NICE National Institute for Health and Care Excellence

For Public: Contains no confidential information [Fully redacted]

Sotorasib for previously treated KRAS p.G12C mutated, locally advanced or metastatic non-small cell lung cancer [ID3780]

Lead team presentation

Lead team: Guy Makin, Malcolm Oswald, Ed Wilson
Chair: Lindsay Smith
ERG: Kleijnen Systematic Reviews
Technical team: Summaya Mohammad, Caron Jones, Jasdeep Hayre
Company: Amgen UK
ACM1: 15 December 2021

Key issues

- **Issue 7:** Exclusion of platinum-based chemotherapy as comparator in 2nd line
- **Issue 9:** No waning of treatment effect
- **Issue 5:** Validity of ITC without a common comparator
- **Issue 8:** Docetaxel plus nintedanib modelling approach leading to worse survival
- **Issue 11:** Time-to-death utilities do not seem well-informed
- **Issue 12:** Disutility for IV administration not well justified
- **Issue 13:** Relative dose intensity and wastage not justified
- **Consideration for Cancer Drugs Fund**
- **Consideration for End-of-Life**

Disease background

Non-squamous NSCLC is predominant subtype, KRAS G12C most common mutation; late stage diagnosis with palliative treatment aims

Prevalence

- Around 48,000 new lung cancer cases and 35,000 deaths in UK every year
- 3rd most common cancer and most common cause of cancer death in UK (2017)
- Majority lung cancer diagnosed at advanced stage (around 67% stage III-IV)

Histology:

- Non-small cell lung cancer (NCSLC) most common type in UK (80-85%)
- Non-squamous cell (adenocarcinoma & large cell) → predominant subtype (66% & 2%)
- Squamous cell → 23%

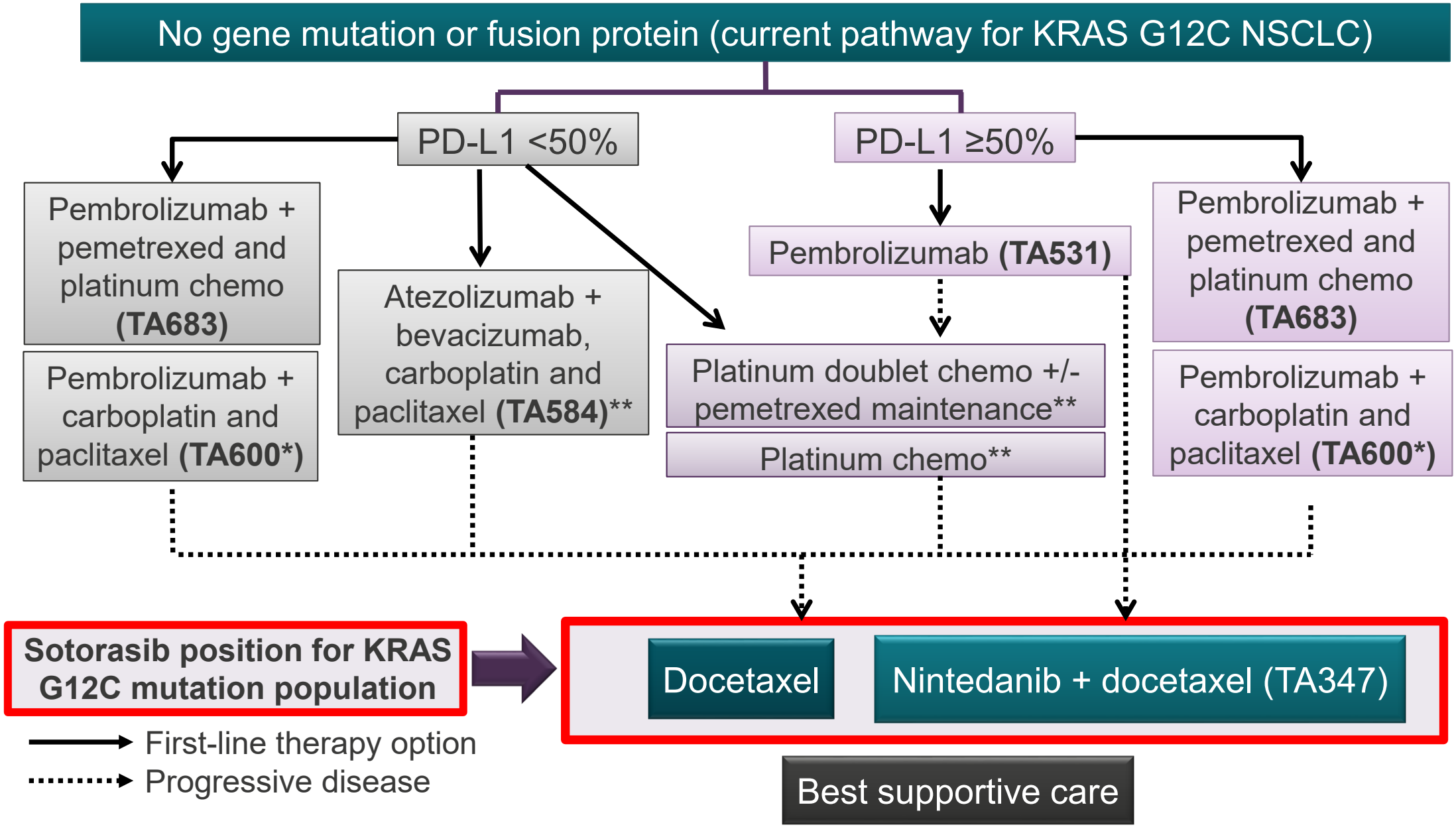
KRAS G12C mutation

- KRAS most frequently mutated oncogene in cancer
- KRAS G12C most common mutation in NSCLC (12%; 2,300 to 3,300 cases in UK)
- More common in non-squamous NSCLC
- Not usually occurring with other known oncogenic mutations in NSCLC (e.g. EGFR-TK, ALK, ROS-1)
- No targeted treatment available for KRAS G12C mutation

Treatment aim

- Prolong survival and improve quality of life

Treatment pathway



*Subject to ongoing CDF review
** This/some combinations do not have UK MA for 1 or more indications

