and PFS) compared to CAS RWE study (HRs are closer to 1 – highlighted in yellow)
- 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	363	0.633 (0.54, 0.75)	394	363	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

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;

Key clinical trial results – CodeBreak 200

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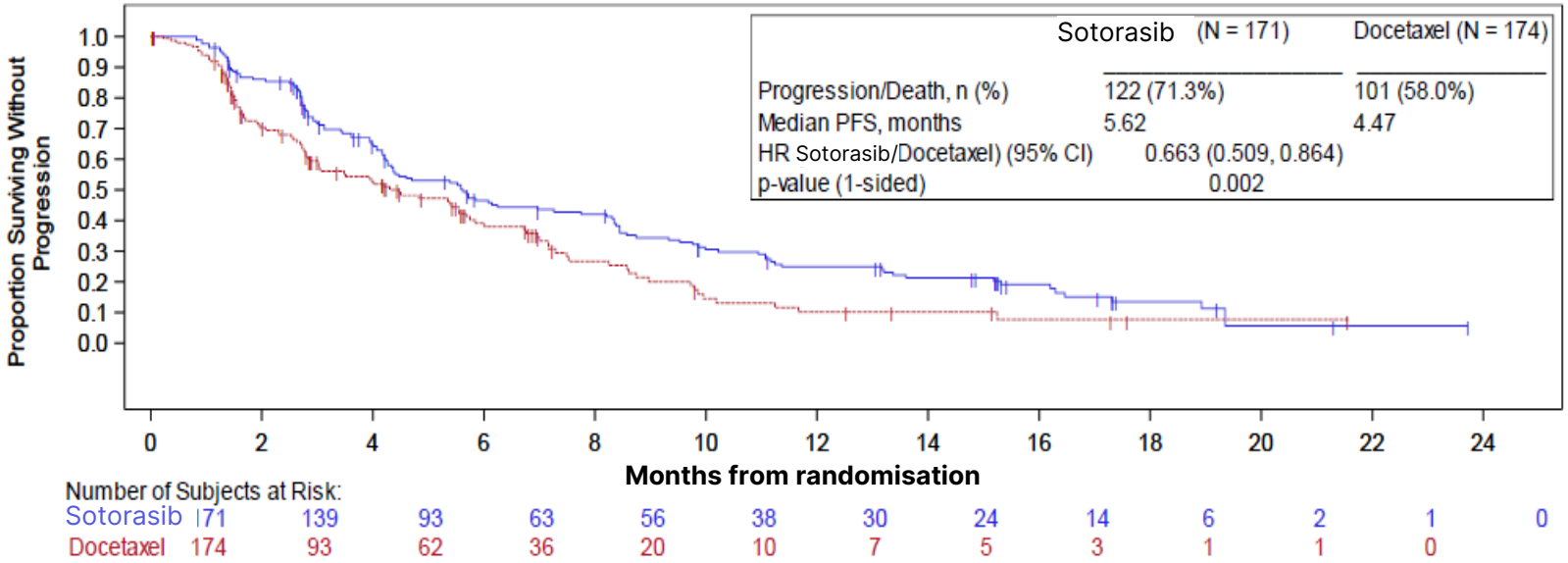
Sotorasib shows statistically significant improvement in primary end point, PFS

