Adagrasib for previously treated KRAS G12C mutation-positive advanced non-small-cell lung cancer (ID6339)

For public and zoom – redacted

Technology appraisal committee D [10 April 2025]

Chair: Megan John

Lead team: Carole Pitkeathley, Savvas Vlachos and Giles Monnickendam

External assessment group: York Technology Assessment Group

Technical team: Zain Hussain, Rufaro Kausi and Christian Griffiths

Company: Bristol Myers Squibb

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

- ✓ **Background**
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations: Managed access and severity
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on KRAS G12C positive advanced NSCLC

Non-squamous NSCLC is predominant subtype, KRAS G12C most common mutation

Prevalence

- Around 49,200 new lung cancer cases and 34,800 deaths in UK every year
- Third most common cancer and most common cause of cancer death in UK
- Majority lung cancer diagnosed at advanced stage

Histology

- NSCLC is most common type in UK (80-85%)
- Non-squamous cell (adenocarcinoma & large cell) → predominant subtype

KRAS G12C mutation

- KRAS G12C most common mutation in NSCLC (11% in the UK) ➔ More common in non-squamous NSCLC
- Associated with increased risk of brain metastasis
- Not usually occurring with other known oncogenic mutations in NSCLC (e.g. EGFR-TK, ALK, ROS-1)
- Limited targeted treatments available for treated KRAS G12C mutation ➔ Sotorasib approved for use in the Cancer Drugs Fund

Treatment aim

- Prolong survival and improve quality of life

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ALK: Anaplastic lymphoma kinase; EGFR-TK: Epidermal growth factor receptor tyrosine kinase; ROS-1: c-ros oncogene 1

Patient and carer perspectives

KRAS G12 mutated lung cancer is associated with poor prognosis

Roy Castle Lung Cancer Foundation:

- Symptoms, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy ➔ Distressing for family members and carers to observe as well
  - **Company submission:** Evidence shows progression to later lines of therapy and decline in ECOG performance status in NSCLC patients are associated with higher anxiety, depression, and financial costs for caregivers
- KRAS G12C mutation has a poor prognosis
- Adagrasib provides an additional treatment option for KRAS G12C mutation positive advanced NSCLC
  - Evidence suggests survival outcomes of treatment are an advantage of this technology
  - Adagrasib shown to have intracranial activity in patients with KRAS G12C mutated NSCLC and untreated brain metastasis
- Side effects with adagrasib are common and can lead to treatment discontinuation

"Adagrasib has been found to penetrate the central nervous system and as such, could slow down the growth of cancer cells in the brain"

Clinical perspectives

There is a high unmet need for more effective and tolerable treatments for previously treated KRAS G12C mutation-positive advanced NSCLC

Association of Respiratory Nurses and 2 clinical experts

- Aim of treatment is to extend survival, delay progression, and maintain or improve quality of life
- First-line treatment of KRAS G12C NSCLC typically involves platinum-based chemotherapy with immunotherapy. Second-line options include docetaxel with or without nintedanib or sotorasib (Cancer Drugs Fund), with platinum-based chemotherapy considered if immunotherapy is used first
- There is a high unmet need for more effective and tolerable treatments for previously treated KRAS G12C mutation-positive advanced NSCLC
- Adagrasib provides an additional option, showing better response and progression-free survival than docetaxel. But overall survival data is still immature
    - ➢ Side effects are significant but manageable with dose adjustments and supportive care

"This is a step-change technology alongside Sotorasib on the CDF. The KRAS mutations were seen as undruggable and this novel approach of targeting KRAS has reinvigorated drug development in this area"

When considering investment to introduce Adagrasib incorporate "Training of oncology nurses to administer the drug. Education to oncologists and pharmacists to understand the regime and protocol. Resource in pharmacy to produce the correct drug mix for patients"

CDF: Cancer Drugs Fund; KRAS: Kirsten rat sarcoma virus

Equality considerations

Equality issues

- No equality issues raised

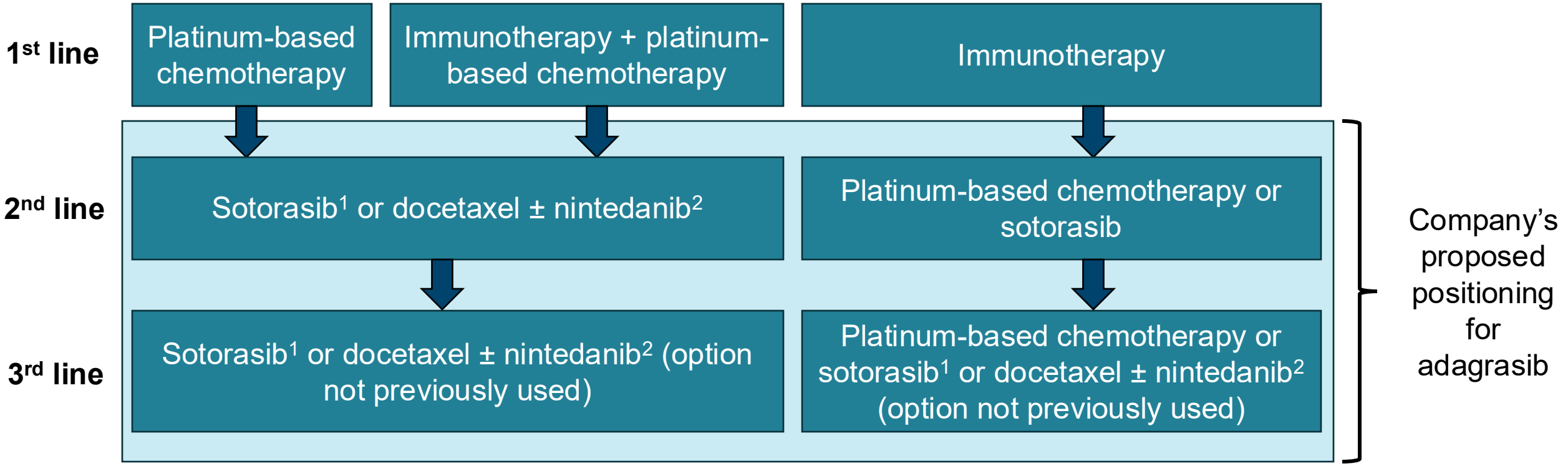
Are there any relevant equality issues?

Adagrasib (Krazati, Bristol Myers Squibb)

Marketing authorisation	MHRA conditional approval granted on 03 November 2023 for use *"as monotherapy is indicated for the treatment of adult patients with advanced NSCLC with KRAS G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy"*
Mechanism of action	A selective, irreversible inhibitor of KRAS G12C that binds to the mutant cysteine in KRAS G12C, locking the protein in an inactive state. This prevents KRAS-dependent signalling without affecting normal KRAS proteins. Adagrasib provides sustained inhibition of KRAS G12C, leading to suppression of tumour cell growth and viability in KRAS G12C-mutant cells, and it causes tumour regression in preclinical models with minimal off-target effects
Administration	Oral tablets • 600mg (three 200mg tablets) orally twice daily, with or without food
Price	• The list price for adagrasib is confidential • Company has a confidential PAS discount in place

MHRA: Medicines & Healthcare Products Regulatory Agency; PAS: Patient access scheme

KRAS G12C positive advanced NSCLC treatment pathway and proposed positioning of adagrasib



[1] Sotorasib is recommended for use within the Cancer Drugs Fund
[2] Nintedanib is reimbursed only for adenocarcinoma histology; patients with other histology receive docetaxel monotherapy

Where in the treatment pathway is adagrasib expected to be used in NHS clinical practice?