Source: Based on figure 1 in company submission

Current treatments

- Treatment choices influenced by **biological markers, histology, prior treatments**
- **Currently no targeted treatment for KRAS G12C mutation**
- Clinical and patient experts: **unmet need for effective and tolerable therapies**
- Clinical experts – **palliative treatment aims:** 1st-line platinum-based chemotherapy, immune checkpoint inhibitor/combination
  - ‘Subsequently, few ‘standard care’ options: docetaxel±nintedanib are relevant comparators’
- Chemotherapy is intravenous, myelosuppressive, cytotoxic
- Side effects of non-targeted therapies including: (febrile) neutropenia, dyspnoea, fatigue, infection, anaemia, diarrhoea, stomatitis, nausea, vomiting
- Affect health-related quality of life
- Approx. 50% people with previously treated KRAS-mutated advanced NSCLC have symptom progression 1 month after starting docetaxel treatment

Patient organisation perspective

Royal Castle Lung Cancer Foundation:

- **First targeted therapy** specific for KRAS G12C mutation in NSCLC
- Current systemic treatment (1st and 2nd–line): combination chemotherapy and immunotherapy
- Poor outlook in lung cancer, with impact on family and carers → 1-year survival: 37% (National Lung Cancer Audit)
    - **Poorer prognosis in NSCLC with KRAS G12C mutation**
- Lung cancer symptoms difficult to treat without active anti-cancer therapy: E.g. breathlessness, cough, weight loss – *'distressing for loved ones to observe'*
- Sotorasib once a day, oral tablet: home/ease of administration, reduced inpatient time at hospital – *'important in COVID world'*
- Most common side-effects: diarrhoea, musculoskeletal pain, nausea – majority mild, but 20% more serious → 28% treatment delays and/or dose reductions, 7% stopped
- **Consider CDF:** ongoing clinical trials, reassess after data matures and new data emerges

Professional organisation

British Thoracic Oncology Group:

- Response rate and PFS important in early assessment of targeted therapies
- Seemingly higher sotorasib efficacy but no randomised comparisons
- **Unmet need** in large subgroup – generally mutually exclusive with other mutations that have therapies (e.g. EGFR, ALK, ROS-1, RET)
- KRAS most commonly mutated in adenocarcinoma NSCLC – **50% are KRAS G12C** (sotorasib target) (Burns et al., 2020)
- *'KRAS oncogene previously described as undruggable'* because not a protein kinase
- Sotorasib is oral targeted therapy – generally better tolerated (but not without side effects), less resource-intensive than comparator chemotherapy-based treatment
- Side effects (even long-term) *'preferable to universally-experienced myelosuppression, alopecia and common nausea, vomiting associated with comparator chemotherapy'*
- KRAS testing: simple PCR test but variation in current routine testing

Sotorasib (Lumykras, Amgen)

Marketing authorisation	Monotherapy for treatment of adult patients with KRAS p.G12C-mutated locally advanced or metastatic non-small cell lung cancer, who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy. • Conditional licensing approval through Project Orbis granted
Mechanism of action	Irreversible small-molecule inhibitor of KRAS G12C protein, locking into inactive state to prevent downstream signalling and control cell proliferation and survival
Administration	960 mg dose (8 x 120 mg tablets) taken orally, once daily, until disease progression or unacceptable toxicity
KRAS G12C testing	KRAS G12C now included routinely in national service for cancer genomic testing – no additional tests beyond routine in NSCLC needed • But there may be variation in testing in practice (clinical expert)
Price	• List price: [redacted] per 30-day supply (240 x 120 mg tablets) • Simple PAS discount approved • [redacted] per 30-day supply (240 x 120 mg tablets) • Undiscounted average per patient cost of treatment*: [redacted]

*based on modelled drug utilisation and duration of therapy used in economic evaluation

Background

Population	**Scope:** Adults with previously treated KRAS G12C mutated, locally advanced or metastatic NSCLC **Company:** as per marketing authorisation
Key trial	CodeBreaK100: Single-arm, phase II in 47 centres (N=126) • Inclusion criteria: 1-3 lines of prior anti-cancer therapy, measurable disease per RECIST 1.1 criteria and ECOG performance status 0 or 1 ➢ 1-line: 43%; 2-lines: 35%; 3-lines: 22%
Comparisons	No direct comparative data and no common trial arms for anchored indirect treatment comparisons or network meta-analyses • Indirect comparison of sotorasib vs docetaxel±nintedanib • No evidence vs platinum-doublet chemotherapy
Key trial results	**Primary:** Objective response rate* (ORR) = **37.1%** (95%CI: 28.6-46.2), **Secondary:** Duration of response, OS; PFS; adverse events (CodeBreaK100 not powered for survival outcomes)

*ORR calculated as complete response (2.4%) + partial response (34.7%), assessed by blinded independent central review per RECIST criteria 1.1

- Pre-specified ORR benchmark for clinical significance: 23%

Summary of key clinical evidence

CodeBreaK100 phase II, global, multi-centre, open-label

250 adults with mutated KRAS G12C advanced solid tumours

NSCLC (n=126) → Sotorasib (n=124: full analysis set, n=126: safety analysis set)

Treatment until disease progression, discontinuation or end of study

- Safety follow-up: 30 (+7) days after end of treatment
- Long-term follow-up (OS): every 12 weeks for 3 years

