Amivantamab for treating EGFR Exon 20 positive NSCLC after platinum-based chemotherapy

Part 1 slides for public – redacted

Slide 36 updated post-ACM1

Technology appraisal committee D [04 August 2022]

Chair: Dr Megan John

Lead team: Bernard Khoo and Malcolm Oswald

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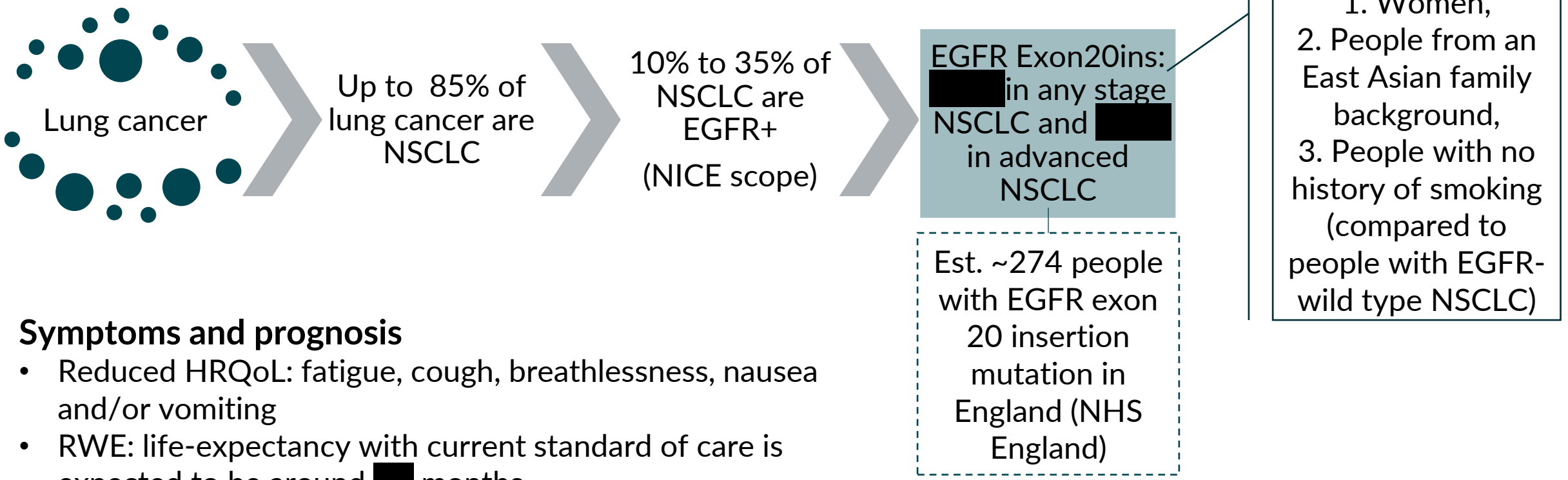
Company: Janssen

NICE

Background on disease

EGFR Exon 20 positive NSCLC is a rare form of lung cancer

Figure 1 Overview of population



Symptoms and prognosis

- Reduced HRQoL: fatigue, cough, breathlessness, nausea and/or vomiting
- RWE: life-expectancy with current standard of care is expected to be around [redacted] months

EGFR: epidermal growth factor receptor; HRQoL: health-related quality of life; NSCLC: non-small cell lung cancer; RWE: real world evidence

Company's proposed treatment pathway

There is no established SoC for EGFR Exon20ins mutated NSCLC

- There are no specific treatment options for EGFR Exon20ins mutated NSCLC
- RWE shows there is no definitive standard of care therapy across treatment centres and clinicians
- Treatment is influenced by physicians choice, line of therapy and PD-L1 status

Table 1: potential treatment pathways for people with EGFR Exon20ins mutated NSCLC in UK clinical practice (based on company submission)

	First-line	Second-line	Third-line	Fourth-line
1	Pembrolizumab + pemetrexed + platinum-based chemotherapy	Docetaxel +/- nintedanib	BSC	
2	Platinum-based chemotherapy	Immuno-oncology monotherapy (atezolizumab or pembrolizumab or nivolumab)	Docetaxel +/- nintedanib	BSC
3	Immuno-oncology monotherapy (pembrolizumab or atezolizumab)	Platinum-based chemotherapy	Docetaxel +/- nintedanib	BSC

EGFR TKIs? (key issue to be discussed later in slides)

ID3836 and ID3984 are under evaluation for positioning after platinum-based chemotherapy

Amivantamab (ID3836)

Mobocertinib (ID3984)

SoC: standard of care; RWE: real world evidence; Source: company submission

Patient perspectives

EGFR Exon20ins NSCLC is a distinct population with poor prognosis

Submissions from Roy Castle Lung Cancer Foundation and 3 from EGFR Positive UK

- People with EGFR Exon20ins have a worse prognosis, a propensity for brain and bone metastases and do not respond as well to available treatment options
- EGFR Positive UK sought opinions from 20 people with EGFR Exon20ins mutations
- There is little conformity in current treatment options offered and there is no targeted therapy for EGFR Exon 20 NSCLC

"Diagnosis is often late at stage 4…devastating for patients"

"The young doctor showed me a chart of targeted therapies available for treating EGFR and then told me that none of them would work for Exon 20"

<u>Amivantamab:</u>

- Would be the first targeted therapy for this indication (very important to patients) and would begin to meet a significant unmet need
- Offers progression free survival and quality of life benefits and has a low toxicity profile
- Has the potential to be used in sequence or in combination with other new treatments

