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

Technology appraisal committee D [5th October 2022]

Part 1 slides for public – redacted

ACM2 Meeting

Chair: Dr Megan John

Evidence Review Group: KSR

Technical team: Fatima Chunara, Alex Sampson, Ross Dent

Company: Janssen

Recap from ACM1

Not recommended for treating EGFR exon 20 insertion mutation positive NSCLC after platinum-based chemotherapy as ICERs above the range considered cost-effective	
End of life	Met (overall survival <24 months and survival gain >3 months)
Cancer Drugs Fund	Not suitable (as amivantamab data already mature)
Equalities issues	None identified
Innovation	All benefits captured by the model
Outstanding uncertainties	The following sources of uncertainty were identified by the committee: • lack of direct comparative evidence between amivantamab and comparators (blended comparator) • potential for residual confounding in the indirect treatment comparison • uncertainty around extent of bias because of a lack of detailed information on real-world evidence provenance and suitability • lack of transparency around identifying real-world evidence sources

Committee concluded maximum acceptable ICER was "substantially less than £50,000 per QALY gained"

EGFR, epidermal growth factor receptor; QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio; NSCLC, non-small cell lung cancer

Appraisal specific key issues for discussion

Some issues resolved at ACM1, others remain

Table 1 Key issues

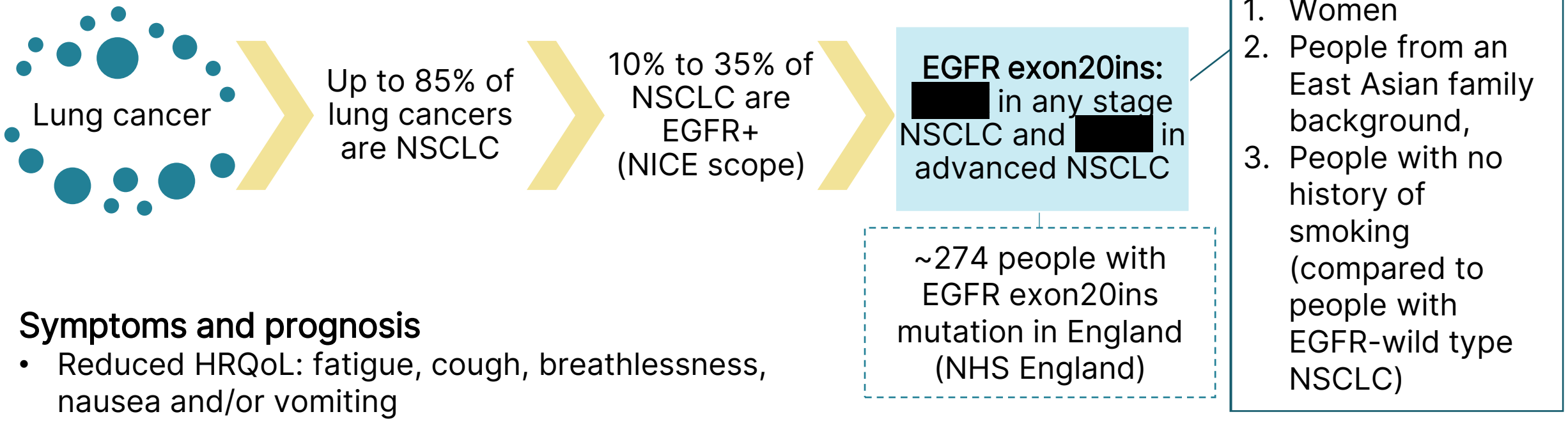
Issue	Resolved?	ICER impact
ITC data sources: Non-clinical trial RWE used. Unclear if RWE included has been selected systematically. Introduces uncertainty and risk of bias to the model outcomes.	For discussion	Unknown
Time on treatment: Is the company's or ERGs approach to time on treatment preferred for decision-making?	Company base case differs from committee conclusions at ACM1	Moderate
Comparators: should EGFR TKIs be included or excluded within the comparator basket?	Resolved (TKIs excluded)	
Survival curves: should KM curves or parametric curves be used to model survival outcomes in the standard of care arm?	Resolved (parametric)	
Treatment waning: should treatment waning scenarios be considered in decision-making?	Resolved (exclude treatment waning)	
Diagnostic testing costs – should they be included?	Resolved (scenario provided)	