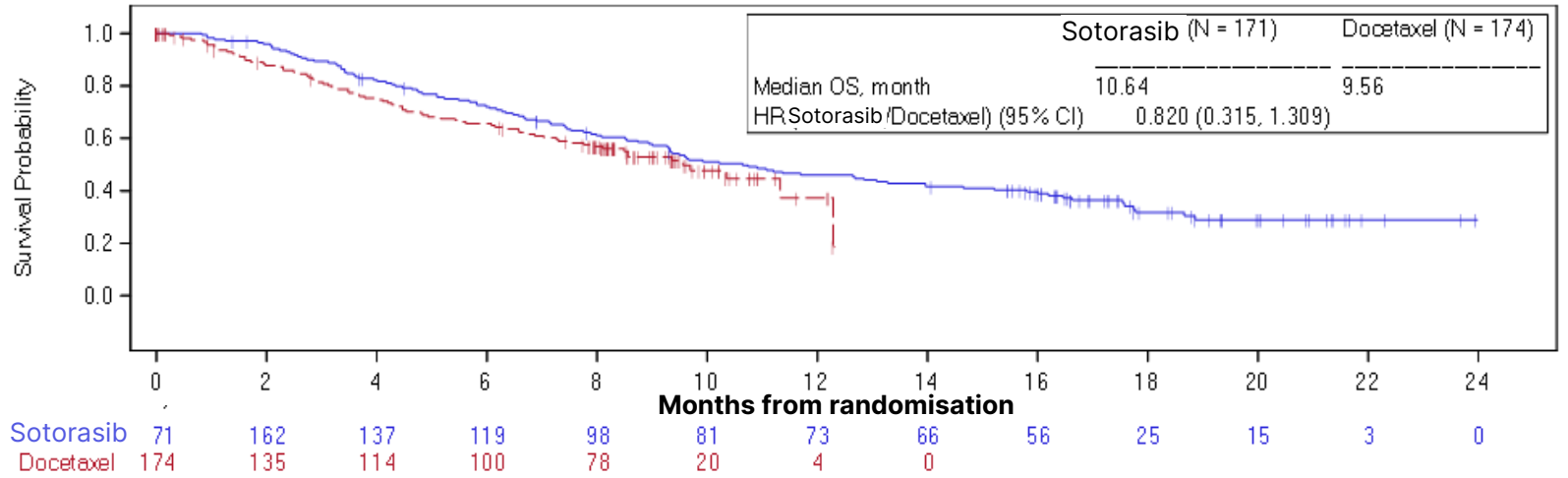
PFS by BICR (FAS) KM plot

- 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



NICE ACM1: Appraisal committee meeting 1; BICR: Blinded independent central review; CI: Confidence interval; FAS: Final analysis set; HR: Hazard ratio; KM: Kaplan-Meier; OS: Overall survival; PFS: Progression-free survival;

Key clinical study results – CAS RWE

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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

ACM1: Appraisal committee meeting 1; ATT: Average treatment effect in the treated; CAS RWE: Cancer Analysis System real world evidence; CI: Confidence interval; HR: Hazard ratio; KM: Kaplan-Meier; OS: Overall survival; PFS: Progression-free survival; SMRW: Standardised mortality ratio weighting; TTNTD: Time to next treatment or death