Clinical perspectives

Participation from 2 clinical experts

- A clinically significant improvement is to improve survival and/or quality of life by more than 2 months
- There are poor outcomes with standard therapies and a need for novel therapies
    - There is some variation in treatment regimen
    - Benefits of single-agent immunotherapy is unclear

Amivantamab

- Is the first licensed agent of its type (bi-specific antibody)
- Will require frequent infusions at day units (especially during the first few weeks of treatment)
- Infusion reaction is the main adverse event

Resolved issues

A number of issues were resolved at the technical engagement stage

Table 2 Resolved issues

Issue	Company technical engagement response	ICER impact
Use of concomitant medicines in intervention group (potential exaggeration of amivantamab benefits)	Scenario analysis with concomitant radiotherapy excluded provided to demonstrate limited impact	Small
Limited trial follow-up data provided	Longer overall survival follow-up data provided	Small
Lack of age-adjustment in health utilities	Incorporated as requested by ERG	Small
Lack of fixed random seed in PSA	Fixed random seed implemented in model	Small

Model driver
Unknown impact
Small/Moderate impact

ITT: intention-to-treat; PSA: probabilistic sensitivity analyses; TE: technical engagement

Appraisal specific key issues for discussion

There are number of key issues and areas of uncertainty to be aware of

Model driver
Unknown impact
Small/Moderate impact

Table 3 Key issues

Issue	ICER impact
ITC data sources: Non-clinical trial RWE used. Introduces uncertainty and risk of bias to the model outcomes	Unknown
ITC data sources: it is unclear if RWE included has been selected systematically	Unknown
Comparators: should EGFR TKIs be included or excluded within the comparator basket?	Small
Blended comparator arm and lack of fully incremental analysis causes uncertainty	Potential model driver
Survival curves: should KM curves or parametric curves be used to model survival outcomes in the standard of care arm?	Small
Time to treatment discontinuation: Is the company's or ERGs approach to time on treatment preferred for decision-making?	Small
Treatment waning: should treatment waning scenarios be considered in decision-making?	Small

TKIs: tyrosine kinase inhibitors; KM: Kaplan-Meier; RWE: real world evidence

Appraisal specific key unresolvable issues for consideration

Table 4 Areas of uncertainty unresolvable with current submission

Additional areas of uncertainty that cannot be currently resolved. Committee should be aware of these when making its recommendations	ICER impact
The lack of direct comparative evidence creates significant uncertainty	Unknown
Generalisability of the clinical evidence to the UK setting	Unknown
Differences between efficacy and safety populations	Small

Model driver

Unknown impact

Small/Moderate impact

Technology (Rybrevant, Janssen)

Table 5 Technology details

Marketing authorisation	• Amivantamab is indicated for treatment of adults with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy • MHRA marketing authorisation gained: November 2021 • EMA marketing authorisation gained: February 2022
Mechanism of action	• Bispecific antibody that targets both EGFR and the proto-oncogene MET
Administration	• Intravenous infusion
Price	• List price per pack: £1079 • List price for average course of treatment: [redacted] (based on an estimated mean time on treatment of [redacted] months) • Confidential simple patient access scheme is applicable

MET: Mesenchymal epithelial transition

Decision problem: The population is narrower than the scope due to changes to the marketing authorisation

Table 6 Population, intervention, comparators and outcomes from the scope

	Final scope	Company
Population	Adults with EGFR Exon20ins-positive NSCLC after previous platinum-based chemotherapy	Adults with locally advanced or metastatic NSCLC with activating EGFR Exon20ins, whose disease has progressed on or after platinum-based chemotherapy (aligned with marketing authorisation)
Intervention	Amivantamab	Amivantamab
Comparator	ECM without amivantamab including ATZ, NIVO, PEMBRO and chemotherapy such as docetaxel alone or with nintedanib, pemetrexed and carboplatin	UK standard of care consisting of tyrosine kinase inhibitors, immuno-oncology agents, platinum-based chemotherapy and non-platinum-based chemotherapy.
Outcomes	• Overall survival • PFS or disease-free survival • Response rate • Time to treatment discontinuation • Adverse events • HRQoL	• Overall response rate • Clinical benefit rate • Duration of response • Progression free survival • TTF • Overall survival • Adverse events • HRQoL

Key issue discussed in more detail later in the presentation

ATZ, atezolizumab; ECM: established clinical management; HRQoL, health related quality of life; NIVO: nivolumab; PEMBRO: pembrolizumab; TTF, time to treatment failure

Clinical effectiveness

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Key clinical trial
Clinical data for amivantamab is from the CHRYSALIS trial

Table 7 Clinical trial designs and outcomes

	CHRYSALIS trial
Design	Phase 1b, single arm, open-label, 2-part trial
Population	Adults with metastatic or unresectable NSCLC (full population, N=285; efficacy population in submission, n=114)
Intervention	Amivantamab
Comparator(s)	NA (single-arm)
Duration	Ongoing, median follow-up (overall survival data): [redacted]
Primary outcome	Overall response rate
Key secondary outcomes	• Complete benefit rate • Duration of response • Progression free survival • Health-related quality of life • Time to treatment failure • The best % change from baseline in SoD
Locations	Australia, Canada, China, France, Italy, Japan, South Korea, Spain, Taiwan, UK, USA
Used in model?	Yes

SoD, sum of diameters

CHRYSALIS results: progression free survival
March 2021 results show a median PFS of 6.74 months

Figure 2 PFS Kaplan-Meier curves (30th March 2021 data-cut off), blinded independent committee review

Median progression free survival:

- Blinded independent review committee: 6.74 months (95% CI: 5.45, 9.66)
- Investigator assessed: 6.93 months (95% CI: 5.55 to 8.64)

Median follow-up: [redacted] months.