ACM1 = 1st appraisal committee meeting; ERG = Evidence Review Group; ITC = indirect treatment comparison; KM = Kaplan-Meier; RWE = real world evidence; TKIs = tyrosine kinase inhibitors

Disease background

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 NSCLC

- There are no specific treatment options for EGFR exon20ins 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 2 Potential treatment pathways for people with EGFR exon20ins NSCLC in UK clinical practice

	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

ID3836 (amivantamab) and ID3984 (mobocertinib) are under evaluation for positioning after platinum-based chemotherapy

BSC = best supportive care; SoC = standard of care; RWE = real world evidence

Technology (Rybrevant, Janssen)

Table 3 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: December 2021
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

Table 4 Population, intervention, comparators and outcomes

	Final scope	ACM1
Population	Adults with EGFR Exon 20 insertion-positive non-small-cell lung cancer 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 (***as per marketing authorisation***)
Intervention	Amivantamab	As in scope
Comparator	Established clinical management without amivantamab	• Blended comparator including immunotherapy, platinum-based and non-platinum based chemotherapy. • **Exclude EGFR TKIs - not used in NHS routine practice**
Outcomes	• OS • PFS • Response rate • Time to treatment discontinuation • Adverse events • HRQoL	As in scope

HRQoL = health related quality of life; OS = overall survival; PFS = progression free survival

Clinical effectiveness

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Clinical data for amivantamab

CHRYSALIS is the key clinical trial

Table 5 Clinical trial design 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	• Health-related quality of life
	• Duration of response	• Time to treatment failure
	• Progression free survival	• 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

ITC methodology: comparators and sources

The company chose a blended comparator based on RWE

- No established standard of care, decisions are made on a case-by-case basis
- Lack of specific clinical guidelines for this population
- No comparator data from CHYRSALIS trial
- No relevant trials identified in systematic literature review comparing amivantamab to 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: routine population-level data available through NCRAS, n=[redacted] → **Included as scenario**

Committee concluded:

- Using a blended comparator arm increases uncertainty
- Of the two sources identified, US real-world evidence preferred
- Methods for choosing and using RWE associated with several areas of uncertainty and may bias the results
- Insufficient information on data provenance, accuracy and suitability. Effect of missing data not explored
- ITC is suitable for decision making but is associated with uncertainty

ITC =indirect treatment comparison; NCRAS =National Cancer Registration and Analysis Service; PHE = Public Health England; RWE = real world evidence;

ITC results

Amivantamab improves overall survival vs standard of care

Figure 2 Kaplan-Meier curve for OS for CHRYSALIS vs. US RWE cohort – 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.
- Using the PHE dataset increased treatment effect on OS – using US RWE considered conservative

ATT = average treatment effect on the treated; 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

Amivantamab improves progression free survival vs standard of care

Figure 3 Kaplan-Meier curve for PFS for CHRYSALIS vs. US RWE cohort – (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

Committee concluded:

- Results from the indirect treatment comparison show statistically significant improvements to OS and PFS with amivantamab (vs. SoC), but exact level of improvement was uncertain

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;