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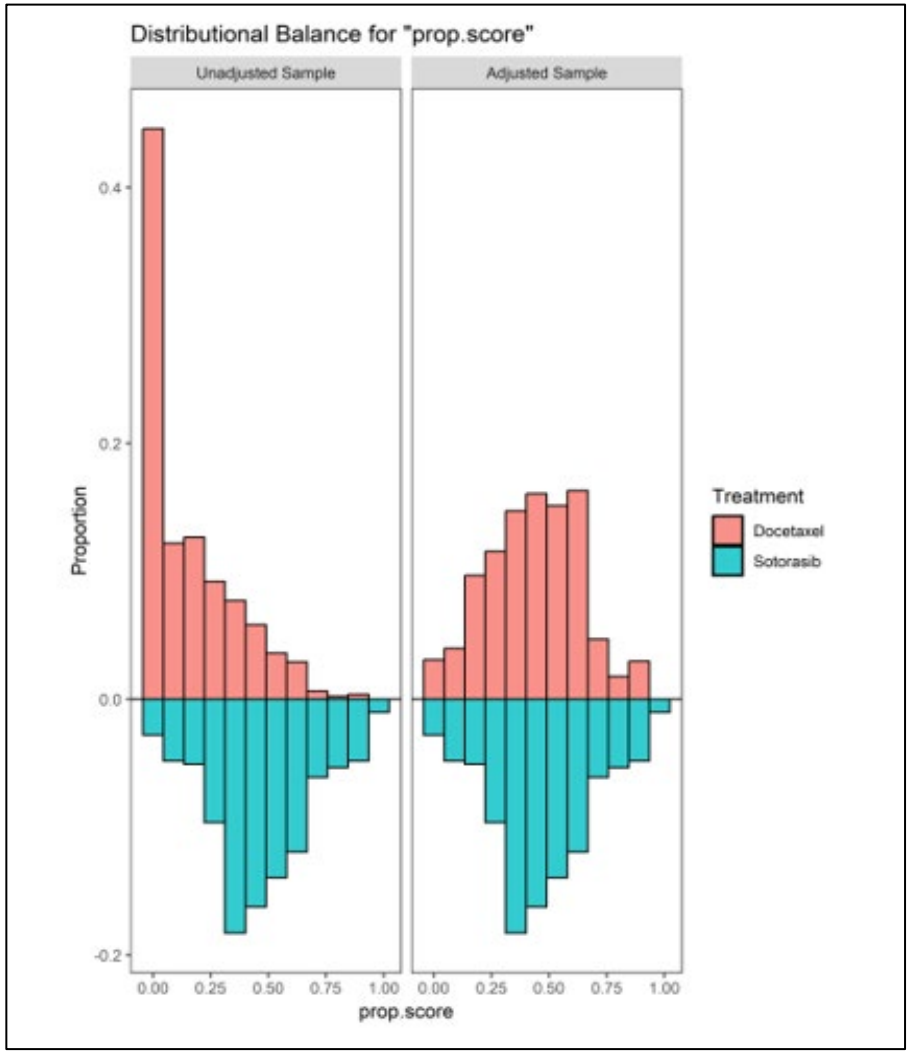
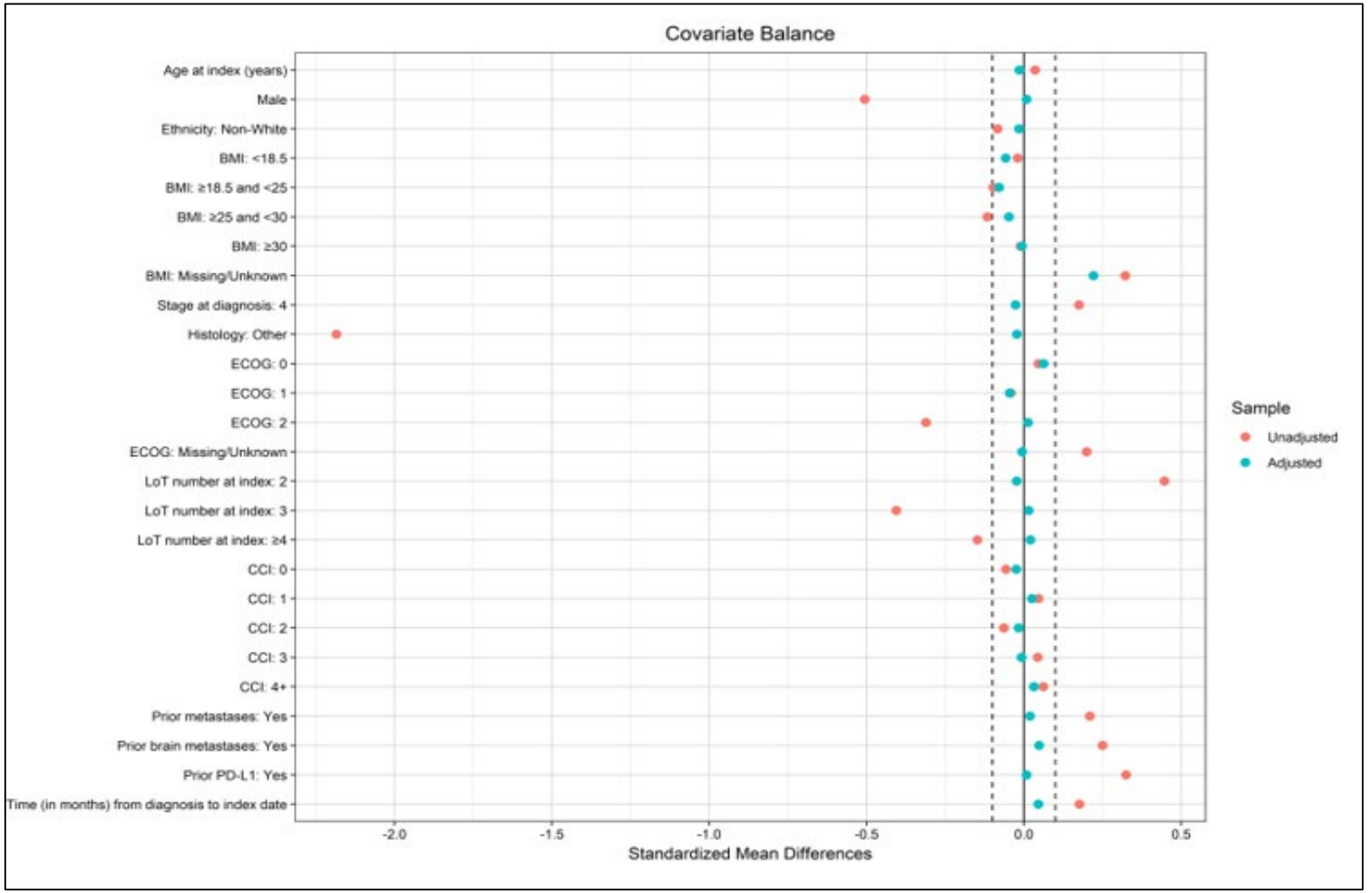
Propensity score diagnostics for 2L+ Analysis Set (ATT Estimand)