See appendix slide: Decision problem

Key issues for discussion

Issue	ICER impact*
Clinical effectiveness	
1. Lack of blinding and risk of bias in KRYSTAL-12	Unknown
2. Effect of adagrasib relative to docetaxel with or without nintedanib on overall survival is unknown	Large
3. Safety of adagrasib compared with docetaxel with or without nintedanib	Unknown
4. Validity of the surrogacy analysis between progression and survival	Large
5. Limitations of the evidence used to inform the network meta-analysis	Unknown
Cost-effectiveness	
6. Use of treatment-specific utility value for the progressed disease health state in the model	Moderate

*** Both the company and EAG applied a severity weight of 1.7 to the cost effectiveness results**

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ICER: Incremental cost-effectiveness ratio

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KRYSTAL-12 and KRYSTAL-1: Study designs and outcomes

	KRYSTAL-12 (N=453)	KRYSTAL-1 (Cohort A, N=116)
Design	Ongoing phase 3, multicentre, open-label	Phase 1/2 multicentre, open-label, single-arm dose-escalation and multiple expansion cohort
Population	Adults with NSCLC with KRAS G12C mutation, who have received prior platinum-based regimen and immune checkpoint inhibitor	Adults with selected solid tumour malignancies with KRAS G12C mutation
Intervention	Adagrasib	Adagrasib
Comparator	Docetaxel	N/A
Duration (median) follow up	PFS: 9.43 months	OS: 15.6 months
Data cut off	PFS (31 December 2023)	PFS (October 2021); OS (January 2022)
Primary outcome	PFS	ORR
Other outcomes	OS, ORR, DoR, AEs, HRQoL	OS, PFS, AEs
Locations	International: 304 sites (5 UK sites)	US (29 sites)
Used in model?	Yes	Yes (surrogacy analysis)

See appendix slide: Baseline characteristics of trials

AEs: Adverse events; DoR: Duration of response; HRQoL: Health-related quality of life; N/A: Not applicable; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival

KRYSTAL-12 and KRYSTAL-1: Clinical results

	KRYSTAL-12		KRYSTAL-1
	Adagrasib (n=302)	Docetaxel (n=152)	Adagrasib (n=116)
Data cut	31 December 2023		PFS (October 2021); OS (January 2022)
Median follow-up, months	9.43		PFS: 12.9 OS: 15.6
Progression-free survival			
Events, n (%)	164 (54.5%)	93 (61.2%)	66 (58.9%)
Median PFS, months (95% CI)	5.49 (4.53, 6.67)	3.84 (2.73, 4.73)	6.5 (4.7, 8.4)
HR for progression or death (95% CI, p-value)	0.58 (0.45, 0.76, p<0.0001)		
Overall survival (Interim analysis)			
Median OS, months (95% CI)	[redacted]	[redacted]	12.6 (9.2 to 19.2)
OS HR (95% CI, p-value)	[redacted], p = not statistically significant		-
Progression-free survival 2			
Median PFS2, months (95% CI)	[redacted]	[redacted]	-
PFS2 HR (95% CI)	[redacted]		-
Adverse events			
Any TEAEs, n (%)	298 (100)	138 (98.6)	116 (100)
Grade ≥ 3 TEAEs, n (%)	213 (71.5)	93 (66.4)	94 (81)

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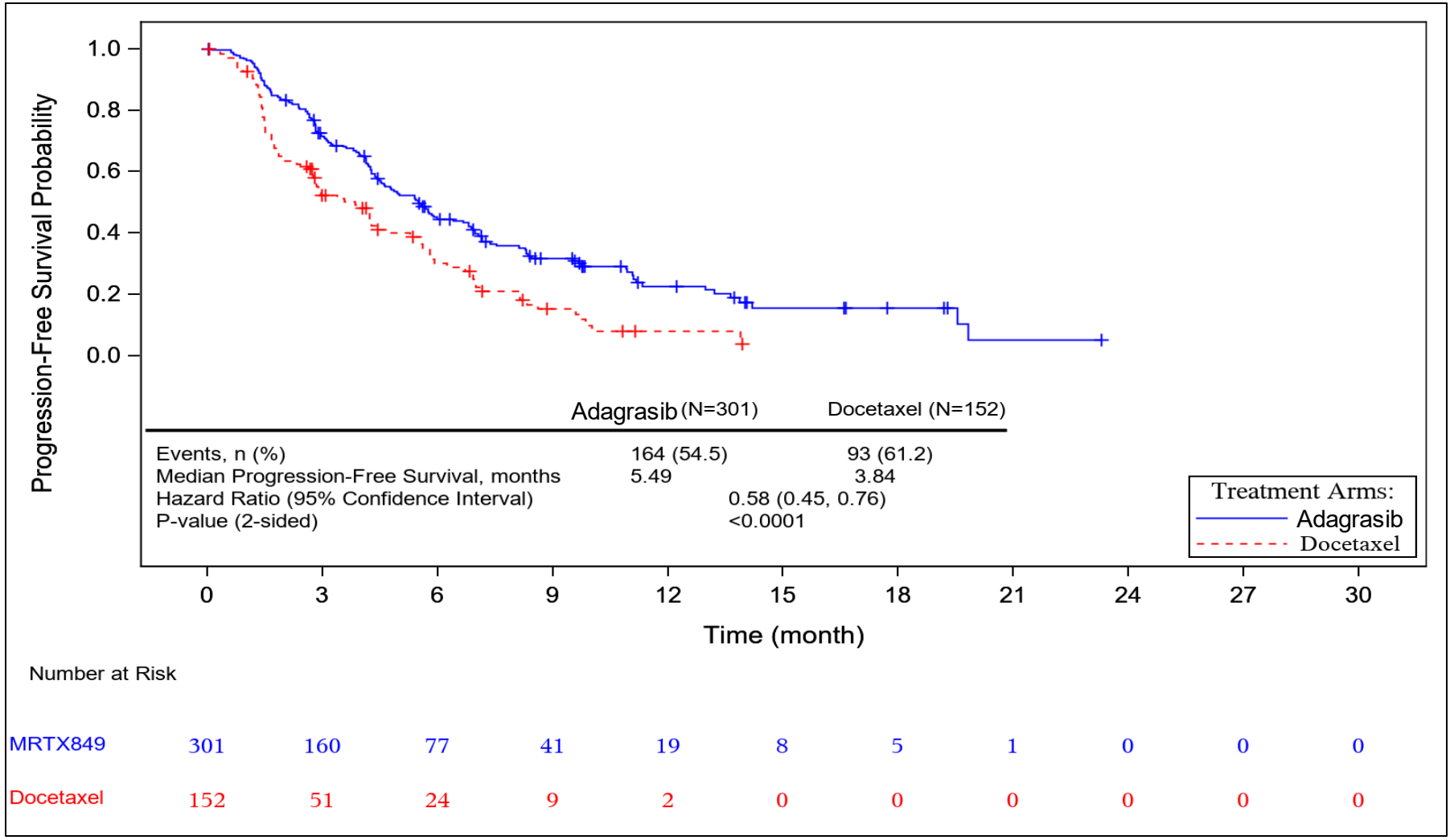
CI: Confidence interval; HR: Hazard ratio; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; TEAEs: Treatment-emergent adverse events

KRYSTAL-12: PFS per BICR, (December 2023 data cut-off)

K-M curves for PFS show separation of the survival curves from 2 to 3 months post-randomisation. PFS results by investigator assessment were generally similar to BICR assessments



BICR: Blinded independent central review; K-M: Kaplan-Meier; OS Overall Survival; PFS: Progression-free survival

KRYSTAL-12: Overall Survival (Intention to treat population) Interim analysis, (December 2023 data cut-off)

- The p-value for OS was not statistically significant and [redacted]

KRYSTAL-12: Investigator assessed PFS2, (December 2023 data cut-off)

- PFS2 provides potentially useful information where analysis of OS could be confounded by subsequent treatments.
- PFS2 Kaplan-Meier curves closely overlap between adagrasib and docetaxel suggesting [redacted] in PFS2 between treatment arms following subsequent treatment

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KM: Kaplan-Meier; OS: Overall survival; PFS2: Progression-free survival 2

Unknown impact ?