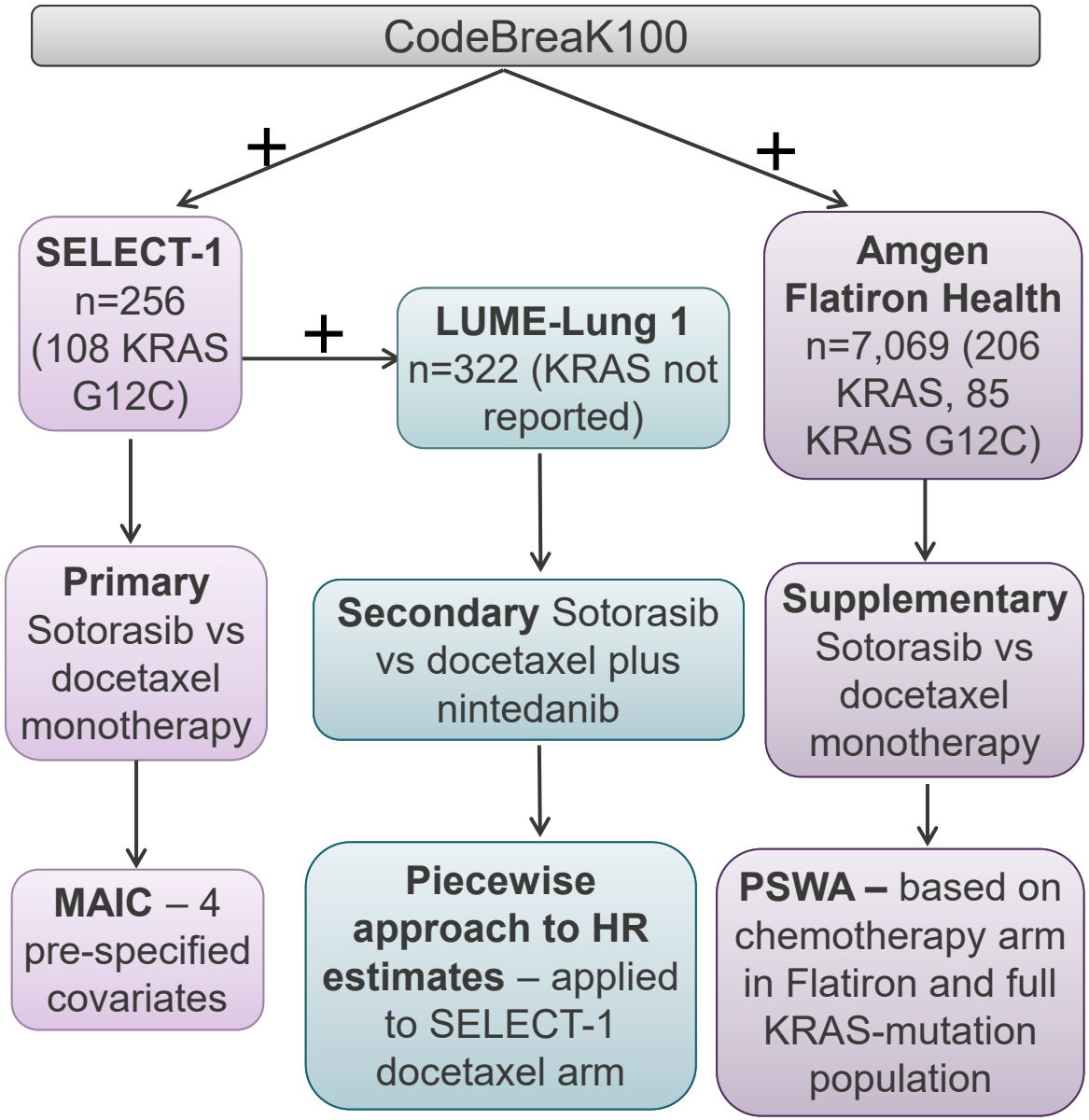
Latest available data

- **Patient reported outcomes:** September 2020
- **Safety and efficacy analysis:** March 2021
- **Patient-level data** (for indirect treatment comparison): December 2020

Baseline characteristics		
Male/Female		50%
Mean age (SD)		62.9 (9.3)
Metastases		41%
Non-squamous		99%
ECOG PS	0	30%
	1	70%
Prior lines of therapy	1	43%
	2	35%
	3	22%
Types of prior therapy	Platinum-based chemotherapy	90%
	PD-1/PD-L1 inhibitors	91%
	Combination	81%
Current/former smoker		93%

Indirect treatment comparison overview

No direct comparative data and no common trial arms for anchored ITCs or NMAs



	Characteristics		
Study	**SELECT-1** (docetaxel monotherapy)	**LUME-Lung 1** (docetaxel plus nintedanib)	**Flatiron** (inc. docetaxel monotherapy)
	Double-blinded	Double-blinded	Real-world evidence
Cohort	2013-2016	2008-2011	2011-2020
Inclusion	1 prior therapy	1 prior therapy (platinum-based, allow (neo)adjuvant)	At least 1 prior therapy – up to 4 lines
	No brain metastases		
	No prior MEK inhibitor or docetaxel regimen	No *active* brain metastases	Only chemotherapy-based regimens included for PSWA, including docetaxel
		No prior VEGFR inhibitor (except bevacizumab) or docetaxel	
Endpoint	PFS, OS	PFS, OS	PFS, OS

Abbreviations: HR: Hazard ratio; ITC: Indirect Treatment Comparison; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; PSWA: Propensity score weighting analysis; NMA: network meta-analysis

Indirect treatment comparison results

	March 2021 data-cut		
Sotorasib vs comparator	**Primary** (vs. docetaxel monotherapy)	**Supplementary** (vs. docetaxel monotherapy)	**Secondary** (vs. docetaxel plus nintedanib)
ESS	109 (OS)/106 (PFS)	105	Not provided
OS median months [HR, (95%CI)]	[redacted]	[redacted]	[redacted] HR: 0-6 months: [redacted] 6-26 months: [redacted] 26+ months: [redacted]
PFS median months [HR, (95%CI)]	[redacted]	[redacted]	[redacted] HR: 0-2 months: [redacted] 2-6 months: [redacted] 6+ months: [redacted]