Distribution of propensity scores by treatment group before and after SMRW

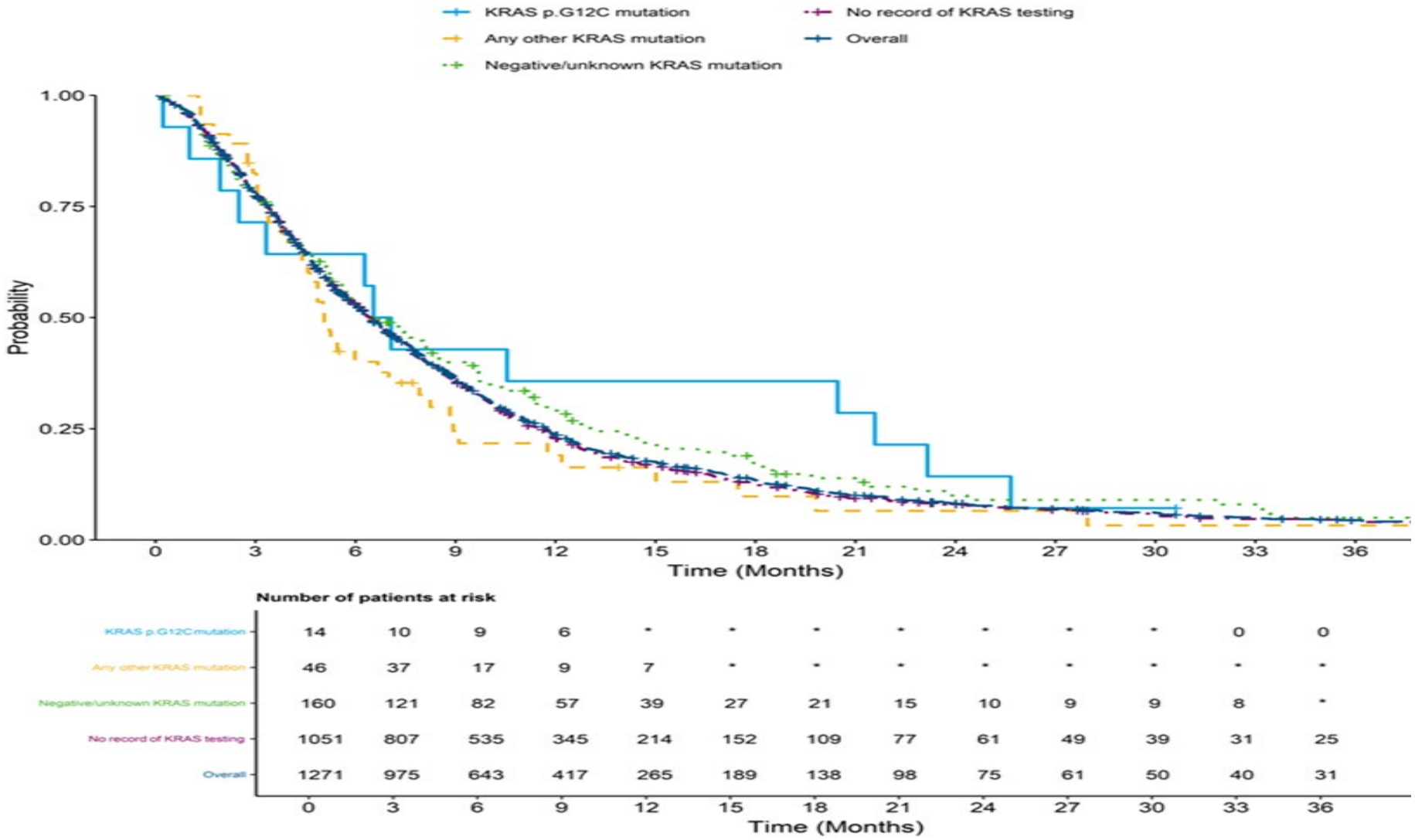


Covariate balance before and after SMRW



2L+: Second line treatment or later; ATT: Average treatment effect in the treated; SMRW: Standardised mortality ratio weighting

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



KM: Kaplan-Meier; KRAS: Kirsten ras sarcoma; OS: Overall survival

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ASCO 2020 – OS by KRAS G12C mutation status

People with KRAS G12C mutation positive NSCLC have a similar OS to people without KRAS G12C mutation NSCLC

Study therapy	Median OS, months (95% CI)		