Key issue 1: Lack of blinding and risk of bias in KRYSTAL-12 (1)

Background

- KRYSTAL-12 has an open label design with patients having knowledge of the intervention received
  - Early withdrawals prior to receiving treatment were significantly lower for adagrasib (n=3, 1.0%) than docetaxel (n=12, 7.9%) ➔ 11 of 12 withdrawals in docetaxel arm were 'withdrawal by patient'
    - ➢ Following treatment initiation, 'withdrawal by patient' was approximately twice as high in the docetaxel arm (13.8%) compared with adagrasib arm (7.0%)
  - [redacted] patients in the adagrasib arm and [redacted] in the docetaxel arm received subsequent therapy before progressive disease

Company

- Quality assessment of the KRYSTAL-12 concluded low risk of bias in the trial
- Lack of blinding is unlikely to have substantially affected interpretation of response or progression because these endpoints were assessed by blinded independent central reviews

HRQoL: Health-related quality of life; OS: Overall survival

Unknown impact ?

Key issue 1: Lack of blinding and risk of bias in KRYSTAL-12 (2)

EAG comments

- Knowledge of the intervention received (and possible expectation of higher benefit with adagrasib over docetaxel), may have affected patient retention in the docetaxel arm
- Company's tipping point analyses [redacted] ➔ But it is unclear if prognosis of patients who remained in control group was balanced with those remaining in the adagrasib group
  - ➢ Also uncertain if withdrawal biased overall survival, objective response rates and safety outcomes
- Although KRYSTAL-12 found that adagrasib led to improvement in symptom burden and HRQoL compared with docetaxel, the subjective nature of patient-reported outcomes and lack of blinding means that HRQoL outcomes in KRYSTAL-12 may have been overestimated

Are the results from KRYSTAL-12, for progression-free survival, overall survival, objective response rates and safety outcomes, reliable and appropriate for decision making?

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HRQoL: Health-related quality of life

Large impact

Key issue 2: Effect of adagrasib relative to docetaxel with or without nintedanib on overall survival (1/2)

Background

- Company did not present the results of the overall survival analysis in its original submission ➔ Provided interim overall survival analysis of KRYSTAL-12 following request from EAG at clarification
  - Interim overall survival is immature ➔ NICE TSD 14 provides guidance on extrapolating OS data
  - Median OS was [redacted] in the adagrasib arm and [redacted] in the docetaxel arm, resulting in a hazard ratio of
- Protocol amendment in KRYSTAL-12 permitted patients in docetaxel arm to crossover to adagrasib arm ➔ NICE TSD 16 provides guidance on adjustment methods that may be used in the presence of crossover

Company

- Interim overall survival data is highly immature and inconclusive ➔ presence of potential confounding effect of crossover was also not adjusted for

EAG

- Immature overall survival data to quantify the treatment effect for adagrasib compared with docetaxel with or without nintedanib leads to substantial uncertainty in the cost-effectiveness analysis
- Concerns with KRYSTAL-12 design, including the impact of crossover and subsequent KRAS G12C therapies in the control arm ➔ In the absence of crossover-adjusted analyses, the potential impact of crossover and subsequent KRAS G12C inhibitors in docetaxel arm on OS is uncertain

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CI: Confidence interval

Large impact

Key issue 2: Effect of adagrasib relative to docetaxel with or without nintedanib on overall survival (2/2)

EAG (continued)

- Mature OS evidence from KRYSTAL-12 required to address this uncertainty ➔ EAG concerned that it is [redacted]
- Explored alternative estimates of OS hazard ratio of adagrasib compared with docetaxel:
  1. No effect of adagrasib on OS (HR = 1) **– EAG base case 1** ➔ ICER versus docetaxel increases
  2. Same effect of adagrasib on OS (HR = 0.89) for sotorasib (the only other KRAS inhibitor with data in the relevant population) based on the effect from the two-step crossover adjusted analysis for sotorasib compared with docetaxel from CodeBreaK 200* **– EAG base case 2** ➔ ICER versus docetaxel increases

* CodeBreaK 200 suggested that sotorasib, a KRAG G12C inhibitor, had a PFS gain, but it did not demonstrate an OS benefit compared with docetaxel. This was attributed to crossover in CodeBreak 200, but the OS results were consistently non-significant when adjusted for crossover and treatment benefit varied across different adjustment methods

See appendix slide: CodeBreaK 200

In the absence of mature OS data from KRYSTAL-12, are any of the EAG's alternative OS HR estimates for adagrasib compared with docetaxel appropriate for decision making?

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HR: Hazard ratio; HRQoL: Health-related quality of life ICER: Incremental cost-effectiveness ratio; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life year

KRYSTAL-12 and KRYSTAL-1: Safety outcomes

Adverse event category	KRYSTAL-12		KRYSTAL-1
	Adagrasib (n=298)	Docetaxel (n=140)	Adagrasib (n=116)
Duration of treatment exposure (months), mean (SD)	5.56 (4.98)	3.17 (2.56)	5.8 (4.02)
Compliance (%), mean (SD)	98.3 (5.1)	NR	85.9 (16.7)
Dose intensity (%), mean (SD)	77.7 (20.5)	92% (12)	75.5 (22.2)
Any treatment-emergent adverse events (TEAEs), n (%)	298 (100)	138 (98.6)	116 (100)
Fatal TEAEs, n (%) ➢ Classed as treatment-related by investigator, n(%)	48 (16.1) 4 (1.3)	10 (7.1) 1 (0.7)	- 2 (1.7)
Grade ≥ 3 TEAEs, n (%)	213 (71.5)	93 (66.4)	94 (81)
Serious TEAEs, n (%)	149 (50)	50 (35.7)	70 (60.3)
TEAEs leading to treatment discontinuation, n (%)	40 (30.4)	25 (17.9)	17 (14.7)
TEAEs leading to dose reductions or interruption, n (%)	237 (79.5)	67 (47.9)	95 (81.9)

See appendix slide: NMA results: Safety outcomes

NR: Not reported; SD: Standard deviation; TEAE: Treatment-emergent adverse events

Key issue 3: Safety of adagrasib compared with docetaxel with or without nintedanib

Background

- Standard of care therapies have limited efficacy and significant toxicity ➔ There is need for effective targeted therapy with less toxicity than standard of care

Company

- Consider that the low-grade nature of key TEAEs along with patient reported outcomes indicate that adagrasib is generally tolerable with a manageable safety profile

EAG comments

- Despite adagrasib being targeted therapy and given the known toxicity of docetaxel, there is insufficient evidence to show that safety and tolerability of adagrasib is superior to docetaxel
  - ➢ In KRYSTAL-12, there were higher incidences of fatal TEAEs, grade ≥ 3 TEAEs, and TEAEs leading to dose reduction or interruption in the adagrasib arm compared with docetaxel arm
    - Knowledge of the safety profile of treatments and lack of blinding may have affected the rates of discontinuation and switching to newer generation therapies in the docetaxel arm
  - ➢ Company's network meta-analysis results for safety outcomes suggests similar trend
- Longer-term follow-up from KRYSTAL-12 and surveillance data needed to inform safety with adagrasib

Is the data informing safety appropriately captured in the modelling and sufficient for decision making?