Cost effectiveness

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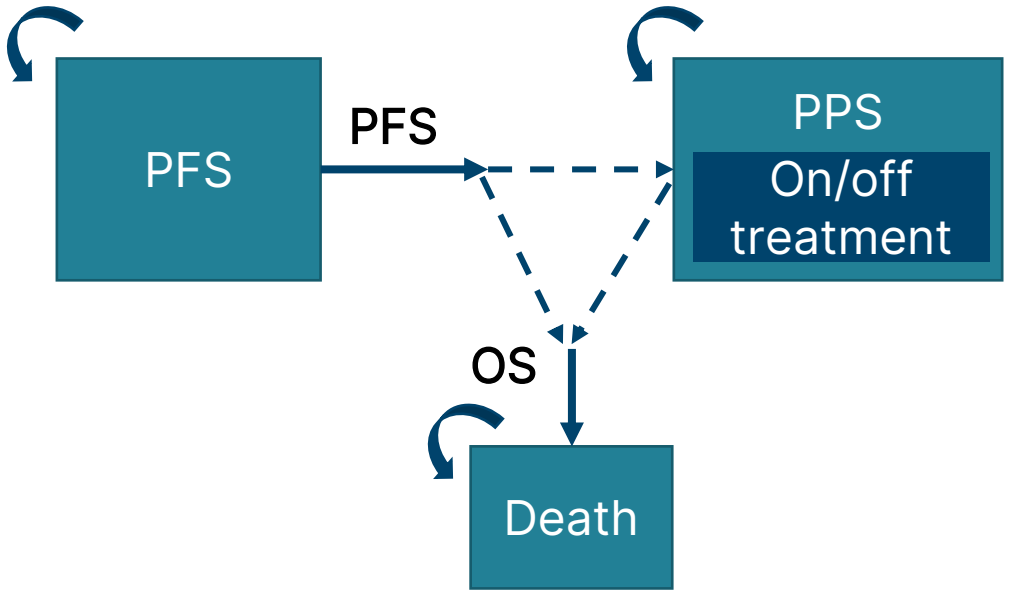
Company's model overview

Partitioned survival model with 3 states

Figure 4 Model structure



Committee concluded that exon 20 insertion mutation testing costs should be included in a scenario analysis

Table 6 Cost effectiveness model inputs

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
Costs and resource use	Administration-related costs: NHS Reference Costs Resource use costs: TA520 EoL costs: TA520
Adverse events	CHRYSALIS trial (for amivantamab), AURA3 for platinum-based chemotherapy (as per TA653), previous NICE appraisals (TA520) for IO agents & non-platinum-based chemo.

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

Consultation comments

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ACD consultation responses – patient experts

Large unmet need and treatment benefits have not been fully recognised

Consultation comments
Comments received from: • EGFR Positive UK • Roy Castle Lung Cancer Foundation

Key themes have been summarised over the next two slides

Unmet need
• ‘Massive’ unmet need was not given sufficient recognition in ACD • People with this condition, whose diagnosis is often missed, are placed on a variety of treatment pathways which have limited efficacy and often have a high toxicity. • Amivantamab would be the first NICE recommended treatment for this small, highly selected group of patients • These patients are at the end of their lives and “don’t have time to wait” • Having access to a targeted therapy that prolongs life and positively impacts quality of life would be a “game changer” for patients.

ACD = appraisal consultation document

ACD consultation responses – patient experts

Large unmet need and treatment benefits have not been fully recognised

Emotional burden

- Knowing that a treatment is available yet you cannot access it has a negative impact on people. “Both drugs are approved and used in other countries yet in the UK patients with Exon 20 ins are denied this opportunity”

Benefits not captured by QALYs

- The emotional, social and economic impact on quality life when living with EGFR Positive lung cancer has not been fully recognised

Cancer Drugs Fund

- Urge further collaboration between NICE and manufacturer around cost and potential for use in the Cancer Drugs Fund

ACD = appraisal consultation document

ACD consultation responses – Company

New commercial discount and supporting information to reduce uncertainty

Changes to company submission:

- TKIs excluded from blended comparator
- Treatment waning excluded
- Use parametric curves for the SoC arm
- Still using PFS for time on treatment - not committee's preferred assumption
- Updated PAS and scenario added which includes testing costs

Key themes in ACD response	Change to ACM1 base case?	Updated information or analyses
Uncertainty around how RWE was chosen & used	No	Information provided to reduce uncertainty around the choice and use of RWE in the comparator arm
Benefits not captured by QALYs	No	Information provided to recognise benefits not captured within the cost per QALY framework (inc. patient and caregiver preferences and reduction of stigma)
Approach for amivantamab time-on-treatment	No	Justification for use of PFS to model time on treatment. Also rationale for using Gompertz curve in scenario based on TTD.