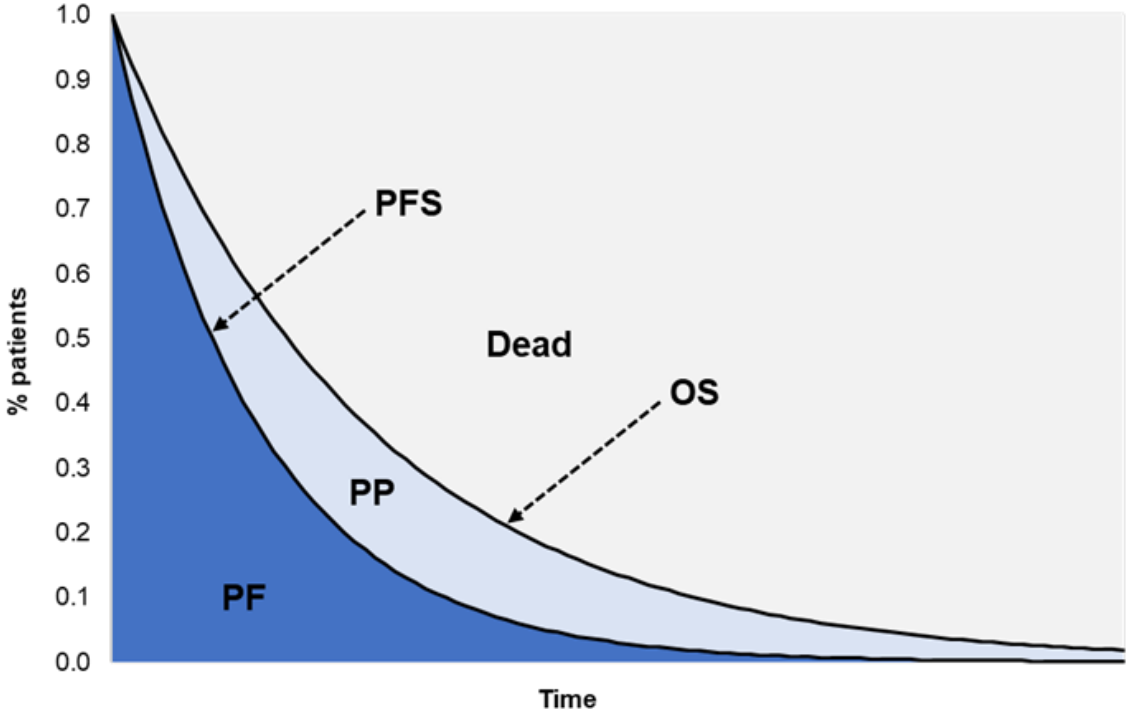
ESS: Effective Sample Size; CI: confidence interval; HR: Hazard ratio; OS: overall survival; PFS: progression-free survival

Results:

- Sotorasib statistically and clinically superior to docetaxel monotherapy for OS and PFS
- Supplementary analysis supports primary analysis results

NICE Note: MAIC model sensitivity analysis using 'all available covariates' can be found Table 1 clarification addendum (March 2021 data-cut)

Economic model structure:



OS: Overall survival; PF: Progression-free; PFS: Progression-free survival; PP: Post-progression

Structure	Cost-utility, partitioned survival model (progression-free, post-progression, death)
Time horizon	20 years
Cycle length	1 week with half-cycle correction
Discount rate	3.5%
Perspective	NHS/PSS
Utility values	CodeBreaK100: EQ-5D-5L mapped to EQ-5D-3L; literature; NICE appraisals in NSCLC (TA428, TA484)

Issues resolved after technical engagement

Summary	Company responses	ERG response
Key issue 10: TTD modelling approach inconsistent with OS and PFS modelling	• Base-case approach of connecting TTD to PFS with fitted HR is reasonable and consistent with sotorasib clinical use • Mature TTD data means applying parametric curves has limited impact on ICER – so agree with ERG approach	Agree - resolved
Key issue 13: Relative dose intensity and wastage assumption not justified	• Base case updated to include of wastage	Partially resolved (wastage)

Abbreviations: HR: Hazard ratio; OS: Overall survival; PFS: progression-free survival; TTD: Time-to-treatment discontinuation

Issues unresolvable after technical engagement and contributing to uncertainty

Summary	Company responses	ERG response
Key issue 1: Trial population License and key trial population narrower than scope. ECOG PS 2 included in phase I CodeBreaK100 but not phase II	Considered resolved: • NICE scope broader than licensed population • ECOG ➔ Sotorasib should be an option available to clinicians when relevant	• No evidence from company that sotorasib should be an option for ECOG PS 2 group • Unresolvable with available evidence • Potentially relevant to decision-making
Key issue 2: Generalisability/lack of UK participants Unclear generalisability to NHS clinical practice – no UK centres and issue of ethnic balance	Considered resolved: • Not unusual for small/no numbers of UK patients in targeted NSCLC trials • Experts consulted agree demographics including ethnicity representative clinical practice.	• Unresolvable with available evidence • Potentially relevant to decision-making
Key issue 4: High number of serious adverse events observed in CodeBreaK100	Treatment-related adverse events considered more relevant by company	19.8% participants in CodeBreaK100 had Grade 3+ treatment-related adverse events
Key issue 6: Partitioned Survival Model structure not validated or justified	Do not consider model problems to be solved with state transition model	State transition modelling could help in verifying extrapolation plausibility, exploring clinical uncertainties, reducing structural uncertainty

Outstanding issues after technical engagement

Key issues	Impact on ICER	Slides
7. Exclusion of platinum-based chemotherapy as comparator in 2nd line		17
9. No waning of treatment effect		18
5. Validity of ITC without a common comparator		19-21
8. Docetaxel plus nintedanib modelling approach leading to worse survival		22-23
11. Time-to-death utilities do not seem well-informed		24-25
12. Disutility for IV administration not well justified		26
13. Relative dose intensity not justified		27

 **Model driver**

 **Unknown impact**

 **Small/Moderate impact**

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Issue 7: Platinum-based chemotherapy excluded as relevant comparator in 2nd line

Immunotherapy comparator in 1st-line – company argue it is diminishing population

Company reasons for excluding comparators from scope:

- Re-challenge using chemotherapy/immunotherapy not routine according to clinical expert
- KRAS G12C mutation usually mutually exclusive to other oncogenic drivers
- Docetaxel monotherapy considered key 2nd/subsequent line option – agreed by NICE scientific advice and EUnetHTA

ERG:

- Platinum-based chemotherapy excluded – affects 40% population in scope
- Implementing in model would resolve issue and reduce uncertainty

Company after TE: First-line immunotherapy is decreasing

- 90% CodeBreaK100 pre-treated with platinum-doublet chemotherapy
- No KRAS trial SLR with platinum-doublet chemotherapy arm – unanchored MAIC not possible
- Retrospective analysis with Oncology Dynamics™ data support most UK patients with recent docetaxel, likely to have had immunotherapy and platinum-doublet chemotherapy
- Company suggest PSWA reasonable proxy for platinum-based chemotherapy comparator because most common regimen → **KRAS mutant:** 31% platinum; **KRAS G12C:** 29% platinum
- **ERG:** conclusions on cost-effectiveness should not be drawn from PSWA

- Is platinum-based chemotherapy a relevant comparator?