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TEAE: Treatment-emergent adverse events

Company's surrogacy analysis using KRYSTAL-1 to inform overall survival in KRYSTAL-12

- Because of immature interim OS data from KRYSTAL-12, company did a post-hoc exploratory analysis using OS from KRYSTAL-1 (a single-arm phase1/2 study) to inform a patient-level surrogacy analysis in order to:
  i. Assess the relationship between progression and survival at individual patient level for KRAS G12C mutation-positive NSCLC, and
  ii. Predict OS for KRYSTAL-12 in censored patients for both adagrasib and docetaxel using the surrogacy relationship derived from KRYSTAL-1 and applied to progression data from KRYSTAL-12

Surrogacy analysis results	Adagrasib	Docetaxel
Overall survival		
Median overall survival, months (95% CI)	[redacted]	[redacted]
Overall survival hazard ratio HR (95% CI)	[redacted]	

- The predicted KRYSTAL-12 overall survival from the surrogacy analysis is used to inform the company's network meta-analysis and cost-effectiveness analysis

NICE technical team view:

- In the absence of final clinical endpoint, NICE process and methods manual provides guidance on using surrogate outcomes to infer the effect of the technology on the final clinical endpoint
  - ➢ Despite immaturity of the data, interim OS results are available from KRYSTAL-12

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CI: Confidence interval; HR: Hazard ratio; NE: Not estimable

See appendix slide: KRYSTAL-12 predicted OS

Large impact

Key issue 4: Validity of the surrogacy analysis between progression and survival (1/2)

Background

- In absence of mature OS data from KRYSTAL-12, company conducted a surrogacy analysis using OS data from KRYSTAL-1 to predict OS for KRYSTAL-12 in censored patients, for both adagrasib and docetaxel, based on progression data from KRYSTAL-12

Company

- Adapted the joint frailty-copula model proposed by Emura et al. (2017) which focuses on the association between TTP and OS in the form of a bivariate model and leverages the Rondeau et al., (2015) model

EAG

- Company did not follow recommendations set out in NICE manual to inform the surrogacy analysis ➔ Used a within-study relationship based on analysis of the KRYSTAL-1 single-arm phase 1/2 trial to predict absolute OS (rather than surrogacy based on relative effect as recommended in NICE methods guide)
- Company's surrogacy analysis has several limitations:
  - ➢ No evidence to suggest that PFS benefits translate to OS benefits, or that PFS is a reliable surrogate of OS in second line plus KRAS G12C NSCLC
  - ➢ Surrogacy analysis has not been externally validated in the KRAS G2C NSCLC population

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CI: Confidence interval; NE: Not estimable; OS: Overall survival; PFE: Progression-free survival; TTP: Time to progression

Large impact

Key issue 4: Validity of the surrogacy analysis between progression and survival (2/2)

EAG

- Company's surrogacy analysis has several limitations:
  - ➢ It cannot be demonstrated whether the relative effect of adagrasib on progression is predictive of relative OS based on a single-arm study
    - ❖ OS predictions from de-novo analysis based on adapting the joint frailty-copula model of Emura et al. (2017) not assessed relative to other bivariate models and different copulas
  - ➢ Surrogacy relationship unlikely to be exchangeable between KRAS-targeted and non-targeted therapies because that the strength of the association can vary by treatment class and line of treatment
- Predicting OS for the same follow-up time as KRYSTAL-1, but with data from KRYSTAL-1 censored when 5% or less of participants are still at risk of a progression suggests predicted OS estimates are overly precise
- Explored scenario using effect of adagrasib on OS (i.e. hazard ratio = [redacted] using company's surrogacy analysis based on KRYSTAL-1 data and assuming that there is no class effect for KRAS G12C inhibitors, where the PH assumption appears to hold and avoids the uncertainty introduced by using the time-varying HRs ➔ ICER versus docetaxel increases

- Is the OS generated from the surrogacy analysis acceptable and suitable for decision making?
- Is PFS a reliable surrogate for overall survival in second line or later KRAS G12C mutation?

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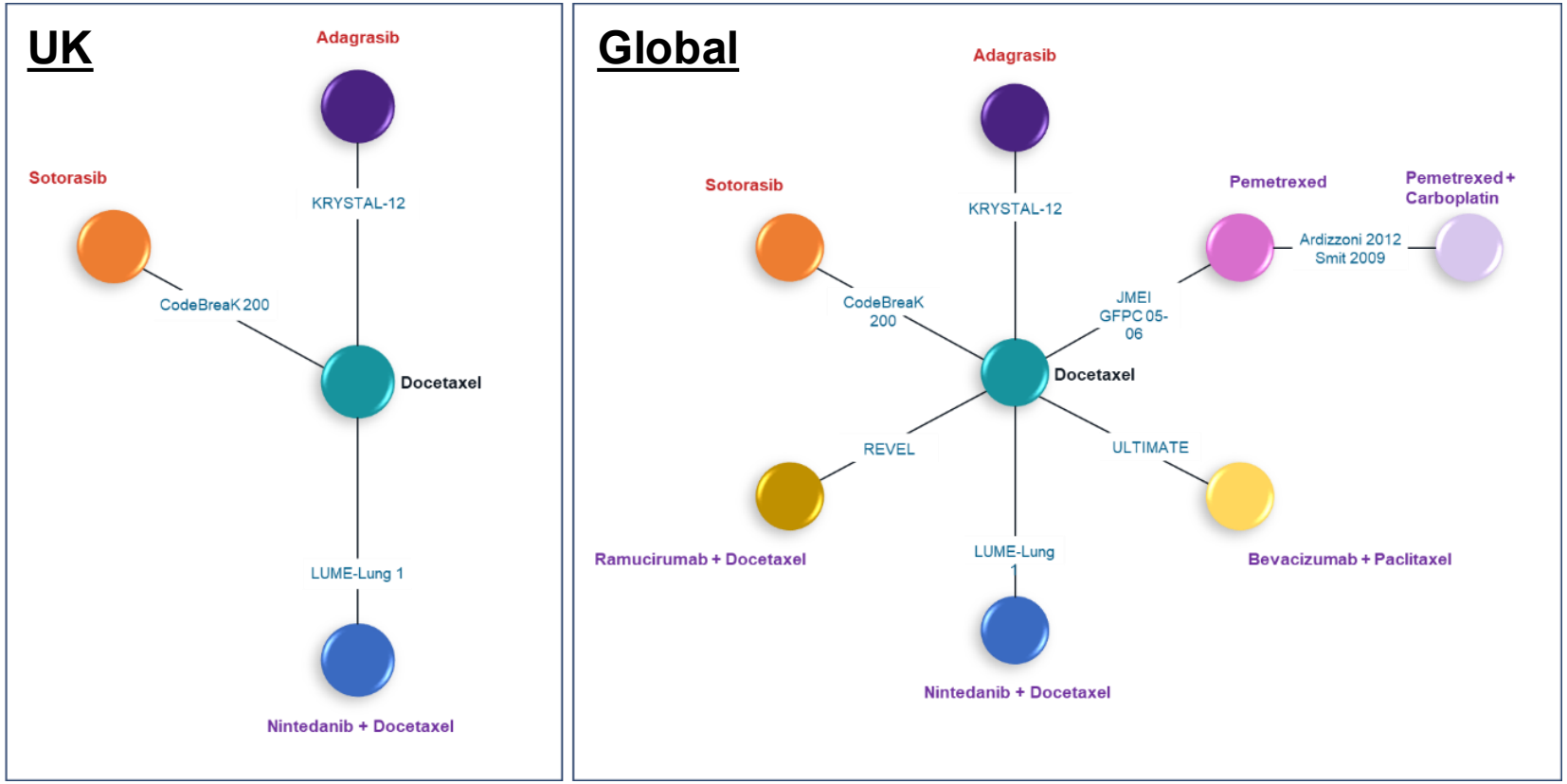
ICER: Incremental cost effectiveness ratio; NMA: Network meta-analysis; OS: Overall survival; PFS: Progression-free survival