ACD = appraisal consultation document; PAS = patient access scheme; PFS = progression free survival; RWE = real world evidence; SoC = standard of care; QALY = quality-adjusted life year

Key issue: Uncertainty around how RWE was chosen & used

Company aiming to reassure that RWE is robust, reliable, and fit for purpose

Committee comments at ACM1

- Company had not provided enough information on data provenance, data accuracy and data suitability, and had not explored the effect of missing data
- May be additional RWE sources that were not identified by the company
- Way the company chose and used RWE may not be robust and is associated with uncertainty
- Uncertainty could be reduced by:
  - Using well-validated real-world evidence checklists and reporting tools
  - Doing sensitivity analysis using multiple imputation approach to assess impact of missing data
  - Providing further detail on the 3 US real-world evidence sources, and explaining how they were chosen and assessed for suitability
  - Providing outcomes for US RWE sources individually and explaining why it was suitable to pool the evidence

Company response to ACD

- DataSAT RWE checklist now completed
- Sensitivity analyses assessing the impact of missing data conducted
- Further information on US data sources provided, including eligibility criteria, data provenance, study variables and outcomes, missing data, study protocol and time frame for data collection

ACD = appraisal consultation document; RWE = real world evidence

Information provided by company on RWE sources

Differences noted between data sources but pooled results conservative

Checklist item	ERG comment
Eligibility criteria	General conformity between the three data sources, although do reveal some potential selection bias due to excluding patients with “insufficient EHR data” for ConcertAI and COT
DataSAT checklist	DataSAT checklist was completed, but was not used to affect the choice of data source
Baseline characteristics	Differences in baseline characteristic between data sources, particularly between COTA and the other two in brain metastases (more common in COTA), ECOG PS (higher in COTA) and number of metastatic locations (more in COTA). Baseline characteristics of COTA more dissimilar to CHRYSALIS; Flatiron most similar to CHRYSALIS.
Care setting	There were differences in terms of care setting: Flatiron and Concert AI patients were “primarily in the community oncology setting” whereas 79% those in COTA were treated at academic medical centres, the remainder in the community.

Despite potential issues described above, results for the pooled analysis were conservative (higher HR) for all outcomes (OS, PFS and TTNT) relative to all those based on any single data source in most cases (see next slide)

HR = hazard ratio; OS = overall survival; PFS = progression free survival; RWE = real world evidence; TTNT = time to next treatment

Adjusted comparisons using individual data RWE sources

Results of sensitivity analyses are generally consistent across the 3 datasets

Table 7: Adjusted comparisons inc. sensitivity analyses utilising a multiple imputation approach to account for missing data (HRs, 95% confidence intervals and p values)

ATT-adjusted results	AMI versus Pooled US	AMI versus Flatiron	AMI versus ConcertAI	AMI versus COTA
OS (March 2022)				
No imputation, excluding EGFR TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding EGFR TKIs	[redacted]	[redacted]	[redacted]	[redacted]
PFS IRC				
No imputation, excluding EGFR TKIs	[redacted]	[redacted]	[redacted]	[redacted]
With imputation, excluding EGFR TKIs	[redacted]	[redacted]	[redacted]	[redacted]

Table 12 from company ACD response

ERG comment: base-case HRs are mostly conservative (higher HRs) relative to results based on any single data source

*Imputation not necessary as there were no missing values.

ATT = Average treatment effect among the treated; PFS = progression free survival; OS = overall survival

Key issue: Uncertainty around how RWE was chosen & used

Company aiming to reassure that RWE is robust, reliable, and fit for purpose

ERG comments

- ✓ Company responded appropriately in providing DataSAT checklist, explanation of how patients/LOTs were selected from the RWD, the extent of missing data, additional analyses based on EGFR TKI inclusion and number of lines of metastatic treatment.
- ✓ Results for the pooled analysis were conservative (higher HR) for all outcomes (OS, PFS and TTNT) relative to all those based on any single data source in most cases.
- ✗ Company provided eligibility criteria for data sources that were used, but did not provide information on how those sources were chosen from the pool of all potential data sources.
- ✗ Although the company completed the DataSAT checklist, this was not used to affect in any way the choice of data source and a full search for all relevant studies has still not been conducted.