Abbreviations: MAIC: Matching-adjusted indirect comparison; PSWA: Propensity score weighting analysis; SLR: Systematic literature review

Issue 9: No treatment effect waning (TEW)

ERG prefer TEW at 2 years, decreasing over 5 years; company discontinuation incorporated within trial period, inappropriate to apply TEW early

Company at clarification: TEW useful for sensitivities but blunt tool

- Impact of discontinuation on OS and PFS 'baked' into hazard function and survival estimates → within trial period
- Sotorasib and docetaxel very different so applying TEW is more uncertain
- March 2021 data (15 months): sotorasib arm in better average health state (~80% discontinue treatment, ~40% alive, 20% yet to progress → ½ patients alive would remain on sotorasib

ERG: Company assumption of continued sotorasib effect not justified – immature evidence

- Suggest TEW at 2-year timepoint and **gradually** decrease to HR=1 over 5 years – **ERG base case** (exploratory analysis for 3 and 7 years)

Company after TE: Inappropriate to apply TEW early → bias cost-effectiveness results if sotorasib arm accrue cost of treatment but not relative benefits of treatment

ERG: Immature data, assumptions on sustained treatment effects uncertain

- TEW in ERG base case could be considered optimistic given evidence
- In line with other NSCLC appraisals, the ERG did additional scenarios with TEW at 3 and 5 years after starting treatment (TA683, TA724, TA654)

- Should treatment effect waning be included in the model? If so, what duration of treatment effect waning should be included?

Abbreviations: HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival; TEW: Treatment effect waning

Matched adjusted indirect comparison (MAIC)

Very important

Somewhat important

Additional covariates in other MAIC

21 potential covariates

Ranked by 6 physicians: 2 from Canada and 1 each from UK, US, Germany, France

Based on:
- SELECT-1 data availability
- Prognostic importance,
- Matching feasibility,
- Preserving sample size

8 covariates included in MAIC

Primary:
Covariates previously identified as **at least 'somewhat important'**
- ECOG
- Age
- Metastatic disease stage at baseline
- Smoking status

Sensitivity:
All 8 available covariates
- Primary covariates
- PD-L1 expression* level
- Gender
- Histology
- Race

Covariates	Docetaxel SELECT-1	Sotorasib CodeBreaK100	Post-matching
ECOG (% PS1 vs PS 0)	59	70	[redacted]
Age (mean)	60.9	62.9	[redacted]
Disease stage (% IIIB vs IV)	4	4	[redacted]
Smoking status (% ever smoker	92	93	[redacted]
Gender (% female)	43	50	[redacted]
Histology (%non-squamous)	95	99	[redacted]
Race (% White)	95	82	[redacted]

*After clinician feedback: PDL-1 clarified as not a relevant prognostic factor for treatment with sotorasib and docetaxel

Issue 5: Validity of ITC without common comparator

Uncertainty in MAIC; ERG suggest mutation status covariate would be informative

Company:

- **KRAS G12C status, brain metastasis, some baseline characteristics** excluded from matching but identified 'very important' by clinical experts
  - Because missing data/trial differences

Unlikely bias and likely conservative results:

- OS/PFS similar despite **KRAS** status without targeted therapies
- All studies exclude *active* **brain metastasis**, assume CodeBreaK100 highest proportion – so any negative effects favour comparator

ERG:

- Reasonable conclude OS/PFS consistent with/without **KRAS** mutation
  - ➢ But potential informative analysis to include
- **Brain metastases** seem to affect prognosis from subgroup analysis
  - ➢ Favourability to comparator is speculation
- CodeBreaK100 more heavily pre-treated than SELECT-1 – associated with poorer outcomes, adding to uncertainty

Company after TE: Exclusion of potential treatment effect modifiers but –

- SELECT-1 data limitations; clinicians suggest *active* brain metastases more likely modifier
- 42% KRAS G12C (SELECT-1) vs 100% (CodeBreaK100); MAIC: 'weight away' CodebreaK100 sample – Not possible to match
- **ERG:** Accept weighting MAIC by mutation status infeasible but could select KRAS G12C mutation SELECT-1 data

NICE **Abbreviations:** ITC: Indirect Treatment Comparison; MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival;

Issue 5: Validity of ITC without common comparator (2)

Flatiron supplementary analysis may be more appropriate for primary comparison

Company: Amgen Flatiron Health RWE supplementary comparison → PSWA analysis

- Chemotherapy comparator only (immunotherapy not relevant)
  → includes minority with docetaxel: representing docetaxel monotherapy efficacy
- Patients aligned with CodeBreaK100 using eligibility criteria
- KRAS mutation population preferred because differences adjusted closer to 0 and bigger ESS than KRAS G12C (subgroup)

ERG: Weights applied to comparator only → gives ATT not ATE – limits applicability to sotorasib

- Can be issue – depends on treatment effect heterogeneity and CodeBreaK100 applicability
- **Informative scenarios:** apply PSW to all patients; limit to docetaxel monotherapy; use other methods e.g. regression adjustment or doubly robust combination

PSWA results may be less biased than MAIC:

- Weights on Flatiron to CodeBreaK100 (other way around in MAIC) → may be more relevant to sotorasib in UK; little ESS difference in PSWA vs MAIC, 13 covariates inc. brain metastases

Company after TE: Little difference to ICER using ATE instead of ATT

- PSWA presented with base-case MAIC as difficult to assess which is more robust

ERG: No results for scenarios on other methods, and PSWA not limited to docetaxel only data

- Is the MAIC analysis used by the company appropriate for decision-making?