Network used to inform the Company's NMA

- In the absence of direct comparison between adagrasib and docetaxel with nintedanib or sotorasib, the company conducted a NMA using evidence for adagrasib from KRYSTAL-12 docetaxel with nintedanib from LUME-Lung 1 and sotorasib from CodeBreaK 200
  - ➢ For OS, a surrogacy analysis including data from KRYSTAL-1 and SELECT-1 trials was used

Company's network diagrams



Company:

Global NMA is used to inform the cost-effectiveness analysis as NMA results would be consistent between the UK-based and global NMA

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NMA: Network meta-analysis; OS: Overall survival

See appendix: NMA results: Constant HRs and CodeBreaK 200

Company NMA results: OS and PFS

Company preferred fixed effect time varying NMA in its base case as PH assumption violated in PFS for LUME-Lung1 and OS for CodeBreaK 200

Estimated time-varying HRs (95% CrI) from the fixed-effects NMA (gamma model) for PFS

Adagrasib*vs	Time-varying HR (95% CrI)					
	3 months	6 months	9 months	12 months	18 months	24 months
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: All estimates below 1 favour adagrasib, and estimates above 1 favour the comparators

Estimated time-varying HRs (95% CrI) from the fixed-effects NMA (gamma model) for overall survival*

Adagrasib*vs	Time-varying HR (95% CrI)					
	3 months	6 months	9 months	12 months	18 months	24 months
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nintedanib + docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sotorasib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* For the network meta-analysis of overall survival, surrogacy analysis of KRYSTAL-1 was used for KRYSTAL-12
Note: All estimates below 1 favour adagrasib, and estimates above 1 favour the comparators

CrI: Credible intervals; HR: Hazard ratio; NMA: Network meta-analysis; OS: Overall survival; PFS: Progression-free survival; PH: Proportional hazards

Company NMA results: Safety outcomes

Odd ratios (95% CrI) for adagrasib versus relevant comparators

Safety outcme	Model	Docetaxel	Docetaxel with nintedanib	Sotorasib
Grade ≥ 3 TEAEs	Fixed effects	1.26 (0.82, 1.95)	0.91 (0.56, 1.49)	0.76 (0.40, 1.43)
	Random effects	1.27 (0.33, 4.87)	0.92 (0.14, 6.07)	0.76 (0.11, 5.25)
Serious TEAEs	Fixed effects	**1.81 (1.20, 2.74)**	1.58 (0.99, 2.55)	NA
	Random effects	1.81 (0.50, 6.69)	1.59 (0.26, 9.72)	NA
Serious TRAEs	Fixed effects	1.35 (0.80, 2.32)	**3.33 (1.49, 7.66)**	NA
	Random effects	1.35 (0.34, 5.28)	3.33 (0.47, 23.25)	NA
Grade ≥ 3 hepatoxicity	Fixed effects	**10.26 (3.54, 45.73)**	NA	0.50 (0.06, 3.53)
	Random effects	**10.39 (1.98, 70.49)**	NA	0.50 (0.03, 6.82)
Note: All estimates below 1 favour adagrasib, and estimates above 1 favour the comparator				

EAG:

- All NMA results for safety outcomes are imprecise as shown by the wide credible intervals

Back to Safety Outcomes

CrI: Credible intervals; NA: Not applicable; NMA: Network meta-analysis; TEAE: Treatment-emergent adverse events; TRAE; Treatment-related adverse events

Key issue 5: Limitations of the evidence used to inform the network meta-analysis (1/3)

Background

- As KRYSTAL-12 only provides evidence on the efficacy and safety of adagrasib against docetaxel, company conducted a network meta-analysis to compare the relative efficacy and safety of adagrasib to docetaxel with nintedanib, and sotorasib

Company

- Conducted two-stage time-varying network meta-analysis (assumes non-proportional hazards) and standard network meta-analysis (assumes proportional hazards) used to evaluate progression-free survival and overall survival
- Analyses were conducted for progression-free survival, Grade ≥ 3 TEAEs, serious TEAE, serious TRAEs, and grade ≥ 3 hepatoxicity using available data from the most recent data cut-offs from KRYSTAL-12 (adagrasib), LUME-Lung1 (docetaxel with nintedanib) and CodeBreaK 200 (sotorasib)
- For the network meta-analysis of overall survival, most recent data cut-off from LUME-Lung1 and CodeBreaK 200 were used while estimates from the surrogacy analysis of KRYSTAL-1 was used for KRYSTAL-12

TEAE: Treatment-emergent adverse events; TRAE: Treatment-related adverse events

Key issue 5: Limitations of the evidence used to inform the network meta-analysis (2/3)

EAG

- Concerns with the validity of NMA results due to limitations of the evidence, including:
  1. The validity of the OS data for adagrasib
  2. Risk of bias in KRYSTAL-12
  3. The population from LUME-Lung 1, which has limited comparability with KRYSTAL-12
  4. The lack of loops in the evidence and limited number of studies, preventing any assessment of consistency and heterogeneity
- Also consider CodeBreaK 200 to have significant quality issues due to concerns with early asymmetric dropout, censoring and crossover, the duration of interval between assessments, and lack of blinding
- Populations of LUME-Lung 1 trial differs substantially from KRYSTAL-12 and CodeBreaK 200, most notably in prior immunotherapy exposure and histology
  - Uncertain whether prior immunotherapy exposure may affect the relative overall survival benefits of nintedanib with docetaxel compared with docetaxel monotherapy
  - Adenocarcinoma histology might be a treatment effect modifier for network meta-analysis comparisons between nintedanib with docetaxel* against adagrasib or docetaxel, although the evidence is limited and uncertain

* TA347 only recommends docetaxel with nintedanib in adenocarcinoma histology

NMA: Network meta-analysis. OS: Overall survival

Key issue 5: Limitations of the evidence used to inform the network meta-analysis (3/3)

EAG comments

- LUME-Lung 1 patients were recruited between 2008 and 2011 and may not have benefited from improvements in treatment and management of tolerability and safety over the past decade
- Narrow credible intervals of the NMA results is not considered given the heterogeneity in the characteristics of the studies included
- In the presence of substantial uncertainties in the evidence informing the NMA, results of the NMA should be interpreted with caution
- Incorporating results from the subgroup of patients with adenocarcinoma from LUME-Lung 1 may partially address concern about the comparability of this trial
- Mature OS evidence from KRYSTAL-12 is required, although it is uncertain whether the final KRYSTAL-12 results will be conclusive

Is the company's network meta-analysis reliable and appropriate for decision making?