Has the additional information provided by the company reduced the uncertainty around the choice and use of RWE? How much has it reduced?

HR = hazard ratio; OS = overall survival; LOTs = lines of treatment; PFS = progression free survival; RWE = real world evidence; TTNT = time to next treatment

Key issue: Approach for amivantamab time-on-treatment

Company maintains time to treatment discontinuation is equal to PFS

Committee comments at ACM1

- Time-on-treatment should be based on the CHRYSALIS time to treatment discontinuation data with the exponential curve (as the best statistical fit)

Company response to ACD

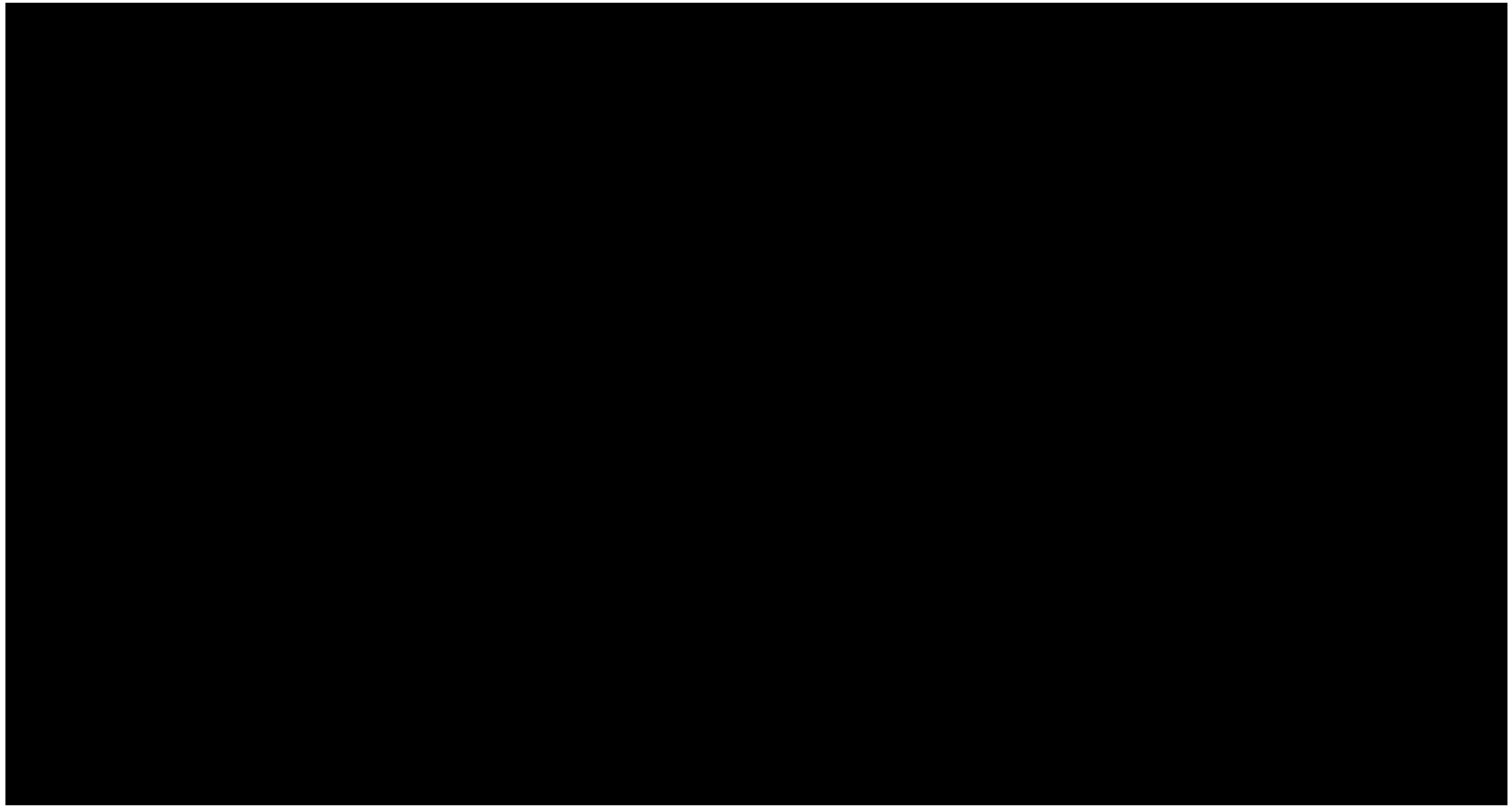
- Maintain time on treatment should be considered equal to PFS (as in marketing authorisation)
- Clinicians said people would discontinue treatment upon progression, therefore TTD is equal to PFS
- Progression in CHRYSALIS would be detected earlier than in real-world (due to closer monitoring)
- Exponential curve is not the most appropriate curve choice to select:
  - it assumes constant hazards over time - not aligned with the hazards demonstrated for TTD
  - it has people remaining on treatment beyond progression - particularly prominent towards tail
- Assuming treatment beyond progression for amivantamab penalises amivantamab arm unfairly
- Scenario provided for revised base case using Gompertz curve for amivantamab TTD, which is most aligned with smoothed hazard curve for TTD