NICE CI: confidence intervals; KM: Kaplan-Meier; PFS: progression free survival

CHRYSALIS results: overall survival

March 2022 results show a median OS of [redacted] months

Figure 3 Overlaid OS KM curves from March 2021 and March 2022 data-cuts

[redacted]

Median overall survival data

- March 2021: 22.77 (95% CI: 17.48, NE)
- March 2022: [redacted]

NICE CI: confidence intervals; KM: Kaplan-Meier; OS: overall survival

Key considerations when using real world evidence from routine clinical practice

- A single-arm trial is compared to RWD to determine treatment effectiveness in the company submission
- A clinical trial has a protocol, pre-defined patient selection criteria and endpoint assessment criteria. This is scrutinized by regulatory bodies. And it needs to meet regulatory standards to be considered unbiased. RWD doesn't follow this rigorous assessment pathway. Combined use of clinical trial and RWE should be treated with caution
- A Phase 3 head-to-head RCT supplemented with a NMA (using RCTs) to inform treatment effectiveness is preferred. Given the rarity of the condition and small sample sizes, producing gold standards of evidence may not be possible

Issues with using real-world evidence to inform comparator arms

Endpoints may not be consistent with clinical trial measures:

- PFS in clinical trials is determined by RECIST criteria. This is not commonly done in routine practice which informs RWE. Data may be collected using different inconsistent methods
- Patients are rigorously followed-up to determine date of death in clinical trials. Not the case in routine practice. Data may be incomplete depending on data cleaning/linkage processes across sites and countries

Baseline comparability of patients could introduce bias:

- When comparing with an external comparator, how the index date is determined is important. If it is the point of treatment initiation, that could be some time later than in a clinical trial. This can bias estimates of time-to-event data

NMA, Network meta-analysis; RECIST, Response Evaluation Criteria in Solid Tumours; RCT, Randomised controlled trial; RWD, Real world data

ITC methodology: comparators and sources

The company chose a basket of comparators based on RWE

Choice of comparators	Company rationale
UK standard of care including: • Chemotherapy • Immuno-oncology agents • EGFR-TKIs	• Clinical expert feedback: no established standard of care, decisions are made on a case-by-case basis • Lack of specific clinical guidelines for this population • RWE shows lack of definitive standard of care

Key issue for discussion in later slides

Comparator data sources

- No comparator data from CHYRSALIS trial
- No relevant trials identified in systematic literature review comparing amivantamab to the relevant comparator (or that could be used to conduct an unanchored indirect comparison in the specific population)
- Because of this, adjusted treatment comparisons conducted using 2 RWE sources:

US RWE: US cohort, pooled data from Flatiron, COTA and ConcertAI, n=[redacted] → **Base case** (larger sample size vs PHE + clinicians confirmed generalisability with UK)

Public Health England: using routine population-level data available through NCRAS, n=[redacted] → **Included within a scenario**

NICE technical team consideration: the lack of direct comparative evidence creates significant uncertainty

ITC: indirect treatment comparison; NCRAS: National Cancer Registration and Analysis Service; PHE: Public Health England; RWE: real world evidence; TKI: tyrosine kinase inhibitors

Key issue: It is uncertain if the RWE included in the ITC is comprehensive or been selected systematically

Background

- Comparator data was sourced from US and UK RWE sources. A systematic approach to identifying and selecting these sources was not provided by the company

Company

- Approach taken is pragmatic and utilises accessible data from the US and UK – such databases are commonly used to inform comparator analyses (particularly in rare diseases, where data is limited)
- Selection bias is hard to avoid due to disease rarity – to counteract bias, US data were adjusted for CHRYSALIS population in terms of key prognostic variables and baseline characteristics
- Acknowledge that it cannot be guaranteed that all possible sources of data were identified (systematic search was conducted for 'RWE studies' and not for 'RWE sources' (i.e. databases)

ERG comments

- Unclear whether no other studies might have been suitable for comparison
- Chosen comparator sources are not inappropriate but there is a lack of full, justified rationale for choices
- Demographic and patient data is broadly similar between UK and US sources but without a systematic approach to selecting this evidence, impact of selection bias must be considered

RWE: real world evidence

ITC methodology: methods of adjustment

The base-case comparator population was adjusted by IPW

Table 8 Summary of ITC methodology

	US real world evidence	Public Health England
Adjustment method	• IPW-ATT* (base-case) • Covariate adjustment	• Covariate adjustment only (sample sizes considered too small for IPW)
Outcomes adjustment applied to	• Progression free survival • Time to next treatment • Overall survival • Overall response rate	• Time to next treatment • Overall response rate • No progression free survival or overall response rate data
Baseline covariates adjusted for (based on confounders identified by SLR, clinical expert opinion and data availability for sufficient sample size)	• [redacted] • [redacted] • [redacted] • [redacted]	• [redacted] • [redacted] • [redacted] • [redacted]

ERG: methods for adjustment appear robust but are limited by the covariates chosen (residual confounding likely to remain). Based on limitations in UK data, US RWE was probably more appropriate for use in base-case

*Uses propensity scores to estimate the average treatment effect on the treated (by reweighting only the comparator data)

ATT: average treatment effect on the treated; ECOG: Eastern Cooperative Oncology Group; IPW: inverse probability weighting; RWE: real world evidence; SLR: systematic literature review

ITC results

Overall survival was statistically significantly longer for amivantamab vs standard of care

Figure 4 Kaplan-Meier curve for OS for CHRYSALIS vs. US RWE cohort (amivantamab vs. SoC) – IPW (ATT)

- Median overall survival of amivantamab (March 2022): [redacted]
- Median overall survival for ATT-weighted US RWE standard of care cohort: [redacted]
- Adjusted hazard ratio for amivantamab versus standard of care is [redacted] - amivantamab is statistically significantly favoured over standard of care in terms of overall survival.