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NMA: Network meta-analysis. OS: Overall survival

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

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ✓ **Modelling and key cost effectiveness issues to consider**
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations: Managed access and severity
- ❑ Summary

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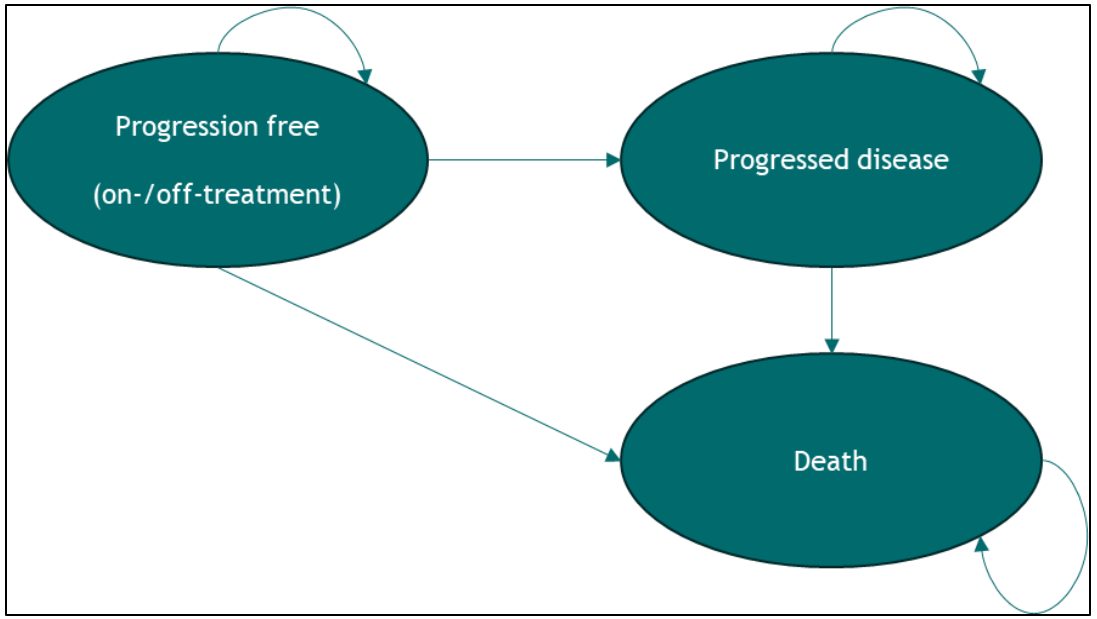
Company's model overview

See appendix: Health related quality of life

- Partitioned survival model
- Life-time horizon (20 years with 1-week cycles
- State occupancy informed by overall survival and progression-free survival from time-varying network meta-analysis



Adagrasib affects QALYs by:

- Increasing proportion alive and progression-free over time relative to comparators
- Assuming a higher utility value compared to docetaxel with or without nintedanib in the progression free and progressed disease health states
- A small difference in QALYs associated with AEs

Adagrasib affects costs by:

- Increased drug acquisition costs
- Increased time-on-treatment compared to the comparators, due to increased time progression-free
- Reduced drug administration costs due to oral regimen

Assumptions with greatest effect on cost effectiveness results:

- Overall survival predictions for adagrasib relative to docetaxel with or without nintedanib
- Utility values for progression free and PD health states

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AEs: Adverse events; PD: Progressed disease; ToT: Time on treatment; QALYs: Quality-adjusted life years

How company incorporated evidence in the base case model

Clinical data	Adagrasib	Docetaxel	Docetaxel + nintedanib
Baseline characteristics	KRYSTAL-12 (applied for the cohort, independent of treatment arm)		
OS	Gamma curve using time-varying NMA (Simulated adagrasib and docetaxel OS surrogacy analysis using KRYSTAL-1 IPD to predict KRYSTAL-12 OS)	Gamma curve using time-varying NMA (Simulated adagrasib and docetaxel OS from surrogacy analysis using KRYSTAL-1 IPD to predict KRYSTAL-12 OS)	Gamma curve using time-varying NMA
PFS	Gamma curve using time-varying NMA	Gamma curve using time-varying NMA	Gamma curve using time-varying NMA
AEs frequency	KRYSTAL-12	KRYSTAL-12	LUME-Lung 1
Health state utility values	Treatment specific values estimated using EQ-5D-5L data from KRYSTAL-12 mapped to EQ-5D-3L using Hernandez-Alava approach		Same as docetaxel alone arm
AE disutilities	Various sources		

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AE: Adverse events; IPD: Individual patient data; NMA: Network meta-analysis; OS: Overall survival; PFS: Progression-free survival

Moderate impact

Key issue 6: Use of treatment-specific utility value for the progressed disease health state in the model

Background

- Applied a utility increment for adagrasib relative to docetaxel with or without nintedanib in the progression-free and progressed disease health states based on an analysis of EQ-5D responses from KRYSTAL-12 (a phase 3, open label trial design)
  - ➢ Based on convenience of oral treatment at home rather than IV administration in hospital for docetaxel

Company

- Treatment-specific health state utility values based on the MMRM model of EQ-5D responses from KRYSTAL-12 demonstrated coefficient for the adagrasib arm was positive, suggesting that people in adagrasib arm have higher utility than docetaxel, while controlling for progression status, age and sex

EAG

- Disagree with a utility increment for adagrasib in the progressed disease health state ➔ Adagrasib is discontinued upon disease progression
- People in the docetaxel arm of KRYSTAL-12 that crossed over to adagrasib were censored from the company's utility analysis resulting in potential selection bias in the post-progression analysis
- Uses same treatment-independent utility value for adagrasib for the progressed disease health state for both adagrasib and docetaxel with or without nintedanib in its base case ➔ ICER versus docetaxel increases

Does the committee prefer the company or EAG approach for the progressed disease health state?

EQ-5D: EuroQol-5 Dimension; MMRM: Mixed models for repeated measures; QALY: Quality-adjusted life year

See appendix: Health related quality of life

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

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- ❑ Summary

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Differences between company and EAG base case assumptions

Assumption	Company base case	EAG base case
Overall survival hazard ratio	Gamma curve using time-varying NMA (Simulated adagrasib and docetaxel OS surrogacy analysis using KRYSTAL-1 IPD to predict KRYSTAL-12 OS)	**Base case 1:** • No effect of adagrasib on overall survival (HR = 1.0 for adagrasib vs. docetaxel) **Base case 2:** • Same effect of adagrasib on overall survival as identified for sotorasib (HR = 0.89 for adagrasib vs. docetaxel based on the effect from the two-step crossover adjusted analysis for sotorasib vs. docetaxel from CodeBreaK 200)
Progressed disease health state utility	Treatment-specific health state utility values (adagrasib = [redacted]; docetaxel = [redacted]) for progressed disease health state	**Base case 1 and 2** • Same progressed disease health state utility value for all treatments based on the value of [redacted] for adagrasib in the company's base case analysis

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HR: Hazard ratio; IPD: Individual patient dataNMA: Network meta-analysis; OS: Overall survival

Cost-effectiveness results*

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- When comparator PAS discounts are included, the company base case is within the range normally considered a cost-effective use of NHS resources
- The EAG base cases are above this range
- Scenarios presented in Part 2 will include alternative OS and utility modelling approaches

* Both the company and EAG applied a severity weight of 1.7 to the ICER

ICER: Incremental cost effectiveness ratio; OS: Overall survival; PAS: Patient access scheme

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

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
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- ❑ Base case assumptions and cost-effectiveness results
- ✓ **Other considerations: Managed access and severity**
- ❑ Summary

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Other considerations

Potential for managed access

- Managed access not proposed by the company
  - However, the company considers if the NICE committee feels unable to make a positive recommendation for routine NHS funding, based on the currently available survival data from the ongoing phase 3 KRYSTAL-12 trial and the completed phase 1/2 KRYSTAL-1 trial, then it would be open to discussions with NICE and NHS England around potential inclusion in the Cancer Drugs Fund

Severity weighting

- Company and EAG agree 1.7 severity weighting is appropriate

See appendix: QALY weightings for severity

Are there any other relevant considerations?

QALY: Quality-adjusted life year

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

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- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions and cost-effectiveness results
- ❑ Other considerations: Managed access and severity
- ✓ **Summary**

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Key issues and questions for committee (1)

Clinical effectiveness issues

1. **Effect of adagrasib relative to docetaxel with or without nintedanib on overall survival is unknown**
   - In the absence of mature overall survival data from KRYSTAL-12, are any of the EAG's alternative overall survival HR estimates for adagrasib compared with docetaxel appropriate for decision making?
2. **Validity of the surrogacy analysis between progression and survival**
   - Is the OS generated from the surrogacy analysis acceptable and suitable for decision making?
   - Is PFS a reliable surrogate for overall survival in second line or later KRAS G12C mutation?
3. **Lack of blinding and risk of bias in KRYSTAL-12**
   - Are the results from KRYSTAL-12, for progression-free survival, overall survival, objective response rates and safety outcomes, reliable and appropriate for decision making?
4. **Safety of adagrasib compared with docetaxel with or without nintedanib**
   - Is the data informing safety appropriately captured in the modelling and sufficient for decision making?