PFS = progression free survival; TTD = time to treatment discontinuation

Key issue: Approach for amivantamab time on treatment (1/2)

Company maintains time to treatment discontinuation is equal to PFS

Figure 5: Relationship between TTD and PFS with Exponential and Gompertz extrapolations



PFS = progression free survival; TTD = time to treatment discontinuation

Company ACD response:

- Although people remain on treatment beyond progression in both Gompertz and Weibull, the difference is not as prominent as exponential TTD curve (ERG base case), and is more aligned throughout with a narrowing at the tail

ERG:

- Gompertz (company scenario) not appropriate as it had the 4th best statistical fit and did not clearly have the best visual fit.

Key issue: Approach for amivantamab time on treatment (2/2)

Majority of recent NSCLC appraisals use TTD to model ToT

TA	Method for modelling time on treatment
Sotorasib [TA781]	Hazard ratio applied to PFS. Close match between modelled treatment duration curve and unadjusted TTD. ERG preferred fitting a parametric curve on TTD data, but agreed at TE that connecting TTD to PFS with fitted HR was reasonable and consistent with clinical use.
Tepotinib [TA789]	Time on treatment data from clinical trial.
Pembrolizumab [TA770]	Time on treatment modelled using cumulative probabilities from the KM estimates of ToT
Osimertinib [TA761]	Patient data corresponding to actual time on treatment
Mobocertinib [ID3984]	ACM1 Conclusion: TTD from clinical trial, with Gompertz curve
Amivantamab [ID3836]	ACM1 Conclusion: TTD from clinical trial, with exponential curve

NICE

HR: hazard ratio: PFS = progression free survival; ToT: time on treatment; TTD = time to treatment discontinuation

Key issue: Approach for amivantamab time on treatment

Company maintains time to treatment discontinuation is equal to PFS

ERG comments

- No compelling new arguments or evidence provided - ERG perspective unchanged:
  - In CHRYSALIS median TTD was longer than median PFS ([redacted] vs 6.74 months)
  - Modelled median TTD was also longer than modelled median PFS ([redacted] vs [redacted] months)*
  - Assumption that PFS = ToT reduces the estimated cost of amivantamab without reducing the estimated effectiveness after progression of amivantamab
  - Gompertz model is the most pessimistic curve (i.e., resulting in the lowest number of people on-treatment over time
- ERG base case continues to model time on treatment on CHRYSALIS time to treatment discontinuation data with exponential curve (best statistical fit)

Committee previously concluded that time on treatment should be based on TTD (exponential), not PFS. Has the committee's view changed?
If TTD is preferred, should the Gompertz or exponential curve be used?