Abbreviations: ATE: Average treatment effect; ATT: Average treatment effect on treated; ESS: Effective sample size; ITC: Indirect treatment comparison; MAIC: Matching-adjusted indirect comparison; PSW(A): Propensity score weighting (analysis); RWE: Real-world evidence

Issue 8: Docetaxel plus nintedanib modelling leads to worse survival

Worse survival for docetaxel plus nintedanib in first 6 months; ERG prefer HR=1

Company: LUME-Lung 1 to compare docetaxel plus nintedanib to docetaxel plus placebo

- Piecewise approach for treatment effect – OS curves do not satisfy proportional hazards assumption
- HRs applied to SELECT-1 data for indirect analysis
- Nintedanib and docetaxel HR modelling consistent with TA347

ERG: Uncertainty with methods

- **OS curve clinical plausibility:** LUME-Lung 1 and SELECT-1 differ in smoking and ECOG/WHO status – no adjustments
- First 6 months HR=[redacted]: major rise in mortality → ERG consider implausible
- OS curve not in-line with Kaplan-Meier curve in LUME-Lung 1
- Piecewise analysis for OS and PFS curves, with 6- and 26-month cut-offs – **no good fit**
- ERG suggest reducing to 1 cut-off point at 6 months
- Lowering HR increases ICER for sotorasib vs docetaxel plus nintedanib

Company after TE: Explore scenario with piecewise HRs for 0-6 and 6+ months – proportional hazards assumption violation less clear at 26 months

- Company disagree with ERG's, HR=1 for 0-6 months – invalidating 2-arm phase III trial

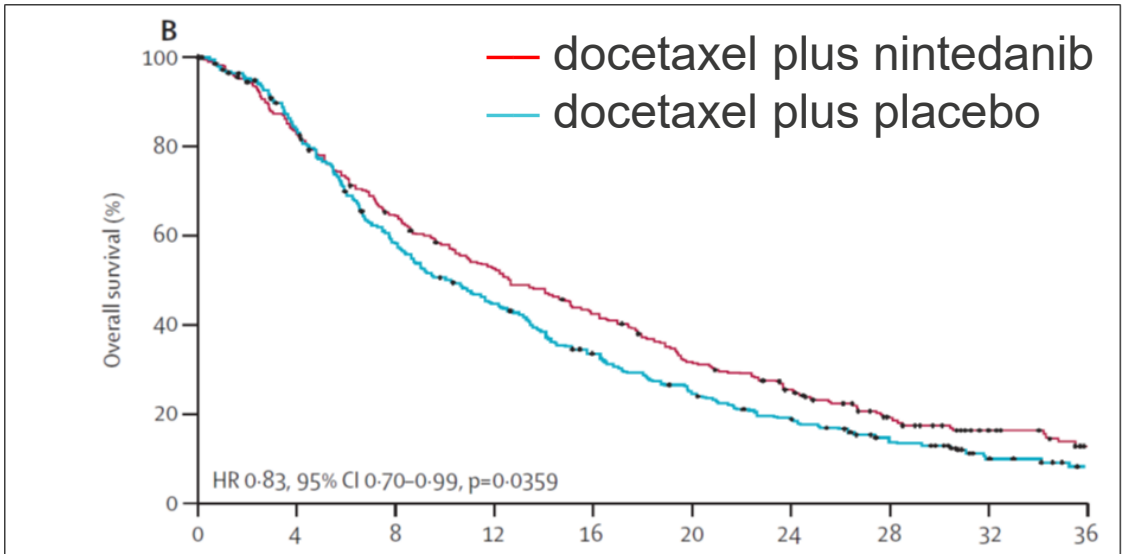
ERG: Trial results should be used, but issue of implausible curves so **still prefer HR=1**

Abbreviations: HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; OS: Overall survival; PFS: Progression-free survival

Issue 8: Docetaxel plus nintedanib modelling leads to worse survival (2)

Worse survival for docetaxel plus nintedanib in first 6 months; ERG prefer HR=1

OS Kaplan-Meier plot from LUME-Lung 1



Modelled OS curves from economic model

ERG after TE:

- Kaplan-Meier show slight benefit of docetaxel compared to plus nintedanib in first 4 months, then transformed to >1 year survival benefit in modelled OS curves – does not reflect Kaplan-Meier data
- No expert opinion or validation to justify

- Is docetaxel plus nintedanib survival modelling appropriate for decision-making?

Issue 11: Time-to-death utilities do not seem well-informed

Company view TTD and health state approach plausible; ERG prefer health state approach

Company: Utilities estimated using combination of datasets for health state and TTD
- **Health state:** MMRM with only progression status based on AN01 used in model
- **TTD:** AN01 but safety analysis dataset – few more people included in comparison

ERG: AN01 completed 1 EQ-5D questionnaire – bare minimum; AN02 at least 2 complete including at baseline – may be more valid
- Suggest utilities based on disease progression as base-case
- Fully specified models including AN02 to assess appropriateness (but potential missing data)

Company after TE: TTD approach is plausible, clinicians tend to favour TTD as a driver
- AN01 includes AN02 as subset so used to max sample size
- No significant impact excluding baseline utility covariate (AN02) so larger AN01 appropriate
- All MMRM include patient level random effect for correlations between observations of same patient – already adjusted for baseline utility

ERG: TTD utilities in base case do not seem well-informed; small sample, especially near death
- Insufficient information to assess reliability

- Is TTD or health state approach more appropriate?

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Abbreviations: MMRM: Mixed models with repeated measures; TTD: Time-to-treatment discontinuation

Issue 11: Time-to-death utilities do not seem well-informed (2)

Company view TTD and health state approach plausible; ERG prefer health state approach

	Mean utility (95%CI)
Time-to-death utilities – Company base case:	
Utility >6 months to death	0.762 (0.698, 0.767)
• Disutility 3-6 months to death vs >6 months	0.047 (0.09, 0.004)
• Disutility 1-3 months to death vs >6 months	0.125 (0.176, 0.074)
• Disutility <1 month to death vs >6 months	0.233 (0.312, 0.153)
*Utility 3-6 months to death	0.715
*Utility 1-3 months to death	0.637
*Utility in last month of life	0.529
Health-state utilities – Sensitivity analysis:	
Progression-free	0.734 (0.7, 0.769)
Disutility in progressed disease	0.064 (0.097, 0.031)
*Post-progression	0.670

Health state utilities in model

TTD utilities in model

Analysis	Full (n)	Safety (n)
AN01	119	122
AN02	84	86

AN01: Completed at least 1 EQ-5D-5L questionnaire
AN02: Completed EQ-5D-5L at least 2 times (including baseline)

*Calculated rather than from CodeBreak100/UK crosswalk tariffs

- Is TTD or health state approach more appropriate?