HR: Hazard ratio

Key issues and questions for committee (2)

Clinical effectiveness issues (continued)

5. **Limitations of the evidence used to inform the network meta-analysis**
   - Is the company's network meta-analysis reliable and appropriate for decision making?

Cost effectiveness issues

6. **Use of treatment-specific utility value for the progressed disease health state in the model**
   - Does the committee prefer the company or EAG approach for the progressed disease health state?

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

Supplementary appendix

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Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	EAG comments on company decision problem
Population	Adults with advanced NSCLC that is positive for a KRAS G12C mutation and is not suitable for, or has progressed after treatment with, platinum chemotherapy and/or an anti-PD-1/PD-L1 immunotherapy	The population addressed in the company submission decision problem is narrower than final scope and in line with the population in the KRYSTAL-12 study which includes patients with KRAS G12C mutation and disease progression on or after prior treatment with a platinum-containing regimen (cisplatin or carboplatin) and an immune checkpoint inhibitor (i.e. anti-PD-1/PD-L1 inhibitor), either concurrently or sequentially The EAG's clinical adviser considered that the trial population is broadly reflective of patients who would receive adagrasib in practice if it were approved
Intervention	Adarasib	In line with NICE scope
Comparators	• Docetaxel with or without nintedanib • Sotorasib (subject to managed access review)	Docetaxel with or without nintedanib as comparators is in line with final scope as sotorasib is only recommended in the Cancer Drugs Fund
Outcomes	PFS, OS, response rates, AEs and HRQoL	In line with NICE scope, and included OS provided by company at clarification

AEs: Adverse events; HRQoL: Health-related quality of life; OS: Overall survival; PFS: Progression-free survival

Baseline characteristics: KRYSTAL-12 and KRYSTAL-1

Baseline characteristics			KRYSTAL-12		KRYSTAL-1
			Adagrasib (n=301)	Docetaxel (n=152)	Adagrasib (n=116)
Age, mean (SD), years			63.6 (8.66)	63.9 (7.81)	64.4 (9.64)
Male, n (%)			193 (64.1)	110 (72.4)	51 (44)
Region, n (%)	Asia-Pacific		78 (25.9)	40 (26.3)	NA
	Non-Asia-Pacific		223 (74.1)	112 (73.7)	NA
Stage, n (%)	Locally advanced		18 (6)	8 (5.3)	13 (11.2)
	Metastatic		283 (94)	144 (94.7)	103 (88.8)
Number of prior systemic therapy, mean (SD)			1.5 (0.77)	1.4 (0.68)	2 (NR)
Type of systemic therapy, n (%)	Platinum agent only		0	0	0
	Checkpoint inhibitor only		0	0	0
	Both platinum and CIT		301 (100)	152 (11)	114 (98.3)
	Concurrent		221 (73.4)	111(73)	82 (70.7)
	Sequential		80 (26.6)	41 (27)	32 (27.6)
ECOG PS, n (%)		0	96 (31.9)	47 (30.9)	18 (15.5)
		1	205 (68.1)	104 (68.4)	97 (83.6)
		2 to 4	0	0	0

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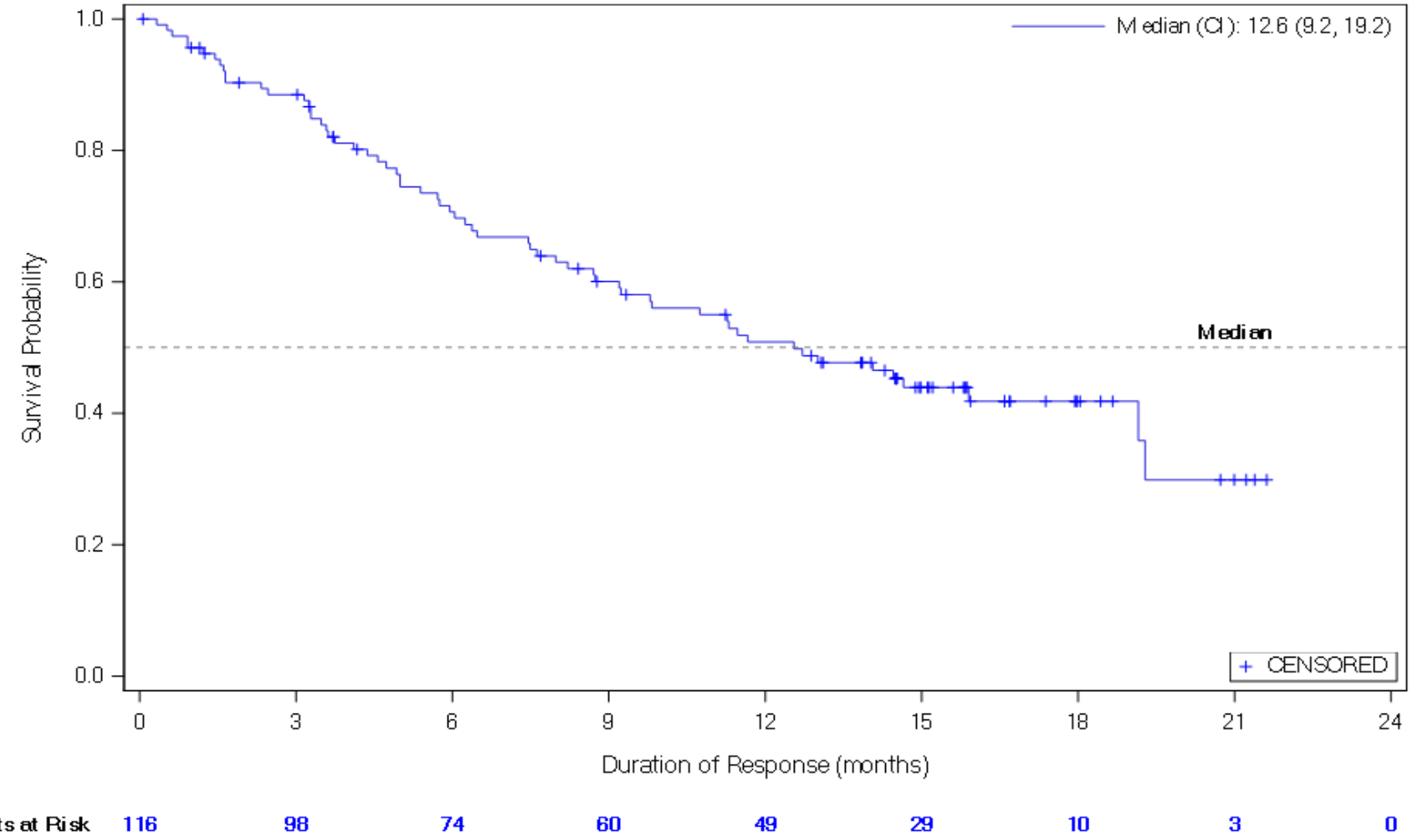
CIT: Chemo-immunotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance status; NA: Not applicable; NR: Not reported; SD: Standard deviation

KRYSTAL-1 results: Kaplan-Meier plot of overall survival, (January 2022 data cut-off)



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CI: Confidence interval

KRYSTAL-12 predicted OS (simulated using KRYSTAL-1)

Predicted OS (point estimate HR) from surrogacy analysis indicate adagrasib is favourable versus docetaxel

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HR: Hazard ratio; OS: Overall survival

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NMA results: OS and PFS using constant HRs

Estimated constant HRs (95% CrI) from the fixed-effects NMA for overall survival

Docetaxel	[redacted]	[redacted]	[redacted]
[redacted]	Nintedanib + docetaxel	[redacted]	[redacted]
[redacted]	[redacted]	Sotorasib	[redacted]
[redacted]	[redacted]	[redacted]	Adagrasib

Estimated constant HRs (95% CrI) from the fixed-effects NMA for progression-free survival

Docetaxel	[redacted]	[redacted]	[redacted]
[redacted]	Nintedanib + docetaxel	[redacted]	[redacted]
[redacted]	[redacted]	Sotorasib	[redacted]
[redacted]	[redacted]	[redacted]	Adagrasib

CrI: Credible intervals; HR: Hazard ratio; NMA: Network meta-analysis

Sotorasib

CodeBreaK 200 PFS benefit with sotorasib do not translate to OS benefit with concerns with asymmetric early dropout and early crossover in the trial.