	Without KRAS mutation	With KRAS mutation	KRAS G12C
ICI + Chemo	18.7 (16.0, 25.2) N=313	22.4 (18.2, NE) N=219	20.8 (11.3, NE) N=58
	HR = 1.12 (0.86, 1.46)		
ICI alone	16.4 (13.4, 19.7) N=240	16.2 (11.1, NE) N=135	11.8 (8.2, NE) N=45
	HR = 1.01 (0.76, 1.34)		
Chemo alone	14.9 (12.2, 16.6) N=322	17.1 (12.3, 18.9) N=201	17.5 (10.7, 21.1) N=54
	HR = 1.12 (0.81, 1.29)		

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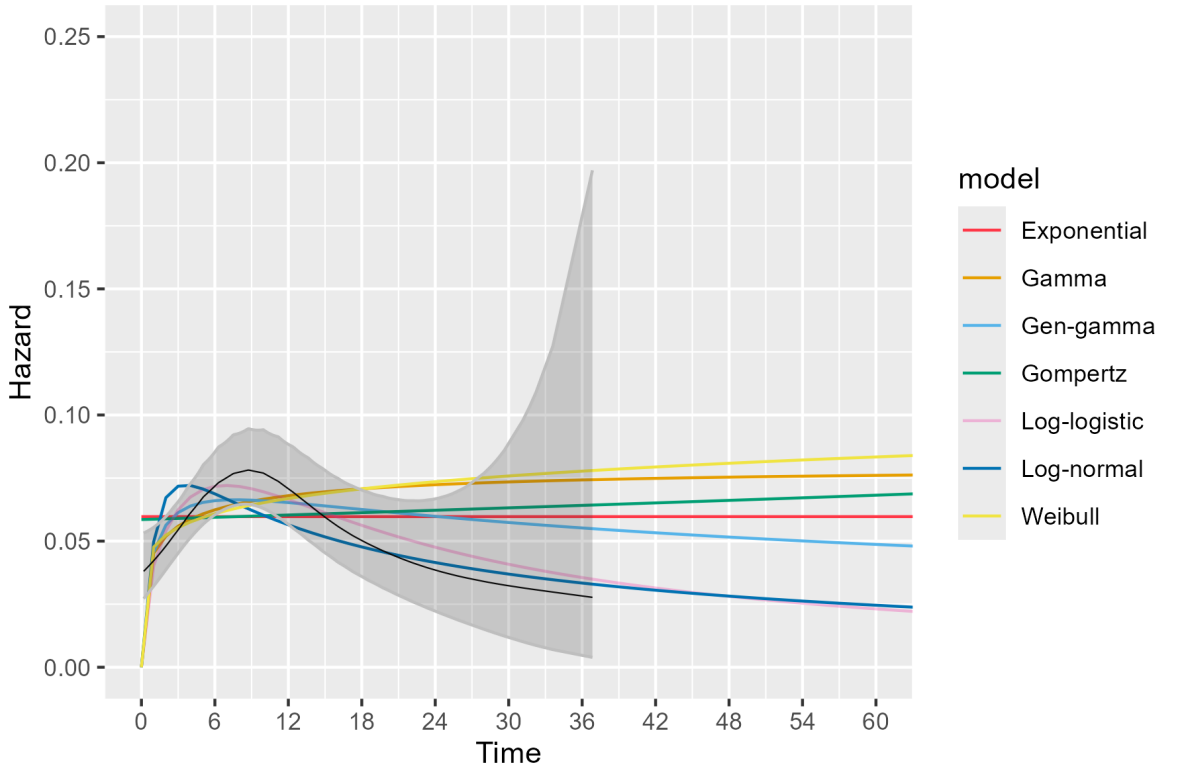
ASCO: American Society of Clinical Oncology; CI: Confidence interval; HR: Hazard ratio; ICI: Immune checkpoint inhibitor; KRAS: Kirsten ras sarcoma; NE: Not estimable; OS: Overall survival