Comparison with the PHE dataset increased the treatment effect on overall survival. ERG consider US RWE use to be conservative relative to using the PHE source

CI: confidence intervals; IPW: inverse probability weighting; ITC: indirect treatment comparison; OS: overall survival; PC: physicians choice; RWE: real world evidence; SoC: standard of care

ITC results
PFS was statistically significantly longer for amivantamab vs standard of care

Figure 5 Kaplan-Meier curve for PFS for CHRYSALIS vs. US RWE cohort (amivantamab vs. SoC (PC)) – (IPW ATT)

- Median progression free survival of amivantamab: [redacted]
- Median progression free survival for ATT-weighted US RWE standard of care cohort: [redacted]
- Adjusted hazard ratio for amivantamab versus standard of care is [redacted]- amivantamab is statistically significantly favoured over standard of care in terms of progression free survival

CI: confidence intervals; HR: hazard ratios; ITC: indirect treatment comparison; PC: physicians choice; PFS: progression free survival; RWE: real world evidence; SoC: standard of care;

Key issue: Comparators (1/3)

There are issues with the inclusion of EGFR TKIs as comparators

Background: company use SoC basket inc. EGFR TKIs. ERG consider there to be significant issues with this

Company

- Base-case assumes [redacted] of comparator basket consists of EGFR TKIs
- Acknowledge EGFR TKIs have relatively limited efficacy in population of interest
- Inclusion in basket is supported by RWE (see Table 9) and market research

ERG:

- Evidence suggests EGFR TKIs have limited to no activity in people with Exon20ins mutations
- Company approach may overestimate amivantamab efficacy. It would be more appropriate to explore a range of treatment basket scenarios and to exclude EGFR TKIs

Table 9 Breakdown of treatment class percentages

Treatment class	PHE data	US RWE data	Reweighted pooled US RWE (used in base case)*
Immuno-oncology agents	[redacted]	[redacted]	[redacted]
Tyrosine kinase inhibitors			
Non-platinum chemotherapy			
Platinum-based chemotherapy			
Other*			-

Are percentages of comparator classes reflective of clinical practice?

PHE: Public Health England; RWE: real world evidence; SoC: standard of care; TKI: tyrosine kinase inhibitors. *Products in the "other" category include clinical study drugs, and other investigational drug usages such as ALK inhibitors, multiple-kinase inhibitors, anti-EGFR monoclonal antibodies, mTOR inhibitors and oestrogen modulators for the US RWE and poziotinib for PHE. Proportion included in "other" category was reweighted and distributed amongst other treatment classes.

Key issue: Comparators (2/3)
Excluding EGFR TKIs had limited impact on hazard ratios

Company

- Scenarios excluding EGFR TKIs show limited impact on hazard ratios
- Excluding TKIs is not robust or suitable for decision-making:
  - RWE shows use of EGFR TKIs
  - No evidence to support which treatments would be used if people did not have EGFR TKIs
  - Some evidence shows a modest anti-tumour effect with EGFR TKIs

Table 10 Indirect treatment comparison results with and without EGFR TKIs

	Base-case	Exc. EGFR TKIs
Overall survival*	[redacted]	[redacted]
Progression free survival	[redacted]	[redacted]
Time to next treatment	[redacted]	[redacted]

ERG comments: appropriateness of EGFR TKIs remains uncertain but also note that there was effectively no difference in outcomes due to exclusion of EGFR-TKIs for PFS and TTNT and only a 0.01, 0.01 and 0.04 difference in the point estimate, lower and upper 95% confidence interval limits for overall survival.

Clinical expert: "I have no reason to believe [the company data] is not correct but I would not use these agents [EGFR TKIs] in clinical practice and I do not think their use is justified by license or funding."

*March 2022 data-cut; PFS: progression-free survival RWE: real world evidence; TTNT: time to next treatment; TKI: tyrosine kinase inhibitors

Key issue: Comparators (3/3)

Exclusion of EFGR TKIs had limited impact on overall survival results

Figure 6 Kaplan-Meier curves for overall survival for CHRYSALIS vs. US RWE cohort (amivantamab vs. standard of care) – IPW (ATT)

A) With EGFR TKIs included in US RWE cohort

B) With EGFR TKIs excluded in US RWE cohort

Should EGFR-TKIs be included or excluded in the comparator basket for decision-making?