Abbreviations: TTD: Time-to-treatment discontinuation

Issue 12: IV administration disutility not well justified

Company: IV administration utility decrement; ERG: potential oral treatment disutility

Company utility decrement: 0.025 per cycle treatment for IV and cytotoxicity of docetaxel±nintedanib → erlotinib vs docetaxel study in advanced NSCLC (Lewis et al., 2010)

- ➢ Here, oral therapy: 0.451 utility; IV: 0.426 utility in PFS (Visual Analogue Scale)

- Assume equal on treatment PFS utilities for sotorasib vs chemotherapy but differential utilities seen in other NICE appraisals

ERG: No sufficient justification for size of docetaxel IV administration disutility or exclusion of potential sotorasib disutility (i.e. dose and frequency: 8 tablets daily)

→Suggest exclude IV disutility in base case

- Progression-free health states in erlotinib study lower utilities than 0.74 in CodeBreaK100
- Utilities in model not adjusted for age → potential bias

Company after TE: Health state utility and 0.025 or 0.04 PFS differential a reasonable compromise – scenarios (0.04 from applying 0.687 (in TA347, TA416) PFS utility from LUME-Lung 1 to PFS base-case utility

ERG: No information on sotorasib potential disutility – observational HRQoL data in comparative setting needed to resolve

- ERG not opposed to treatment-related disutility for IV-administration but maintain preferences

- Are disutilities associated with IV vs oral treatment appropriately captured in the modelling?

Issue 13: Relative dose intensity assumption not justified

ERG prefer conservative average RDI; company disagree with equalising RDIs

Company: Sotorasib relative dose intensity (RDI) 89.0% compared to docetaxel (90.3%) and nintedanib (92.1%)

- No reason to assume RDI truly lower for sotorasibv – differences may be from random sampling error

ERG: RDI lower for sotorasib – reasonable to set RDI for sotorasib, docetaxel and docetaxel plus nintedanib at **90.5% (average)**

Company after TE: Equalised RDIs not appropriate – invalidates trial data, which is considered more valid

ERG: Prefer conservative approach in ERG base-case (average RDI): due to impact on treatment costs, and immaturity of trial data

- Is RDI modelled appropriately?

End-of-life

Both criteria must be met:

1. *Treatment is indicated for patients with a short life expectancy, normally less than 24 months*
2. *Sufficient evidence to indicate the treatment has the prospect of offering an extension to life, normally a mean value of at least added 3 months, compared with current NHS treatment*

In addition, committee should be satisfied that:

- *Estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival**
- *Assumptions used in the reference case economic modelling are plausible, objective and robust*

*Taking account of trials in which crossover has occurred and been accounted for in the effectiveness review

Company:

1. Large real-world evidence studies indicate that with non-targeted 2nd line therapies, OS<10 months, with 3rd line therapies OS<7 months
   - SELECT-1: 2nd line docetaxel monotherapy, OS = 7.9 months
   - LUME-Lung 1: 2nd line nintedanib+docetaxel, OS = 10.9 months
2. **MAIC** show **median OS gain** [redacted] for sotorasib vs docetaxel monotherapy (March 2021); **model** estimates **additional undiscounted mean OS** [redacted] months vs docetaxel and [redacted] months vs docetaxel plus nintedanib

ERG:

1. Consider to be met
2. Based on data from company, agree criterion to be met but concern with validity of indirect treatment comparisons (issue 5)

- Does sotorasib meet the end-of-life criteria?

Abbreviations: MAIC: Matching-adjusted indirect comparison; OS: Overall survival

Cost-effectiveness results

Cost-effectiveness results with confidential PAS discounts for other treatments are reported in private PART 2 slides

Cancer Drugs Fund

Committee decision-making criteria:

Starting point: drug not recommended for routine use due to **clinical uncertainty**

Proceed down if answer to each question is yes

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.

Ongoing studies

- **CodeBreaK100** – estimated completion: **24 February 2025**
- **CodeBreaK200:** Phase III, multi-country, randomised, open-label trial of sotorasib vs docetaxel in around 330 KRAS p.G12C-mutated advanced/metastatic NSCLC patients with ECOG performance score 0-1, after at least 1 prior systemic therapy
  - Expected data: **January 2022** primary PFS analysis cut-off; [redacted] **final completion, 2026**
- **Expanded access study:** safety profile of sotorasib in US, Brazil, Israel – ongoing; TBD
- **UK retrospective chart review:** retrospective cohort study describing characteristics, treatment patterns, outcomes, healthcare resource in KRAS mutant or wild-type in NSCLC, 2018-19 – expected data: **Q1/2 2022**
- **PRO cross-sectional and retrospective chart review:** HRQoL in KRAS mutant or KRAS wild-type NSCLC in UK, France and Germany, 2020-21 – expected data **Q1/2 2022**

Innovation

Company considers sotorasib to be innovative:

- Innovative, targeted, oral monotherapy
- May provide step-change in therapy in KRAS G12C mutated NSCLC where there is no targeted therapy option
  - No other protein identified where sotorasib binds – potential to be relatively tolerable
- First KRAS p.G12C inhibitor filed for regulatory approval
- Innovation Passport under the Innovative Licensing and Access Pathway (Feb 2021)
- Promising Innovative Medicine under the Early Access to Medicines Scheme
- Accelerated approval by US FDA, 28 May 2021 under Real-Time Oncology Review

- Is sotorasib a step-change in treatments? Does it offer benefits not captured in the modelling?