Large impact

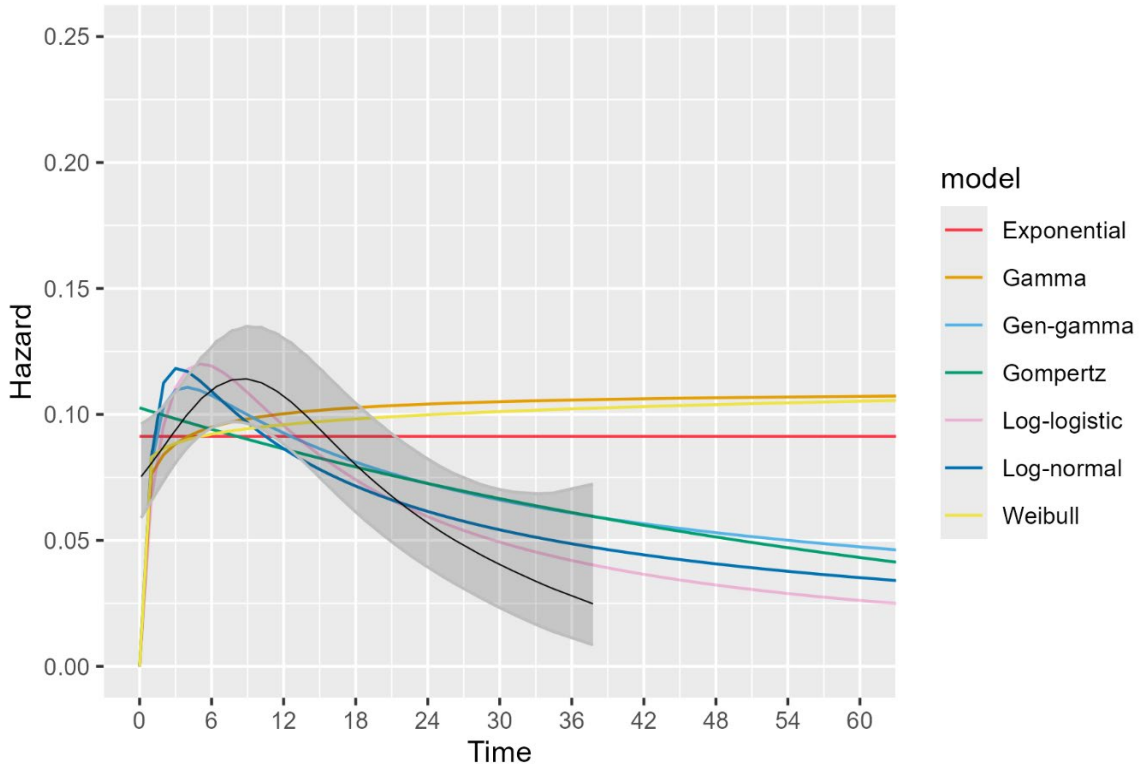
Key issue 2: Modelling OS

Company DG consultation response

Modelled hazards versus observed sotorasib CAS RWE OS smoothed hazard



Modelled hazards versus observed docetaxel CAS RWE OS smoothed hazard



- Only the log-logistic and log-normal closely approximate the profiles observed in CAS for both arms