IPW: inverse probability weighting; RWE: real world evidence; TKIs: tyrosine kinase inhibitors

Key issue: Use of a blended comparator and lack of fully incremental analysis increases cost-effectiveness uncertainty

Background

- Amivantamab was compared with a basket of treatments
- A fully incremental analysis of all relevant comparators was not conducted

Company

- A fully incremental analysis is not possible when the relevant comparator can only be accurately reflected as a basket of treatments
- There is no robust way to define standard of care and so not feasible to identify an single treatment that would be displaced by amivantamab

ERG comments

- Company approach means that amivantamab is compared with the average clinical effectiveness and costs across all treatments in the comparator basket, rather than a fully incremental analysis of all relevant comparators
- This increases the uncertainty estimates of amivantamab cost-effectiveness

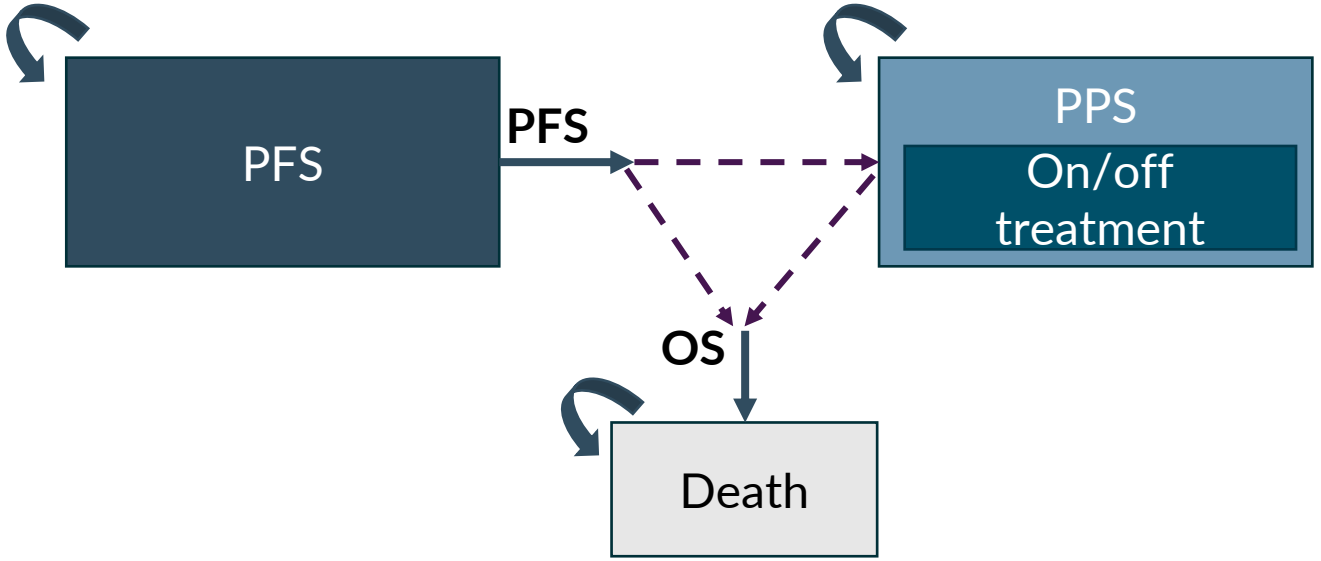
NICE tech team considerations: Efficacy by comparator arm cannot be separated out. **Unresolvable uncertainty remains**

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview
A partitioned survival model with 3 states was used and considered acceptable by the ERG

Figure 7 Model structure



Technology affects **costs** by:
- Higher drug costs
- Administration costs
- Post progression disease management costs

Technology affects **QALYs** by:
- Increased post-progression survival
- Increased progression-free survival

Company submission scenarios that have the greatest impact on the ICER:
- UK standard of care efficacy based on PHE data (decreased ICER)
- Using osimertinib cost to represent EGFR-TKIs (decreased ICER)
- Using investigator-assessment as a measure of progression (increased ICER)

ICERs: incremental cost-effectiveness ratios; PFS: progression free survival; PPS: post-progression survival; QALYs: quality adjusted life years

How company incorporated evidence into model

Table 11 Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	CHRYSALIS trial
Intervention efficacy	CHRYSALIS trial
Comparator efficacy	Base-case: US RWE (Flatiron, ConcertAI and COTA); Scenario: Public Health England
Utilities	PFS state: 0.713, PPS state: 0.569. Source: TA484/TA713 (because number of EQ-5D-5L responses from CHRYSALIS trial was low at time of data cut-off)
Costs and resource use	Administration-related costs: NHS Reference Costs 2019/20 Resource use costs: based on TA520 EoL costs: applied in first cycle post-death and derived by assumptions in TA520
Adverse events	CHRYSALIS trial (for amivantamab), AURA3 for platinum-based chemotherapy (as per TA653) and LUX-Lung-8 for EGFR TKIs) or previous NICE appraisals (TA520 for IO agents and non-platinum-based chemotherapy).

NICE scope: the costs associated with diagnostic testing in people with NSCLC who would not otherwise have been tested should be included
Company: Excluded exon 20ins diagnostic testing costs - considered routine testing
Professional org submissions: no additional testing costs

Is EGFR exon20 testing part of established NHS practice?

EoL: end of life; PFS: progression free survival; PPS: post progression survival; RWE: real world evidence

Key issue: Survival models

KM curves may have led to overfitting of modelled survival outcomes

Background: NICE DSU TSD 14 states "parametric models are likely to represent the preferred method for incorporating survival data into health economic models in the majority of cases". For overall survival/progression free survival in the standard of care arm, the company used KM curves directly, instead of selecting parametric curves

Company:

- KM curves are more appropriate for the base case because mature data means all events are captured
- Parametric modelling scenarios demonstrate minimal impact

ERG comments: prefer parametric approach (Weibull curve for overall survival and log-logistic curve for progression free survival)

- Company approach is not aligned with NICE DSU TSD 14
- 'Stepped' nature of KM curves (due to follow-up at specific intervals) means that at each measurement point all people who have died or progressed will leave the health state at once – this is not valid and is likely to introduce bias
- Implementation of KM data may introduce overfitting of the modelled survival outcomes

Should KM curves or parametric curves be used to model survival outcomes in the standard of care arm?