*using Gompertz distribution for TTD and generalised gamma for PFS
PFS = progression free survival; ToT = time on treatment; TTD = time to treatment discontinuation

Benefits not captured by QALYs

Company says there are additional benefits which have not been recognised

Committee comments at ACM1

- All benefits captured by QALY calculations

Company response to ACD

Impact of stigma

- EGFR-positive NSCLC is associated with smoking behaviours, although this population has a larger proportion of patients who are never-smokers (relative to other lung cancers)
- Evidence demonstrates that stigmatisation contributes to delayed diagnosis and treatment
- This places a higher value on later line therapies for advanced disease; hasn't been accounted for
- NICE's social value judgements recognise that "*relief of stigma may not always be captured by routine quality of life assessments*"
- Relief of stigma via treatment with amivantamab (if patients are less obviously suffering from a disease that may be perceived by society as self-inflicted), would not be captured in generic QoL measures and QALYs
- Stigma can impact peoples' ability to work, which may have productivity implications for some people. This indirect economic burden isn't captured in the model

NICE technical team considerations

- Acknowledge that there is evidence that stigma is associated with lung cancer diagnosis, but there is a lack of strong evidence to demonstrate how amivantamab reduces stigma

Benefits not captured by QALYs

Company suggests there are additional benefits which have not been recognised

Company response to ACD

Patient and caregiver preferences

- Improved health outcomes associated with amivantamab versus UK SoC may improve aspects of daily life most valued by patients, such as being able to undertake daily activities, maintaining independence and 'feeling normal', the value of which is "not intrinsically captured in the QALY framework".
- Value of hope associated with a targeted treatment for NSCLC with EGFR Exon20ins is incredibly high and also not intrinsically captured
- People with NSCLC with EGFR Exon20ins have a poorer prognosis and fewer effective treatment options than people with common EGFR mutations. Therefore, there is additional value in amivantamab being available to people with EGFR Exon20ins

Patient input:

- Patient expert submissions (pre-ACM1) mention that the treatment would give people hope and help 'bring them emotionally and clinically in line' with the wider EGFR population.

Are there benefits which are not captured in the QALY calculations?

ACM1 = 1st appraisal committee meeting; SoC = standard of care

Cost-effectiveness results and scenarios

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

Company base-case

Scenarios provided:

- Include testing costs for EGFR exon 20 mutation - *small ICER impact*
- ToT amivantamab based on CHRYSALIS time to treatment discontinuation – Gompertz *- moderate ICER impact*

ERG base-case

Scenarios provided:

- Company base case, but exponential curve applied to CHRYSALIS TTD for treatment duration - *moderate ICER impact*

ICER = incremental cost effectiveness ratio; TTD = time to treatment discontinuation

Summary of company and ERG base case assumptions

Two key differences in company and ERG base cases

Table 8 Assumptions in company and ERG base case

Assumption	Company base case	ERG base case	ICER impact
Comparators	EGFR TKIs excluded	EGFR TKIs excluded	N/A
Time on treatment	ToT equals PFS	ToT equals TTD (exponential curve)	Moderate
Survival in the blended comparator	Parametric modelling	Parametric modelling	N/A
Treatment waning	Excluded	Excluded	N/A
Utility values	TA713	TA713	N/A
Indirect treatment comparison approach	Inverse probability weighting	Inverse probability weighting	N/A
Cost of NGS diagnostic testing	Not included (only as scenario, aligned with ACD)	Included	Small

PFS = progression free survival; ToT = time on treatment; TTD = time to treatment discontinuation

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Thank you.

Backup slides

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Scenario including diagnostic testing costs

Including cost of diagnostic tests has marginal impact on ICER

Company submission at ACM1

- Company did not include exon 20 testing in economic modelling (as part of routine NHS testing)

Committee comments at ACM1

- Appropriate to consider scenarios with additional testing costs (to reflect switch from PCR testing to next generation sequencing)

Company response to ACD

- Company has conducted scenario analysis including the testing cost of £550 per person with exon 20 insertion mutation-positive NSCLC
- Addition of the testing costs increases the ICER marginally

ERG critique of company response

- Company approach to incorporate testing costs is appropriate
- Testing costs now included in the ERG base case