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CAS RWE: Cancer analysis system real world evidence; DG: Draft guidance; OS: Overall survival

Large impact

Key issue 2: Modelling OS

Company DG consultation response

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

Model	Independent fit – sotorasib		Independent fit – docetaxel	
	AIC	BIC	AIC	BIC
Exponential	1811.85	1815.83	2011.22	2015.11
Gamma	1806.35	1814.30	2008.02	2015.81
Generalised gamma	1805.10	1817.03	1990.26	2001.94
Gompertz	1813.79	1821.74	2009.42	2017.21
Log-normal	1814.48	1822.44	1991.60	1999.39
Log-logistic	1797.85	1805.80	1982.12	1989.91
Weibull	1808.45	1816.40	2011.68	2019.47

→ **Company base case at ACM2**

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AIC: Akaike information criterion; BIC: Bayesian information criterion; DG: Draft guidance; OS: Overall survival

OS model selection

Company base case:

- CAS RWE
- S&D: log logistic

[redacted]

EAG base case:

- Sotorasib: CAS RWE [Generalised gamma])
- Docetaxel: inverse HR from CodeBreaK 200

[redacted]

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CAS RWE: Cancer analysis system real world evidence; D: Docetaxel; OS: Overall survival; PFS: Progression-free survival; S: Sotorasib

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PFS model selection

Estimates	Company base case		EAG base case		EAG clinical expert	
	Sotorasib	Docetaxel	Sotorasib	Docetaxel	Sotorasib	Docetaxel
3-year TTNTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's base case:

- CAS RWE (TTNTD proxy)
- S&D: jointly fitted gen gamma

EAG's base case

- CodeBreaK 200 (PFS)
  S&D: independent log logistic

[redacted]

[redacted]

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D: Docetaxel: PFS: Progression-free survival; CAS RWE: Cancer Analysis system real world evidence; S: Sotorasib; TTNTD: Time to next treatment or death;

CodeBreaK 200 sotorasib Kaplan-Meier for PFS and TTNTD

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CI: Confidence interval; HR: Hazard ratio; PFS: Progression-free survival; TTNTD: Time to next treatment or death

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TTDD model selection

Company base case: CAS RWE + S&D: independent gen gamma

[redacted]

EAG base case: CodeBreaK 200, S: independent log normal, D: independent Weibull

[redacted]

BC: Base case; CAS RWE: Cancer Analysis System Real World Evidence; CB200: CodeBreak 200; D: Docetaxel; PFS: Progression-free survival; S: Sotorasib; TTDD: Time to treatment discontinuation or death

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TTDD model selection

	Company base case		EAG base case	
	Sotorasib	Docetaxel	Sotorasib	Docetaxel
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (months)	[redacted]	[redacted]	[redacted]	[redacted]
On treatment at 6 months	[redacted]	[redacted]	[redacted]	[redacted]
On treatment at 1 year	[redacted]	[redacted]	[redacted]	[redacted]
On treatment at 2 years	[redacted]	[redacted]	[redacted]	[redacted]
On treatment at 3 years	[redacted]	[redacted]	[redacted]	[redacted]
On treatment at 4 years	[redacted]	[redacted]	[redacted]	[redacted]
On treatment at 5 years	[redacted]	[redacted]	[redacted]	[redacted]
On treatment at 10 years	[redacted]	[redacted]	[redacted]	[redacted]

TTDD: Time to treatment discontinuation or death

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Utilities values

Company and EAG base case: Utilities by progression status from MMRM by progression and treatment arm

Treatment arm	Progression status	Mean (SE)
Sotorasib	Pre-progression	[redacted]
	Post-progression	[redacted]
Docetaxel	Pre-progression	[redacted]
	Post-progression	[redacted]

EAG base case: 12-month linear waning of docetaxel post-progression utility decrement (utility increases over 12-months to equal sotorasib post-progression utility

Treatment arm	12-month linear waning of post progression utility decrement
Docetaxel	[redacted]

Scenario: Utilities by both progression status and a decrement related to TTD within 6 months of death

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

Scenario: Progression based, treatment independent utilities

Covariate	Mean (SE)
Pre-progression	[redacted]
Post-progression	[redacted]

NICE

MMRM: Mixed methods regression model; SE: Standard error; TTD: Time-to-death