DSU TSD: decision support unit technical support document; KM: Kaplan-Meier

Key issue: Time to treatment discontinuation (1/2)

Company assumes time to treatment discontinuation to be equal to PFS

Background: CHRYSALIS treatment duration was longer than modelled median PFS ([redacted] months vs. [redacted] months). ERG: company approach reduces estimated costs without reducing estimated effectiveness after progression

Table 12: overview of time on treatment scenarios

Scenario*		Assumptions
Company	Base-case	Time to treatment discontinuation is equal to progression free survival (both arms)
	Scenario 1	CHRYSALIS time to discontinuation data (Gompertz curve) for amivantamab arm
	TE scenario	50% of all people, regardless of treatment arm, discontinue treatment at progression (to reflect clinical reality lays somewhere between company and ERG base case)
ERG base-case		CHRYSALIS time to discontinuation data (exponential) for amivantamab arm

Company: UK clinicians state people would discontinue at progression

- Assuming treatment beyond progression for amivantamab only penalises amivantamab arm unfairly
- Trials include closer monitoring so progression would be detected earlier (i.e. base-case may underestimate amivantamab benefit)
- Cancer Drugs Fund data collection could reduce this uncertainty

Clinical expert: average time on treatment will be 2 to 3 months post-progression, but this will vary widely

Key issue: Time to treatment discontinuation (2/2)

The ERG prefers using the exponential curve for time to treatment discontinuation

Figure 8 CHRYSALIS time to treatment discontinuation hazard plot

[redacted]

Company: Gompertz. Smoothed hazard curves for time to treatment discontinuation shows that hazard does not remain constant over time, instead decreasing initially before increasing from around month 5 (in line with Weibull or Gompertz).

ERG: Exponential (base-case, best fit), Weibull in scenario (may be conservative)

- Gompertz selected by company is most pessimistic (has the lowest number of people on treatment over time) and has 4th best statistical fit.
- TE scenario requires additional assumptions
- Assuming treatment beyond progression for only amivantamab is not unfair: CHRYSALIS shows post-progression treatment but this is unclear for comparator arm
- TTD in ERG base-case and all scenarios is around 1 month longer than company base-case

Is the company's or ERGs approach to time on treatment preferred for decision-making?

Key issue: Treatment waning (1/2)

The company assumes lifelong treatment effect which may be uncertain

Company: base-case excludes waning; scenario with waning provided at technical engagement

- Treatment is continued throughout horizon (amivantamab until progression then subsequent treatment)
- Poor prognosis means waning is unlikely to be experienced in lifespan. If it was, it would be highly unlikely to have a clinically meaningful impact due to the short time periods over which it could apply
- Updated overall survival data shows treatment benefit is maintained at follow-up
- Clinicians confirm outcomes at 2-years and 5-years were aligned with expectations
- Approach taken is aligned with TA789 (NSCLC with MET gene alterations). Appraisals where waning was considered included 2-year stopping rules and not continuous treatments (e.g. TA655 and TA520)
- Technical engagement scenario applies linear waning from 3 years* after amivantamab cessation until efficacy reaches standard of care efficacy

ERG comments: limited evidence to support lifelong treatment effect

- Previous STAs (for example, TA520) concluded that a lifelong treatment effect was implausible (n.b, 2 year stopping rule applied in these STAs).
- Would like to have seen a scenario where time to reach a hazard ratio of 1 was reduced (e.g. to 5 or 10 years) rather than assuming a linear waning until end of time horizon

Clinical expert: amivantamab effect is likely to be somewhere between oral therapies (where there is little benefit post-progression) and immunotherapies (where there may be long-term benefit)

*Aligned with most conservative time point explored in TA428 and TA713

Key issue: Treatment waning (2/2)

Waning has been considered in a number of previous NSCLC appraisals, in cases where stopping rules were used

Table 13: overview of previous time waning scenarios considered by the company and ERG

	Technology	Treatment waning?	Stopping rule?
TA789	Tepotinib for NSCLC with MET gene alterations	No	No
TA713	Nivolumab for NSCLC after chemotherapy	Yes: over 3 years	Yes: 2 years
TA655	Nivolumab for squamous NSCLC after chemotherapy	Yes: over 3 years	Yes: 2 years
TA653	Osimertinib for EGFR T790M mutation NSCLC	No explicit mention of waning	
TA520	Atezolizumab for NSCLC after chemotherapy	Yes: 5 years	Yes: 2 years
TA428	Pembrolizumab for PD-L1 NSCLC after chemotherapy	Yes: 3, 5 and 10 year	Yes: 2 years

Should treatment waning scenarios be considered in decision making?