Key issues

- **Issue 7:** Exclusion of platinum-based chemotherapy as comparator in 2nd line
- **Issue 9:** No waning of treatment effect
- **Issue 5:** Validity of ITC without a common comparator
- **Issue 8:** Docetaxel plus nintedanib modelling approach leading to worse survival
- **Issue 11:** Time-to-death utilities do not seem well-informed
- **Issue 12:** Disutility for IV administration not well justified
- **Issue 13:** Relative dose intensity and wastage not justified
- **Consideration for Cancer Drugs Fund**
- **Consideration for End-of-Life**

Back-up

Issue 1: Population narrower than NICE scope

Licence population and CodeBreaK100 population increasingly narrower than scope

NICE scope: Adults with previously treated KRAS p.G12C mutated, locally advanced or metastatic NSCLC
Licence: Monotherapy for treatment of adults with KRAS p.G12C-mutated locally advanced or metastatic non-small cell lung cancer, who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy
CodeBreaK100: 1-3 lines of prior anti-cancer therapy, measurable disease per RECIST 1.1 criteria and ECOG performance status 0 or 1

ERG:

- Population is narrower than in NICE scope, and more narrow in CodeBreaK100
- ECOG score of 2 (more severe on 5-point scale) included in phase I CodeBreaK100 but not phase II → company stated this should not preclude sotorasib use within licensed indication and should be an option available to clinicians when relevant – **no supporting evidence**

After TE:

- **Company:** Considered issue resolved: initial NICE scope can differ from final licensed population
- **Clinical expert:** Exclusion of PS2 patients is usual in Phase I trials because of safety issues with first-in-human use and physical demands of trials

- Is the CodeBreaK100 population appropriate for decision-making?
- Would sotorasib be used as an option for people with ECOG performance status 2 in UK clinical practice?

Issue 2: Generalisability/lack of UK participants

ERG question generalisability based on ethnicity and no UK centres

Company:

- CodeBreaK100 trial – 47 centres worldwide (n=126)
- 5 UK clinical experts at Amgen Advisory board considered CodebreaK100 population reflective of UK clinical practice and licenced indication

ERG:

- No UK centres
- High proportion of Asian participants (15.1% of sample)
- Generalisability to clinical practice in England and Wales is unclear because:
  - No UK centres
  - Ethnic balance (82% White, 15% Asian, 3% Other)

Company after TE:

- Not unusual for small/no numbers of UK patients in targeted NSCLC trials, experts consulted agree demographics including ethnicity representative clinical practice

- Is the CodeBreaK100 trial population generalisable to the UK?

Issue 3: High risk of bias of CodeBreaK100

ERG rate "serious" risk of bias in CodeBreaK100 compared to "low" by company

ROBINS-I risk of bias tool used for quality assessment of CodeBreaK100

- **Company:** "low to moderate" risk of bias
- **ERG:** "serious" risk of bias in 2/7 domains

ERG assessment:

- ROBINS-I tool not appropriately used – 14 missing entries to signalling questions
- ➢ "Serious" risk of bias related to baseline confounding – lower ECOG performance status 0-1 at baseline favoured sotorasib
- ➢ High risk of bias in classification of interventions
- ➢ Appropriate methods to control for confounders, e.g. stratification, regression, probability weighting not employed
- ➢ "Serious" risk of bias in measurement of outcomes – outcome assessors probably aware of intervention received by participant in trial

Company after TE:

- Risk of bias broadly aligned with other pivotal single-arm trials in NSCLC used as basis in other NICE appraisals
- Blinding and confounding issues inherent in single-arm trials – need for statistical methods e.g. MAIC and PSWA

Stakeholder: No comparison to recent VARGADO RWE study with docetaxel and nintedanib

- ○ Is the risk of bias associated with CodeBreaK100 in-line with other single-arm trials in NSCLC?

Abbreviations: MAIC: Matching-adjusted indirect comparison; PSWA: Propensity-score weighting analysis; RWE: Real-world evidence

Issue 4: High number of serious adverse events in CodeBreaK100

Treatment-related adverse events considered more relevant by company and professional organisation

Adverse events, n (%)	Treatment-emergent adverse events (TEAE)	Treatment-related treatment-emergent adverse events (TRAE)
Total	125 (99)	88 (70)
Serious	63 (50)	10 (8)
Discontinuation	11 (9)	9 (7)
Fatal	20 (16)	0

Frequent treatment-related AE (any grade):

- Diarrhoea, nausea, fatigue, joint pain, increased alanine and aspartate aminotransferase

Treatment related AE leading to dose modification (interruption/reduction): 28 patients (22%)

ERG: Concern high number of TEAEs, 50% patients experienced serious AEs, 16% died

Company after TE: TRAEs considered more relevant than TEAEs here

Professional organisation: Typical of patients in advanced NSCLC to have multiple disease-related symptoms and complications. Important to distinguish treatment-related adverse events

Stakeholder: For comparison no fatal AEs reported in VARGADO real-world evidence study of docetaxel plus nintedanib in 2+line

- Are adverse events appropriate for decision making?

Issue 6: Partitioned Survival Model structure not validated or justified

ERG agree all models have limitations but state transition model can validate results

Company: Model structure aligns with primary objective of treatment in NSCLC

ERG: Concern using partitioned survival model without state transition model for validation

- Request a state transition model as scenario for validation – recommended by NICE DSU TSD 19
- Alternative approaches to estimate size and direction of any bias
- No full incremental analysis to compare sotorasib, docetaxel, docetaxel+nintedanib
  - Company: difficulties in relative treatment effect for sotorasib and docetaxel+nintedanib
  - ➢ Impact validity and generalisability to UK clinical practice

After TE:

- **Company:** problems with partitioned survival model not likely to be resolved by state transition model
- **ERG:** agree additional state transition model may not be necessary but can contribute to verifying plausibility of extrapolations, clinical uncertainties, reducing structural uncertainty

- Is the model appropriate for decision-making?

Background (1/3)

Comparators		
	Non-squamous NSCLC • Pemetrexed with carboplatin (with/without pemetrexed maintenance) • Other platinum doublet chemotherapy (with/without pemetrexed maintenance) • nintedanib with docetaxel (adenocarcinoma) • Docetaxel monotherapy • Atezolizuman • Nivolumab (subject to ongoing CDF) • Pembrolizumab (PD-L1 tumours) • Best supportive care	**Squamous NSCLC** • Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel monotherapy • Pembrolizumab (PD-L1 tumours) • Atezolizumab • Nivolumab • Best supportive care
	KRAS G12C and another driver mutation (inc. EGFR-TK, ALK, ROS-1 • Atezolizumab combination (after EGFR-TK or ALK targeted therapies) • Lorlatinib, brigatinib, ceritinib (after ALK-targeted therapies) • Osimertinib (EGFR T790M positive after EGFR-TK targted therapies) • Pemetrexed with carboplatin • Platinum doublet chemotherapy • nintedanib with docetaxel (adenocarcinoma) • Nivolumab (ongoing CDF review)	