- Sotorasib is a targeted therapy for previously treated KRAS positive G12C advanced or metastatic NSCLC
- Recommended for use within the CDF (TA781) as an option for treating KRAS G12C positive advanced or metastatic NSCLC in adults whose disease has progressed on, or who cannot tolerate, platinum-based chemotherapy or anti-PD-1/PD-L1 immunotherapy ➔ Cinical evidence for sotorasib in TA781 was primarily based on CodeBreaK 100, a phase 2 single arm trial
- Since TA781, the completed phase 3 trial, CodeBreaK 200 showed a statistically significant treatment PFS for sotorasib versus docetaxel on PFS similar to KRYSTAL-12 for adagrasib versus docetaxel ➔ But the OS results from CodeBreaK 200 were not statistically significant (HR 1.01, 95% CI 0.77 to 1.33)
- In May 2021, FDA granted accelerated approval for sotorasib based on CodeBreaK 100 pending CodeBreaK 200 outcomes ➔ But, in October 2023, following CodeBreaK 200 results, FDA rejected the supplemental new drug application for full approval, noting
    - Concerns with asymmetric early dropout and early crossover of patients in the control arm before confirmation of disease progression.
    - PFS benefit did not translate into OS benefit.
- Adagrasib is the only MHRA licenced therapy that targets KRAS G12C mutation-positive NSCLC aside from sotorasib

CDF: Cancer Drugs Fund; CI: Confidence intervals; FDA: Food and Drug Administration; HR: hazard ratio; MHRA: Medicines and Healthcare products Regulatory Agency; OS: Overall survival; PFS: Progression-free survival; TA781: Technology appraisal 781

CodeBreaK 200

- CodeBreaK 200 is a phase 3, open-label multi-centre randomised controlled trial that investigated the efficacy and safety of sotorasib compared with docetaxel in people with previously treated KRAS G12C mutation-positive NSCLC
- Crossover from docetaxel to sotorasib was permitted in CodeBreaK 200
- To explore the impact of crossover on OS in CodeBreaK 200, the German Gemeinsamer Bundesausschuss (G-BA) submission presented OS results adjusted for crossover:

OS analysis	HR (95% CI)
ITT (primary)	1.010 (0.766, 1.331)
Cross-over adjusted	
• RPSFT	1.010 (0.660, 1.492)
• IPCW	0.990 (0.733, 1.337)
• Two-step	0.885 (0.172, 1.328)

EAG comments

- CodeBreaK 200 at high risk of bias ➔ Several concerns about the quality of the CodeBreaK 200 trial, notably due to early asymmetric dropout, censoring and crossover, the duration of interval between assessments, and lack of blinding
- Agree with Olivier et al. (2023) that allowing for crossover is particularly problematic in the absence of any other evidence establishing the OS treatment benefit of sotorasib compared with docetaxel in a randomised setting

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CI: Confidence interval; HR: Hazard ratio; IPCW: Inverse-probability-of-censoring weighting; ITT: Intention to treat; RPSFT: Rank preserving structural failure time model; OS: Overall survival;

Health related quality of life

- Company uses EQ-5D-5L data from KRYSTAL-12 mapped to EQ-5D-3L to inform the utility values for progression-free and progressed disease health states, stratified by treatment arm and disutilities for adverse events
  - A mixed model for repeated measures including progression status, treatment arm, age, sex, and an interaction term for progression status and treatment arm used to analyse mapped EQ-5D-3L values
- Utility values are applied to time spent in the progression-free and progressed disease health states to calculate quality-adjusted life years that reflect the improvement in quality of life

Health state utility values used in the company's base case analysis

Treatment	Progression-free	Progressed disease	Source
Adagrasib	[redacted]	[redacted]	KRYSTAL-12
Docetaxel	[redacted]	[redacted]	KRYSTAL-12
Docetaxel + nintedanib	[redacted]	[redacted]	Assumption*

* The same utility values for docetaxel monotherapy are applied to docetaxel + nintedanib by assuming a class effect

- Disutilities for AEs were applied as a one-off QALY decrement in the first model cycle by multiplying the proportion of patients experiencing the AE with the corresponding disutility value. The resulting one-off QALY decrements for AEs applied in the model are [redacted] (adagrasib), [redacted] (docetaxel), and [redacted] (docetaxel + nintedanib)

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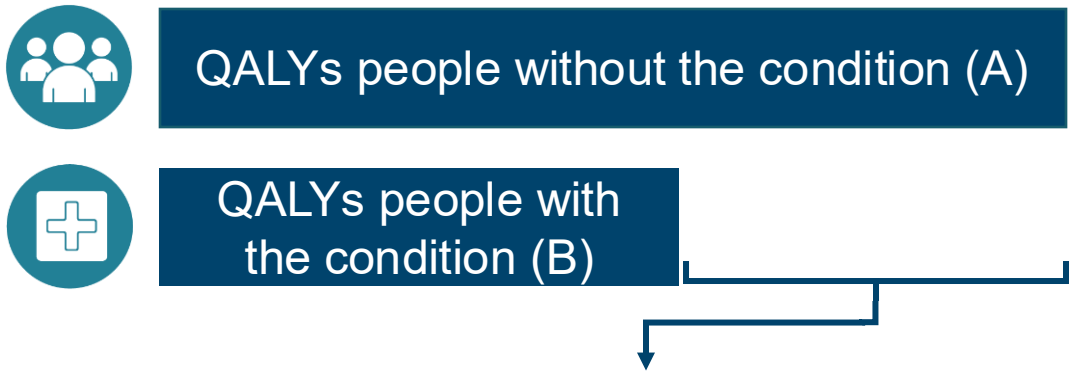
EQ5D: EuroQol-5 Dimension

QALY weightings for severity (1/2)

Severity modifier calculations and components:



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

Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY: Quality-adjusted life year

QALY weightings for severity (2/2)

Company

Company's QALY shortfall analysis:

Component	QALYs / shortfall
Expected total QALYs for the general population	11.28
Total QALYs that people living with a condition would be expected to have with current treatment (docetaxel)	[redacted]
QALY shortfall (absolute)	[redacted]
QALY shortfall (proportional)	[redacted]

Proportional shortfall is 0.95 therefore a severity weighting of 1.7 applies

EAG comments

- Considered both docetaxel with or without nintedanib as standard care in its QALY shortfall analysis
  - Noted that the company considered only docetaxel as standard care in the QALY shortfall analysis when it had highlighted that 85% receive second line sotorasib and 60-80% of people receive docetaxel-based regimen in combination with nintedanib
- Agrees 1.7 QALY weighting is appropriate regardless of docetaxel with or without nintedanib as standard care in the QALY shortfall analysis

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QALY: Quality-adjusted life year

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**