Additional areas of uncertainty

Additional areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations

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Generalisability may be limited because the CHRYSALIS trial only included people with ECOG status 0 to 1

Background: Submission is aligned with MA and Cohort D+ from CHYRSALIS trial

- Cohort D+ is slightly narrower than MA and general population characteristics because trial inclusion criteria restricted recruitment to people with an ECOG status of 0 or 1 (common for oncology treatments)

Company

- UK clinicians confirmed baseline characteristics are comparable to clinical practice
- Compared with typical people with NSCLC, people with EGFR Exon20ins are generally non-smokers who are fitter (and may have lower ECOG figures than would be typical for people with other late-stage lung cancers)
- Market research study of 50 people with EGFR Exon20ins found that 94% had ECOG status 0 to 1 – unlike other cancers, it is unlikely that the exclusion of people with lower ECOG performance scores could lead to an underestimation of adverse events

ERG comments: Fitter population in trial limits generalisability and may have underestimated adverse events

Clinical expert opinion: not considered a major issue - funding is often restricted to ECOG status 0 to 1. Given pattern of toxicity, amivantamab is likely to be tolerable to general population

ECOG: Eastern Cooperative Oncology Group; MA: marketing authorisation

The efficacy and safety populations differ in a way that is likely to exaggerate benefits

Background: larger safety population (n=153) vs. efficacy population (n=114) used in original analysis

Company

- Larger safety population was used in order to gather safety data from large a group as possible
- Technical engagement: n=114 safety data provided and incorporated into base case

ERG comments:

- Unclear how efficacy population (which had two cut-off dates considered) was chosen, as opposed to the safety population, which did not apply those two date criteria
- Unclear why adverse event comparison was made only for earlier data cuts
- ERG recommends an analysis of efficacy for the n=153 population

Table 14: Incidence of Grade ≥3 AEs occurring in ≥5% of people in N=153 and N=114 populations

AE, %	N=153 population	N=114 population
Anaemia	[redacted]	[redacted]
Diarrhoea*	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Thrombocytopaenia	[redacted]	[redacted]

AEs: adverse events

*Due to its clinical relevance, the incidence of diarrhoea was considered at any rate

Summary of company and ERG base case assumptions

The ERG has two preferred base-case positions

Updated post-ACM1

Table 15 Assumptions in company and ERG base case

Assumption	Company base case	ERG base case	
Comparators	Include EGFR TKIs	Include EGFR TKIs but this highly uncertain	
Time on treatment	CHRYSALIS PFS duration	CHRYSALIS TTD (exponential curve)	
Standard of care survival curves	KM curves for PFS and OS	Parametric curves for PFS and OS	
Indirect treatment comparison approach	Inverse probability weighting	Inverse probability weighting	Propensity score matching approach

- Company base-case used IPW, however alternative methods of ITC (for example, PSM) are possible
- IPW method kept CHRYSALIS data unchanged and showed good overlap of propensity score distribution
- At clarification, a PSM method was provided as a sensitivity analysis. This approach only allowed n=[redacted] treatment lines from cohorts to be paired and did not improve the balance between covariates compared to the IPW method
- **The ERG provided 2 base-cases (using each approach) because it remains undecided on the best way to determine comparative effectiveness versus standard of care.**

ITC: indirect treatment comparison; IPW: inverse probability weighting; OS: overall survival; KM: Kaplan-Meier; PFS: progression free survival; PSM: propensity score matching; TKIs: tyrosine kinase inhibitors

End of life criteria

Both criteria are considered to have been met by company and ERG

Table 16 Available data for end-of-life criteria

Criteria	Data available		
	Intervention	Median overall survival	Mean undiscounted life years
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**UK standard of care**	US RWE: [redacted] CEM: [redacted]	1.38 life years
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	**Amivantamab**	CHRYSALIS: 22.77 (17.48, NE) CEM: [redacted]	2.31 life years
	Difference versus amivantamab	US RWE: [redacted] CEM: [redacted]	0.93 life years

ERG comments: Data suggests, first NICE end of life criteria is met

- There is uncertainty around clinical effectiveness but the reported values appear to be well over 3 months. Therefore, the ERG considers the 2nd end-of-life criteria to have also been met

CEM: cost-effectiveness model; RWE: real world evidence

Cost-effectiveness results and scenarios

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Company base-case

- Treatment waning scenario (linear waning from 3-years)
- EGFR TKIs exclusion scenario
- TE treatment discontinuation scenario (assuming 50% in both arms discontinue at progression)
- Company base-case + use of PSM*
- Company base-case + use of parametric survival curves in standard of care arm*
- Company base-case + time to treatment discontinuation informed by CHRYSALIS trial protocol*

ERG base-cases (IPW and PSM approaches)

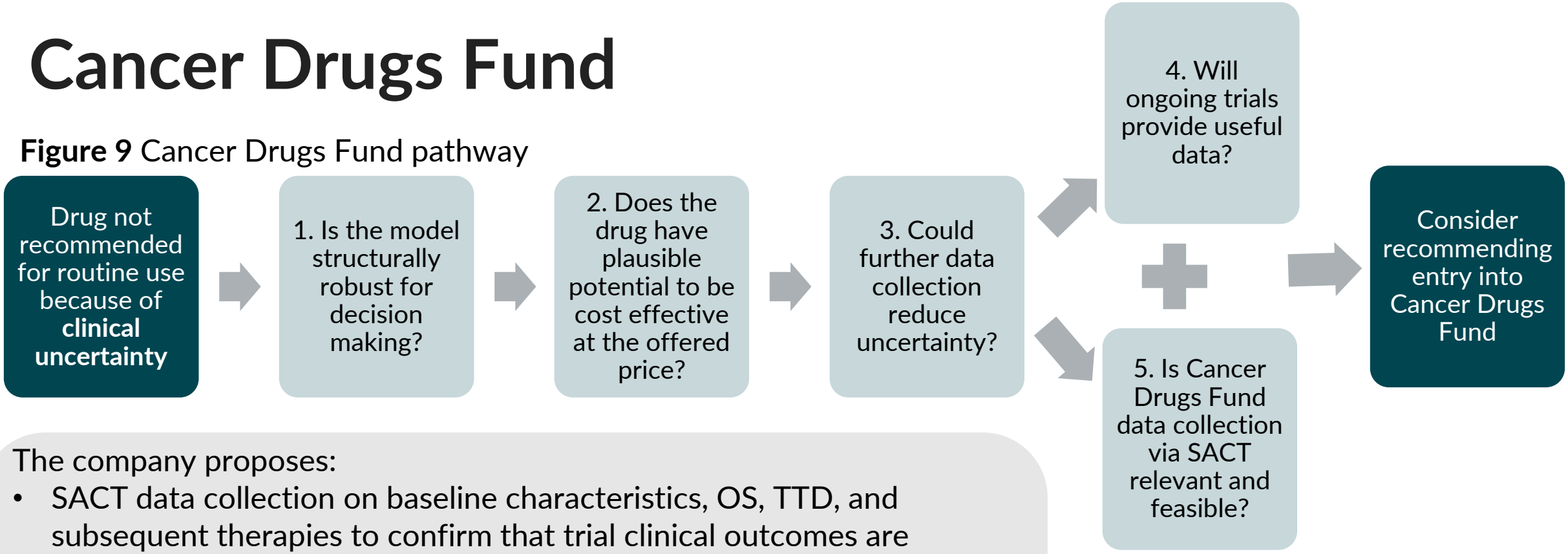
Scenarios applied to each base-case:

- EGFR TKIs exclusion scenario
- Weibull for amivantamab TTD
- CHRYSALIS HRQoL data
- TTNT as proxy for SoC treatment discontinuation

*The ERG have provided these additional scenarios applied to the company base-case for committee consideration
IPW: inverse probability weighting; PAS: patient access scheme; PSM: propensity score matching; TKIs: tyrosine kinase inhibitors

Cancer Drugs Fund

Figure 9 Cancer Drugs Fund pathway



The company proposes:

- SACT data collection on baseline characteristics, OS, TTD, and subsequent therapies to confirm that trial clinical outcomes are representative of those expected in typical UK clinical practice
- Collection on baseline characteristics, OS, and TTNT via an existing Janssen study using the NCRAS and linked datasets.
    - This will require molecular data linkage data to the NCRAS dataset and cover years 2017, 2021 and 2022. This is expected to increase sample size and reduce uncertainty in the adjusted comparison analysis (i.e. may resolve uncertainty with US RWE)

Does amivantamab meet the criteria to be considered for recommendation in the CDF? Is the CDF likely to address uncertainties associated with the appraisal?

NCRAS: National Cancer Registration and Analysis Service; OS: overall survival; SACT: Systemic anti-cancer therapies; TTD: time to treatment discontinuation; TTNT: time to next treatment

Feasibility of further data collection to resolve key uncertainties (NICE MA team perspective)

Table 17 NICE managed access team considerations

Uncertainty	Source of further data collection
EGFR TKIs as comparators	Not resolvable through data collection
Relative effectiveness and robustness of trial vs RWE indirect treatment comparison	• SACT could provide amivantamab data for a RWE vs RWE comparison • No further SACT data collection for comparator arm • Company expected to conduct the comparison with data provided • Committee judgement required on extent of follow-up required
Treatment waning	Could be informed by further follow-up from CHRYSALIS trial
Using PFS=TTD or TTD	Matter of committee judgement. SACT data could only collect TTD or TTNT and would not be able to investigate whether there is a difference between PFS and TTD

NICE **Depending on key uncertainties Managed Access team consider data collection feasible**

MA: managed access; PFS: progression free survival; SACT: systemic anti-cancer therapies; RWE: real world evidence; TTD: time to treatment discontinuation; TTNT: time to next treatment; TKI: tyrosine kinase inhibitors;

Equalities

The company considers there to be a need for additional flexibility

Company: NICE should consider whether a higher threshold/additional flexibility is indicated

- EGFR Exon20ins NSCLC is associated with never-smokers and has higher prevalence in people of East Asian family background
- Delaying diagnosis may be due to stigma (and mediated through characteristics related tor race)
- COVID-19 implications: potential for intersectional discrimination based on race and disease status

Figure 5: potential pathway leading to inequalities

Clinical expert: major issue is often one of equal access to best available treatments as people with EGFR Exon20ins have a lack of targeted treatments (amivantamab would bring people with EGFR Exon20ins in line with other EGFR patients)

NICE technical team considerations: differences in the prevalence cannot be resolved in an appraisal. Please note principle 9 of the NICE principles states that committees should take into account that "stigma may affect people's behaviour in a way that changes the effectiveness of an intervention and routine quality of life assessments may not capture the benefits of treatment"

Does the committee consider that there are any relevant equality or health inequality issues that it should consider in its decision making, and if so how?

Innovation: Amivantamab is considered innovative by the company

Company: treatment options are currently non-targeted and associated with limited efficacy. Amivantamab:

- Is the first targeted therapy to demonstrate efficacy in patients with EGFR Exon20ins mutated NSCLC after progression on platinum based chemotherapy
- Provides a treatment option for people identified by the Genomic Medicines Service
- Represents a step-change in the management of this underserved population

Clinical expert: amivantamab is innovative

- Novel treatment for rare and difficult to treat cancer
- First licensed agent of its type (bi-specific antibody) which may lead to future advances in cancer treatment
- In some people, responses can be long-lasting

For consideration: mobocertinib [ID3984] is also currently undergoing evaluation in EGFR Exon20ins mutated NSCLC after platinum-based chemotherapy

Are there any benefits not captured in the QALY calculation?

NICE National Institute for Health and Care Excellence

Thank you.